Received: 26 September 2017 | Accepted: 12 October 2017

DOI: 10.1111/dom.13129

WILEY

REVIEW ARTICLE

Incretin hormones: Their role in health and disease

Michael A. Nauck MD | Juris J. Meier MD

Diabetes Center Bochum-Hattingen, Medical Department I, St. Josef-Hospital, Ruhr-University, Bochum, Germany

Correspondence
Prof. Dr. med. Dr. h.c. Michael A. Nauck, Diabetes Center Bochum-Hattingen, Medical Department I, St. Josef-Hospital, Ruhr-University Bochum, Gudrunstraße. 56, 44791 Bochum, Germany.
Email: michael.nauck@rub.de

Funding information
Deutsche Forschungsgemeinschaft, Grant/Award number: Me 2096/6-1

Incretin hormones are gut peptides that are secreted after nutrient intake and stimulate insulin secretion together with hyperglycaemia. GIP (glucose-dependent insulinotropic polypeptide) und GLP-1 (glucagon-like peptide-1) are the known incretin hormones from the upper (GIP, K cells) and lower (GLP-1, L cells) gut. Together, they are responsible for the incretin effect: a two- to three-fold higher insulin secretory response to oral as compared to intravenous glucose administration. In subjects with type 2 diabetes, this incretin effect is diminished or no longer present. This is the consequence of a substantially reduced effectiveness of GIP on the diabetic endocrine pancreas, and of the negligible physiological role of GLP-1 in mediating the incretin effect even in healthy subjects. However, the insulinotropic and glucagonostatic effects of GLP-1 are preserved in subjects with type 2 diabetes to the degree that pharmacological stimulation of GLP-1 receptors significantly reduces plasma glucose and improves glycaemic control. Thus, it has become a parent compound of incretin-based glucose-lowering medications (GLP-1 receptor agonists and inhibitors of dipeptidyl peptidase-4 or DPP-4). GLP-1, in addition, has multiple effects on various organ systems. Most relevant are a reduction in appetite and food intake, leading to weight loss in the long term. Since GLP-1 secretion from the gut seems to be impaired in obese subjects, this may even indicate a role in the pathophysiology of obesity. Along these lines, an increased secretion of GLP-1 induced by delivering nutrients to lower parts of the small intestines (rich in L cells) may be one factor (among others like peptide YY) explaining weight loss and improvements in glycaemic control after bariatric surgery (e.g., Roux-en-Y gastric bypass). GIP and GLP-1, originally characterized as incretin hormones, have additional effects in adipose cells, bone, and the cardiovascular system. Especially, the latter have received attention based on recent findings that GLP-1 receptor agonists such as liraglutide reduce cardiovascular events and prolong life in high-risk patients with type 2 diabetes. Thus, incretin hormones have an important role physiologically, namely they are involved in the pathophysiology of obesity and type 2 diabetes, and they have therapeutic potential that can be traced to well-characterized physiological effects.

KEYWORDS

glucose-dependent insulinotropic polypeptide, glucagon, glucagon-like peptide-1, incretin, insulin, type 2 diabetes

1 | INTRODUCTION

Incretin hormones have received much attention because of their important role both in the physiology of glucose homeostasis and in the pathophysiology of type 2 diabetes and, potentially, of other metabolic disorders.[1] Glucagon-like peptide-1 (GLP-1), in particular, has moved into the focus as a suitable parent compound for glucose- and weight-lowering medications.[2] GLP-1 receptor agonists and inhibitors of dipeptidyl peptidase-4 (DPP-4 inhibitors) offer therapeutic effects that are more or less derived from the physiological activities of incretin hormones.[1,2] DPP-4 inhibitors exert their therapeutic effects mainly by just a moderate elevation of GLP-1 concentrations, while effective drug concentrations of GLP-1 receptor agonists clearly extend into the pharmacological range.[2] It is the purpose of this review to summarize the state-of-the-art science on incretin hormones including their role in physiology and in the pathophysiology of obesity and type 2 diabetes, and the therapeutic perspective that can be derived from these findings.

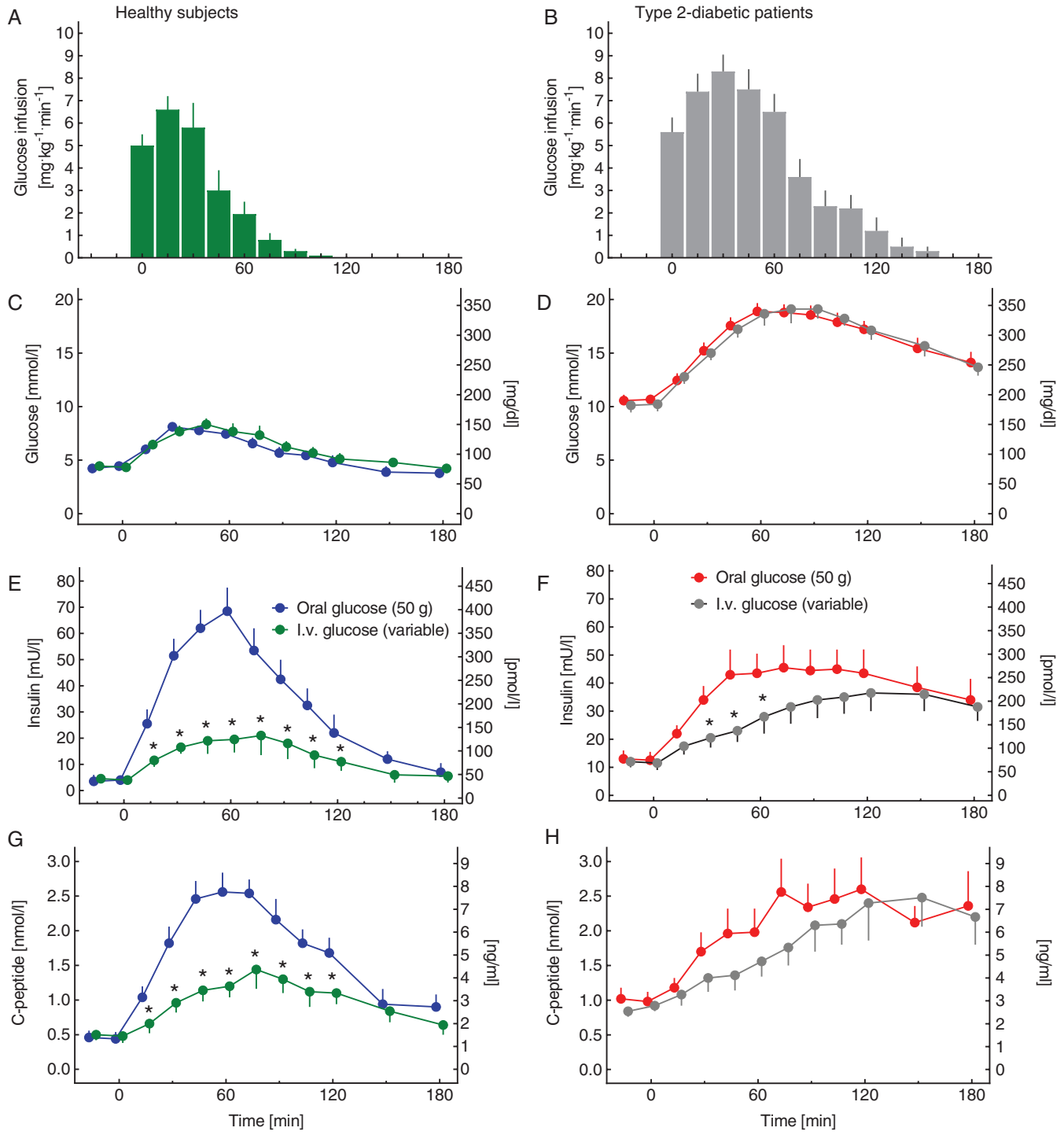

FIGURE 1 Reduced incretin effect in patients with type 2 diabetes (B, D, F, H) as compared to healthy subjects (A, C, E, G). A, B, Glucose infusions rates (during "isoglycaemic" intravenous glucose infusions); C, D, Plasma glucose concentrations; D, E, Plasma insulin concentrations; F, G, C-peptide concentrations are shown for experiments with oral glucose (50 g) administration and with "isoglycaemic" intravenous glucose infusions. Asterisks indicate a significant difference between experiments with oral and intravenous glucose (t-test for paired samples, $P < .05$). Reproduced from Nauck et al.[3] with permission (Diabetologia, Springer)

2 | THE INCRETIN EFFECT

Oral glucose leads to a greater stimulation of insulin secretion than an intravenous glucose infusion even when the same plasma glucose concentration profiles ("isoglycaemia") are achieved (Figure 1A,C,E, G).[4] This phenomenon is called the incretin effect and is attributed to the fact that oral glucose leads to the release of incretin hormones (glucose-dependent insulinotropic polypeptide, GIP, and glucagon-like peptide-1, GLP-1) from specialized entero-endocrine cells in the gut (coupled to the absorption of glucose), while intravenous glucose does not.[4,5] The gut hormones released in response to nutrient absorption are endocrine signals to the islets of Langerhans in the

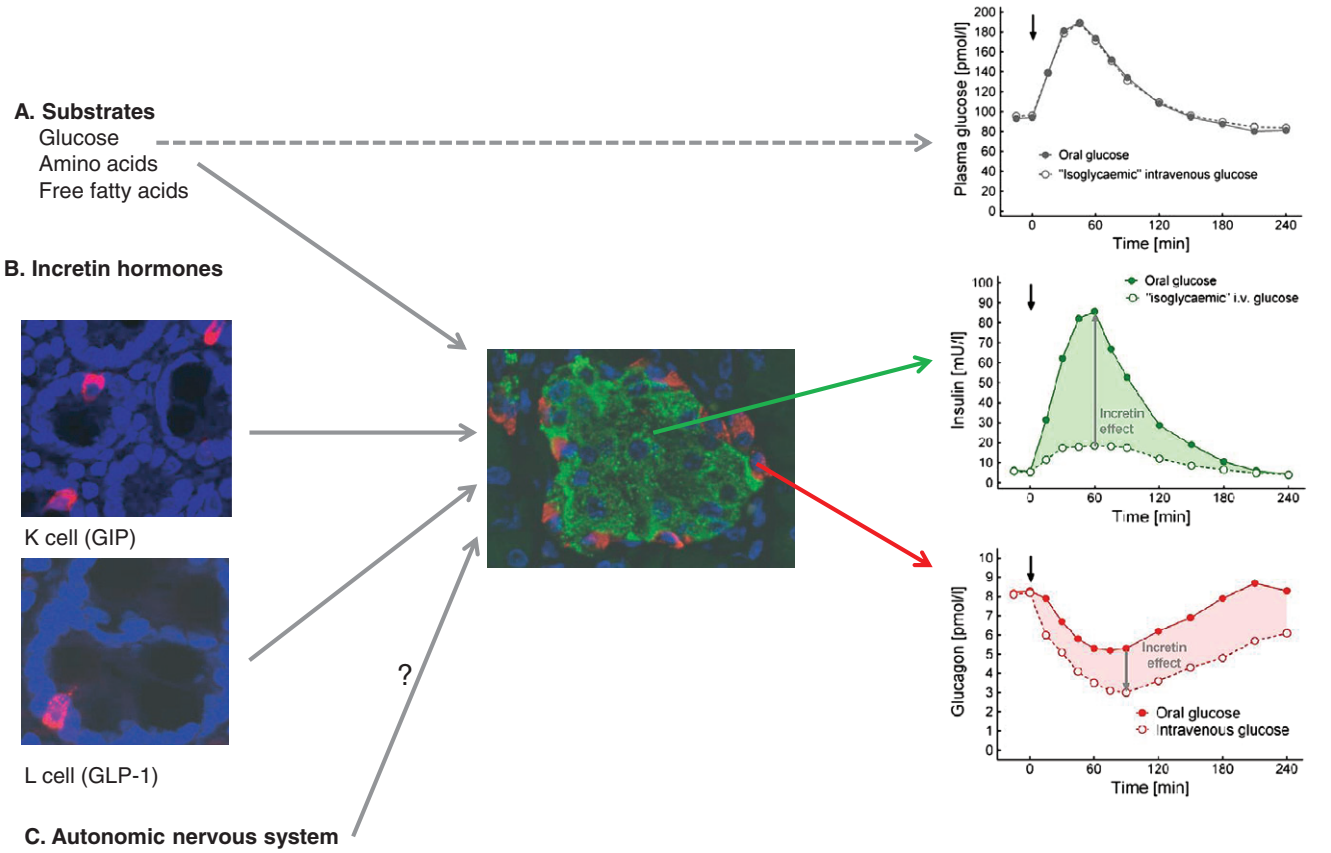

FIGURE 2 Contribution of (A) metabolic substrates, as well as (B) the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), and, potentially, (C) neural transmission (left panels)[5] to the stimulation of insulin secretion ("insulinotropic incretin effect") and the suppression of glucagon secretion ("glucgonostatic incretin effect") in healthy human subjects (islet of Langerhans with α cells and ß cells; central panel). K cells were stained for GIP (red), and L cells were stained for GLP-1 (red) by immunofluorescence. Endocrine pancreatic islets were co-stained for insulin (green) and glucagon (red) by immunofluorescence. In all histology panels, cell nuclei are stained (dark blue) by DAPI. Insulin (green) and glucagon (red) responses to oral and "isoglycaemic" intravenous glucose (grey) are shown schematically in the right panels based on published data.[4,6] Immunofluorescence panels: Courtesy of Dr. Sandra Ueberberg, Bochum, Germany

pancreas, augmenting insulin secretion and modulating glucagon secretion whenever plasma glucose concentrations are above a threshold value of approximately 66 mg dL^{-1}. The physiological stimulation of insulin secretion through incretin hormones is substantial,[7] while physiological degrees of hyperglycaemia are a rather weak stimulus for insulin release.[4] An "isoglycaemic" intravenous glucose infusion leading to identical increments in arterial plasma glucose concentrations as does an oral glucose load causes a rise in insulin secretory responses that is approximately one-third of that elicited by oral glucose (i.e., the combined action of hyperglycaemia and incretin hormones).[8] The difference between these two insulin secretory responses, thus, represents approximately two-thirds of the total response (Figure 1). It is usually expressed as a percentage of the response after oral glucose infusion. The estimate of the contribution of incretin hormones to insulin secretory responses after oral glucose administration depends on the dose of glucose employed, and may vary between 25% and 75%. No doubt, this quantitative contribution speaks in favour of a substantial physiological importance of incretin hormones in the maintenance of proper glucose homeostasis.[4] Of the three signals originating from the gut and reaching the endocrine pancreas (substrates such as glucose, incretin hormones, and neural signals transmitted by the autonomic nervous system, Figure 2),[5] incretin hormones make the most substantial contribution under physiological circumstances.

2.1 | Incretin hormones (GIP, GLP-1)

Glucose-dependent insulinotropic polypeptide was purified using a bioassay measuring the inhibition of gastric acid secretion, and hence the old name "gastric inhibitory polypeptide".[9] The main function later was identified as glucose-dependent augmentation of insulin secretion.[10] GIP is produced in K cells, which are single cells located to the mucosa in the duodenum and upper jejunum.[9] GIP is synthesized as a precursor propeptide (pro-GIP), which is then cleaved to GIP by post-translational processing.[11] Glucagon-like peptide-1 was identified as part of the gene sequence coding for proglucagon,[12] which is expressed in L cells in the small and large intestines, with a gradient from a low density in the duodenum to a higher density in the ileum, but also in the colon and rectum.[13] Proglucagon contains the coding region for pancreatic glucagon and two "glucagon-like" sequences with a predicted similarity to the glucagon amino acid sequence[12] hence the names GLP-1 and GLP-2. Early assumptions regarding post-translational processing were later proven wrong. Therefore, the biologically active forms of GLP-1 are now called GLP-1 [7–36 amide] (amidated GLP-1) and GLP-1 [7–37] (glycine-

extended GLP-1). Both forms are "truncated" in comparison to the originally proposed sequences GLP-1 [1–36 amide] and GLP-1 [1–37] by the N-terminal six amino acids.[14,15] The extended forms neither occur in substantial quantities nor exert insulinotropic effects. The same proglucagon gene is processed in a different manner in α cells of the endocrine pancreas (main products: "pancreatic" glucagon and a "major proglucagon fragment,"), which is not further processed to GLP-1 and GLP-2.[11]

2.2 | Secretion of incretin hormones in healthy human subjects

GIP and GLP-1 have low (basal) plasma concentrations in the low picomolar range (10^{-12} mol L^{-1}) in fasting human subjects. GIP and GLP-1 plasma concentrations start to rise a few minutes after nutrient intake, reach a peak after approximately 1 h, and reach basal concentrations again after several hours. Nutrients that stimulate the secretion of GIP and GLP-1 are glucose and other carbohydrates including sucrose and starch, triglycerides, and some amino acids as well as proteins.[4,16] Protein is a comparatively weak stimulus. Because nutrients have to reach the location of K and L cells in the gut in order to stimulate the release of GIP and GLP-1, respectively, a minimum rate of trans-pyloric delivery (gastric emptying) is necessary to elicit measurable secretory responses.[17] This minimum delivery rate is lower for GIP, most likely because GIP-producing K cells are located more proximally, while nutrients are only delivered to gut areas with significant numbers of L cells, located more distally, if a greater delivery rate is achieved.[17] GLP-1 secretion from L cells occurs early after nutrient intake, almost in parallel with GIP secretion, despite the more distal location of L cells.[4,13] Whether this indicates that the low number of L cells in the duodenum and upper jejunum is sufficient as a source of GLP-1, or whether there are signals from the upper gut that trigger release the of GLP-1 from L cells located more distally, is a matter of debate. The gut autonomic nervous system and GIP have been proposed as signals.[18] In humans, high GIP concentrations do not stimulate GLP-1 secretion.[19] Both fasting and nutrient-stimulated plasma concentrations are higher for GIP as compared to GLP-1.[4] Secretion of the incretin hormones GIP and GLP-1 is usually monitored using "non-specific" immunoassays, which detect "total" GIP and GLP-1, that is, both intact, biologically active forms and fragments such as the metabolites generated by DPP-4-mediated proteolysis. Both GIP and GLP-1 are substrates of DPP-4 and are physiologically degraded and inactivated by DPP-4. Concentrations of "intact" (biologically active) incretin hormones are measured using sandwich immunoassays that require both the amino and carboxy termini of the peptides to be intact (unmodified) and connected. Under most physiological circumstances, intact, biologically active concentrations of GIP and GLP-1 are substantially lower than their "total" levels: approximately 40% to 60% of the "total" concentrations in the case of GIP and approximately15% to 25% in the case of GLP-1.[20,21] "Total" GIP concentrations usually are higher than "total" GLP-1 concentrations, and the difference is even greater when looking at "intact" plasma concentrations.[21]

There is considerable inter-individual variation in GIP as well as in GLP-1 secretion. Interestingly, subjects that secrete little GIP tend to also secrete less GLP-1, and vice versa.[4,22] This has been verified in independent populations, but is difficult to explain, since K cells producing GIP and L cells synthesizing GLP-1 are not only separate entities (with the exception of some entero-endocrine cells that appear to produce both GIP and GLP-1)[23] but also occur in different segments of the gut. At present, it is unclear whether this indicates some inter-individual variation in the number of entero-endocrine cells, or in more functional aspects of the mechanisms that lead to the secretion of incretin hormones (taste receptors, G-protein coupled receptors sensing fatty acid derivatives, exposure to bile acids, the microbiome, etc.).[16]

2.3 | Insulinotropic activitiy of incretin hormones in healthy human subjects

Both GIP and GLP-1 stimulate insulin secretion in a glucose-dependent manner.[7,24] ß cells have GIP and GLP-1 receptors in their cell membranes, which, once stimulated by the binding of their respective ligands, are coupled to adenylate cyclase, which enhances cyclic AMP (adenosine monophosphate) production and thus activates protein kinase A.[25] This pathway cannot initiate the release of pre-formed insulin secretory granules from ß cells, which requires closing of potassium channels, depolarization, and calcium ion influx, as initiated by hyperglycaemia. Therefore, insulinotropic actions of incretin hormones always require a permissive degree of hyperglycaemia. The role of incretin hormones is to augment the insulin secretory responses initiated by hyperglycaemia. Therefore, incretin hormones cannot provoke episodes of hyperglycaemia. The absolute glycaemic threshold below which GLP-1 cannot stimulate insulin secretion, even at supra-physiological concentrations, was identified as approximately 66 mg dL^{-1}.[24] Conversely, the higher the glucose concentrations, the greater the degree of augmentation.

2.4 | Incretin hormones and glucagon secretion

In addition to their insulinotropic activity, incretin hormones affect glucagon release. GIP has been found to stimulate glucagon secretion,[26] especially at lower glucose concentrations, while GLP-1 suppresses glucagon secretion, in particular at hyperglycaemia.[19] The latter leads to a reduced hepatic glucose production.[27] In addition, GLP-1 appears to reduce hepatic glucose output even independent of changes in plasma glucagon.[28] Since the liver does not appear to be equipped with GLP-1 receptors, this has to be mediated indirectly, for example, through the autonomic nervous system.

Using the experimental paradigm typically used to quantify the incretin effect, it has been found that "isoglycaemic" intravenous glucose, in healthy subjects, suppresses glucagon more than oral glucose (Figure 2).[6,29] This probably is the consequence of GIP and GLP-2 being released after oral but not intravenous glucose. Both GIP[26] and GLP-2[30] can stimulate glucagon secretion.

2.5 | Physiological role of individual and combined incretin hormones in healthy human subject

Attempts have been made to quantify the contribution of GIP and GLP-1 to the incretin effect by testing their insulinotropic action in

the presence of a physiological glucose concentration profile (such as after oral glucose loads): GIP and GLP-1 were infused intravenously with the aim of coming close to the physiological concentration profiles as they occur after oral glucose loads. GIP infusion rates of 1.0 pmol kg^{-1} min^{-1} led to slightly higher GIP concentrations than found after oral glucose, and GLP-1 infusions rates of 0.15 pmol kg^{-1} min^{-1} relatively closely matched the "total" GLP-1 concentrations after oral glucose,[31] while 0.3 pmol kg^{-1} min^{-1} GLP-1 intravenously resulted in supra-physiological GLP-1 concentrations. Comparing the insulin secretory responses under these circumstances suggested that GIP explains the majority of the incretin effect after oral glucose, while GLP-1 made only a minor contribution.[31] Another reason why GLP-1 probably is not a major incretin is the fact that it slows gastric emptying.[32,33] With exogenous GLP-1 administration, decelerating gastric emptying reduces the post-meal rises in glucose concentrations substantially, with the consequence that insulin secretory responses are reduced despite the presence of elevated GLP-1 concentrations.[33] However, when experimental approaches are used that disregard the effects of gastric emptying, more similar contributions of GIP and GLP-1 to meal-induced insulin secretion can be estimated.[34] We still tend to believe that GIP is responsible for the majority of the incretin effect in healthy subjects. Novel GIP peptide antagonists[35] will probably help resolve this controversy.

There is no doubt that in healthy human subjects the insulinotropic effects of GIP and GLP-1 are additive, that is, a combined administration of GIP and GLP-1 will lead to an insulin secretory response that is equivalent to the sum of the responses elicited by GIP or GLP-1 alone.[31]

Quantitative considerations as described in this paragraph suggest that, most likely, GIP and GLP-1together explain most, if not all, of the incretin effect.[31] Thus, the active search for other, hitherto undetected incretin hormones has subsided. It is not known whether hormones exist that rather limit the secretion of insulin. Gut-derived somatostatin has been discussed as one such "decretin".[36] The "upper gut hypothesis" claims that excluding the duodenum from the passage of nutrients will explain some of the beneficial effects of bariatric surgery, which includes improvement of metabolic control in type 2 diabetic patients.[37] However, the responsible factors have not been identified.

As the consequence of the dose-dependent secretion and insulinotropic action of the incretin hormones GIP and GLP-1, widely different oral glucose loads lead to an almost uniform plasma glucose concentration profile.[38,39] The explanation is the variation in the quantitative contribution of the incretin effect to the overall insulin secretory response after oral glucose, ranging from low (i.e., approximately 20% with small oral glucose loads, like 25 g) to high (up to 75% with large oral glucose loads, 100 g or higher).

2.6 | Open questions in incretin physiology

Recently, the dogma that proglucagon processing leads to pancreatic glucagon in α cells in the endocrine pancreas and to GLP-1 and GLP-2 in intestinal L cells has been challenged. Intestinal production of glucagon was suggested after total pancreatectomy in human subjects,[40] and GLP-1 has been found to be present in pancreatic α cells.[41] Animal studies suggest that GLP-1 produced in pancreatic α cells may have more impact on glucose homeostasis compared to GLP-1 produced in the gut.[42] This may mean that all-too-simple views on the physiology of incretin hormones may need to be refined. Alternatively, the validity of these findings could be restricted to very special and rare conditions. The proposed detrimental signal form the duodenum ("upper gut hypothesis")[37] is awaiting more thorough characterization.

3 | ADDITIONAL BIOLOGICAL EFFECTS OF INCRETIN HORMONES

The definition of an incretin hormone entirely relates to the secretion from the gut after nutrient intake and the insulinotropic action at physiologically stimulated concentrations.[5] Thus, even additional actions within the endocrine pancreas (such as the suppression of glucagon secretion, the stimulation of proinsulin biosynthesis, the stimulation of ß-cell neogenesis or proliferation, etc.) are beyond the narrow definition of an incretin hormone. However, there is ample evidence that the incretin hormones GIP and GLP-1 have additional biological effects that add important facets to their overall spectrum of activity. This is particularly true in the case of GLP-1 (Table 1, Figure 3).

3.1 | Appetite, caloric intake, body weight

GLP-1 administered into the central nervous system,[43] but also into the general circulation,[44] reduces appetite and food intake and increases satiety. The relevant GLP-1 receptors seem to be in the hypothalamus.[45] GLP-1 may enter the brain from the blood stream through circumventricular organs, which are characterized by a leaky blood–brain barrier. GLP-1 seems to be one of the meal-termination signals. These effects are the basis for weight loss with prolonged stimulation of GLP-1 receptors.[1,2] Such an activity has not been known in the case of GIP, but recently hybrid peptides (also addressing, e.g., glucagon and peptide YY receptors) have been developed for the purpose of promoting more weight loss than GLP-1 receptor agonist alone can provide,[46] by also activating GIP receptors.[47]

3.2 | Triglyceride storage in adipose tissue

GIP receptor knock-out mice do not develop obesity with hypercaloric feeding.[48] This and the fact that GIP induces lipoprotein lipase,[49] the enzyme that releases fatty acids from chylomicron triglycerides in adipose tissue and thus promotes the elimination of chylomicron triglycerides,[50] has led to the hypothesis that GIP may promote fat storage in subcutaneous adipose tissue. Mostly, this is based on animal studies, and it remains uncertain whether this translates to the human situation.

3.3 | Gastric emptying, intestinal transit

GIP has no effect on gastric emptying,[51] while exogenous GLP-1, both at physiological and pharmacological concentrations, slows gastric emptying.[33] Studies with the GLP-1 receptor antagonist exendin$^{9-39}$ suggest that endogenous GLP-1 also retards gastric

TABLE 1 Physiological or pharmacological effects of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) described in various organs/tissues other than the endocrine pancreas in non-diabetic animals and human subjects

Organ/tissue/cell type	Incretin hormone/derivatives: Methodology: Physiological function	Glucose-dependent insulinotropic polypeptide (GIP/GIP RA))		Glucagon-like peptide-1/GLP-1 receptor agonists (GLP-1/ GLP-1 RA)	
		GIP receptor knock-out/ polymorphisms/GIP receptor antagonists	Pharmacological studies using GIP/GIP receptor agonists	GLP-1 receptor knock-out/ polymorphisms/GLP-1 receptor antagonists	Pharmacological studies using GLP-1/GLP-1 receptor agonists
Brain	Regulation of appetite/ satiation	• No obvious effect	• No known effects	• GLP-1 R k.o.: No obvious effect[52]	• GLP-1 and GLP-1 RA generally lead to reduced appetite[2,53]
	Regulation of food (calorie) intake/body weight	• No obvious effect	• Augmentation of GLP-1 effects (?)[47]	• Intra-cerebro-ventricular exendin [9–39] in rats: Food intake ↑[54]	• GLP-1 and GLP-1 RA generally lead to reduced food intake[2,53]
Heart	Heart rate	• No obvious effect	• No obvious effect	• No obvious effect	• ↑[55]
	Glucose uptake	• No obvious effect	• No obvious effect	• Not studied	• ↑ (animal studies)[56]
	Ischaemia tolerance	• Not studied	• Not studied	• Not studied	• Improved[55]
	Infarct size	• Not studied	• Not studied	• Not studied	• Reduced in animals[55] and perhaps human subjects[57]
Pancreas	(Pro-)insulin biosynthesis	• No obvious effect	• Not studied	• Not studied	• GLP-1 increases (pro-) insulin synthesis[58]
	ß-Cell apoptosis	• GIP-R knock-out: Increased susceptibility to ß-cell apoptosis[59]	• Not studied	• Not studied	• GLP-1 and GLP-1 RA reduce ß-cell apoptosis[60,61]
	ß-Cell proliferation/neogenesis	• Not obvious effect	• Not studied	• GLP-1 R knock-out: No major change in ß-cell mass[52]	• Stimulation,[60,62] but only in young rodents[63]
Stomach	Gastric emptying	• Not studied	• No effect[51]	• Acceleration[64] (not confirmed[65])	• GLP-1[32] and GLP-1 RA[2] generally profoundly decelerate gastric emptying
	Acid secretion	• Not studied	• Weak inhibition[66]	• Not studied	• Weak inhibition[66,67]
Gut	Absorption	• Not studied	• GIP: Glucose transport (basolateral membrane) ↑[68] • GIP: Trans-epithelial glucose transport (mouse jejunum) ↑[69] • GIP (via effects on intestinal motility)[70] • GIP: Na, K, water, HCO_3 absorption ↓[71]	• Not studied	• GLP-1: Triglyceride absorption, apolipoprotein production, lymph flow ↓ (rats),[72,73] similar findings in humans[74] • GLP-1: Small intestinal motility, flow, transit, absorption of glucose (healthy humans)[75]
Adipose tissue	Glucose uptake	• Not studied	• GIP: Adipocyte glucose uptake ↑ (rats)[76]	• Not studied	• GLP-1: Human adipocyte glucose uptake ↑ (reduced in obesity)[77] • GLP-1: Lipolysis (humans) unchanged[78]
	Blood flow	• Not studied	• GIP: Adipose tissue blood flow ↑[79]; Effect reduced in obese subjects[80]	• Not studied	• Not studied
	Inflammation	• Not studied	• GIP: Inflammatory response, insulin resistance ↑,[81] reversed in longer-term studies[82]	• Not studied	• GLP-1: adipose tissue macrophage infiltration/inflammation ↓ (obese mice)[83]
	Lipoprotein lipase activity/ chylomicron elimination	• Not studied	• GIP: Lipoprotein lipase activity ↑[84,85]	• Not studied	• Not studied

(*Continues*)

TABLE 1 (Continued)

Organ/tissue/cell type	Incretin hormone/derivatives: Methodology: Physiological function	Glucose-dependent insulinotropic polypeptide (GIP/GIP RA))		Glucagon-like peptide-1/GLP-1 receptor agonists (GLP-1/ GLP-1 RA)	
		GIP receptor knock-out/ polymorphisms/GIP receptor antagonists	Pharmacological studies using GIP/GIP receptor agonists	GLP-1 receptor knock-out/ polymorphisms/GLP-1 receptor antagonists	Pharmacological studies using GLP-1/GLP-1 receptor agonists
			• GIP: Chylomicron elimination,[50] not confirmed[86]		
	Brown adipose tissue activity	• Not studied	• Not studied	• GLP-1 receptor deficiency: Brown adipose tissue thermogenic capacity ↓[87,88]	• Exenatide: Brown remodeling of white adipose tissue ↑ (mice)[89]
Bone	Formation (osteoblasts)	• GIP receptor deficiency: bone marrow haematopoiesis ↓[90] • GIP receptor deficiency: Meal-related bone formation ↓[91]	• GIP: Collagen fibril formation in murine osteoblast cell lines↑[92]	• GLP-1 receptor deficiency: No change in osteoblast numbers (mice)[93] Reduced calcitonin (thyroid); calcitonin treatment reduced bone resorption (mice)[93]}	• During weight loss (humans): Markers ↑ (16%)[94] • Ovariectomized rats ↑[95,96]
	Absorption (osteoclasts)	• GIP receptor deficiency: Number of osteoclasts (especially multi-nuclear ones) ↑, osteoclast apoptosis ↑[91] • GIP overexpression prevents age-related loss in bone mass (mice)[97]	• Osteoclast differentiation and bone resorption (murine and human precursor cells) ↓[98] • GIP: Bone resorption markers (humans) ↓[99]	• GLP-1 receptor deficiency: Osteoclast numbers and bone resorption ↑ (mice)[93]	• Not studied
	Bone mass	• Associations with GIP or GIP receptor polymorphisms (humans)[100] • GIP receptor deficiency (mice) decreases trabecular bone volume and quality[101,102] • GIP receptor overexpression (mice): Bone mass ↑[103]	• No GIP receptor agonist available for long-term studies	• GLP-1 receptor deficiency: Cortical bone ↓, fragility ↑ (mice)[93]	• Not studied
	Fracture risk	• Human GIP receptor polymorphisms: Mineral density ↓, fracture risk ↑[104]	• No GIP receptor agonist available for long-term studies available	• Not studied	• No change in fracture rate[105,106] • Liraglutide ↓, exenatide ↑ (compound-dependent effects)[107]
Muscle	Glucose uptake	• Not studied	• GIP: Muscle glucose uptake ↑ (rats)[108]	• Not studied	• GLP-1: During hyperinsulinaemia ↑ (obese subjects)[109] • Not confirmed by other studies (type 1 diabetic subjects)[110,111]
Kidney	Natriuriesis	• Not studied	• Not studied	• Not studied	• ↑[112]
	Albuminuria	• Not studied	• Not studied	• Not studied	• Liraglutide: ↓[113]
	Glomerular filtration	• Not studied	• Not studied	• Not studied	• Liraglutide: preserved[113]
Blood vessels	Vasodilation	• Not studied	• Not studied	• Not studied	• Improved in type 2 diabetic subjects[114]
	Blood pressure	• No obvious effect	• No obvious effect	• No obvious effect	• GLP-1 RA generally reduce systolic blood pressure[55]

[a] For effects on insulin and glucagon secretion, see Table 2.

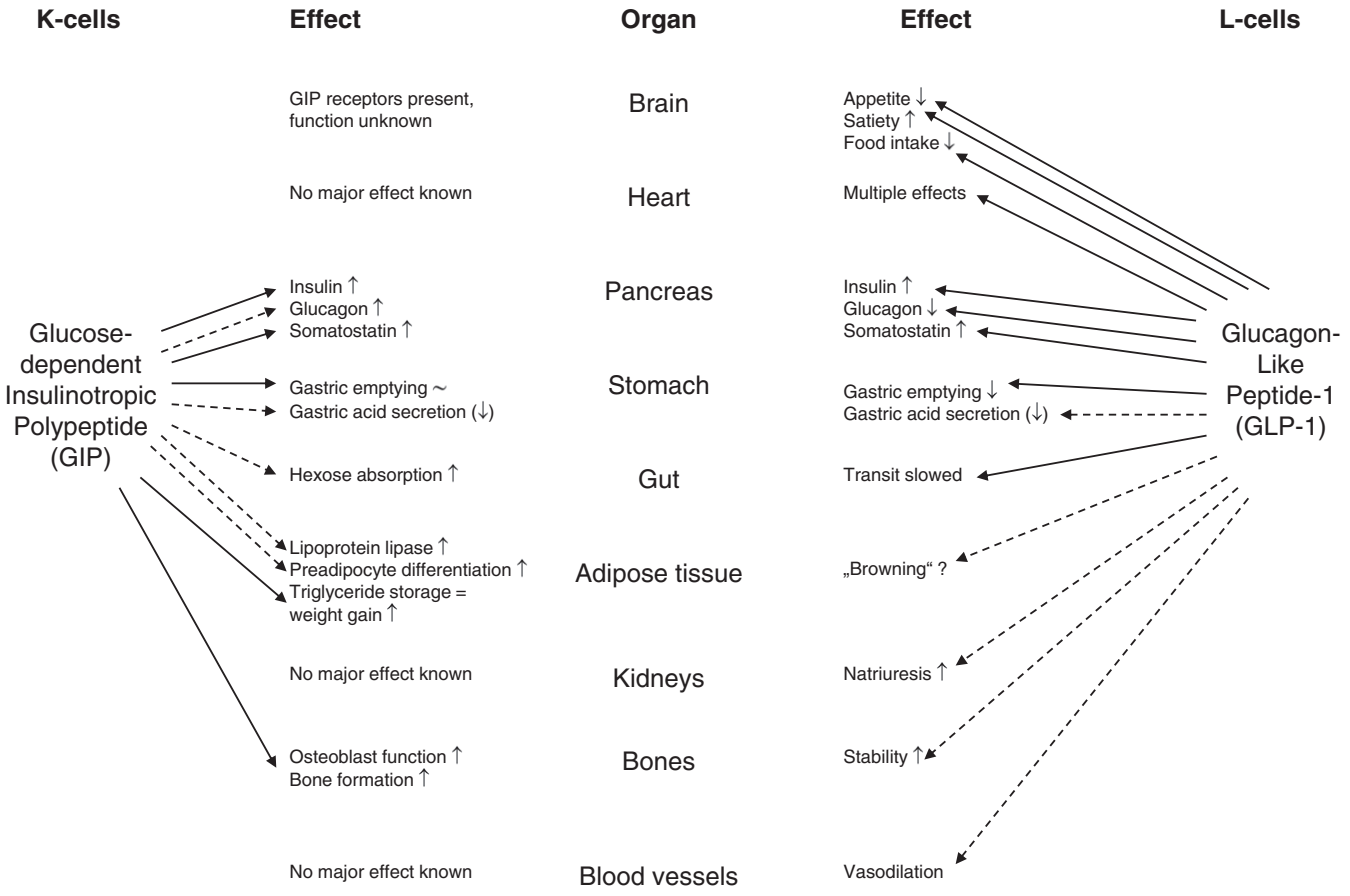

FIGURE 3 Biological effects of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) on various organs. The definition an incretin hormone only refers to the ability to augment insulin secretion under physiological conditions, that is, at the incretin hormone (GIP and GLP-1) concentrations reached after nutrient stimulation. All other effects are beyond the narrow definition of incretin function. Based on our current understanding, GIP addresses less organs and functions compared to GLP-1. For details and literature regarding effects on insulin and glucagon secretion as well as effects on glucose concentrations, see Table 1 and text. For details and literature concerning effects beyond those on the endocrine pancreas, see Table 2 and text

emptying.[64] The consequence is a delayed and reduced delivery of nutrients into the intestinal lumen, and a delayed and reduced absorption leading to flatter rises in glycaemia and triglycerides following meals.[74] Intestinal transit is also slowed.[115] Secondary to slowed gastrointestinal motility, gastric acid and pancreatic exocrine secretions are reduced.[32] It has been suggested that this inhibitory function on upper gastrointestinal motility and secretion may be well compatible with the (otherwise unexplained) location of L cells primarily in the lower small and large intestines.[13] Under normal circumstances, nutrients never reach these areas, but in the case of, for example, diarrhoea, nutrients in the lower gut stimulate GLP-1, which in turn halts motility and secretion to help stop symptoms. This function has been termed the "ileal brake"[116] and may be another important role for GLP-1, perhaps even the primary physiological function.

3.4 | Bone metabolism

Mainly based on the phenotype of GIP and GLP-1 receptor knockout mice, a role for both incretin hormones in the formation and maintenance of bone mass has been suggested (Table 1, Figure 3). GIP receptor signalling in mice seems to limit bone resorption (osteoclast number and function) and to promote bone formation (osteoblast function), especially in conjunction with meal intake.[91] Examination of human polymorphisms regarding the GIP receptor gene shows significant heterogeneity in bone mass and even fracture risk,[100] suggesting that these animal findings have some physiological relevance in humans. The GLP-1 receptor in mice also seems to be linked to a suppression of osteoclast function and bone resorption,[117] thus increasing bone mass and decreasing fragility.[117] GLP-1 receptor agonists in animals have the potential to increase bone formation under conditions where a loss in bone mass is expected (during weight loss[94] and after ovariectomy[95,96]). However, no consistent effects of GLP-1 receptor agonist treatment have been observed in clinical trials.[105,106] Physiologically speaking, the osteogenic effects of the incretin hormones GIP and GLP-1 may be viewed as part of their overall role in anabolic processes, promoting the storage of nutrient substrates for the support and maintenance of important body functions.

3.5 | Cardiovascular function

GLP-1 has multiple effects in the cardiovascular system, which have been extensively reviewed.[55,118] Beneficial effects of GLP-1 receptor agonists in high-risk patients have renewed the interest in elucidating

the mechanisms underlying these benefits.[55,118] There is a long list of divergent actions of GLP-1 and of GLP-1 receptor agonists, for example, on cardiac blood supply, on substrate uptake and performance, on ischaemia tolerance, on endothelial function (vasodilation), on inflammatory responses in adipose tissue and blood vessels and related cytokines, and on the progression of atherosclerosis and plaque stability (Table 1, Figure 3).[55,118] In most cases, these effects were shown with high doses/concentrations of GLP-1. A physiological role of GLP-1 in the cardiovascular system is not known. However, there is a cardiac phenotype of the GLP-1 receptor knock-out mice, suggesting some role for GLP-1 in the embryonic development of the cardiovascular system.[119] Since cardiovascular effects of GLP-1 receptor stimulation are mainly described as therapeutic actions with pharmacological concentrations of GLP-1 or GLP-1 receptors,[55] such effects do not seem to be major physiological actions, and will not further be described in detail in this review.

4 | INCRETIN HORMONES IN OBESITY

Interest in the role of incretin hormones in obese subjects originates from findings indicating roles for GIP as a potential mediator of increased triglyceride storage in adipose tissue and, thus, of weight gain and obesity. Conversely, the appetite-reducing activity of GLP-1 suggests a role in inhibiting food intake and weight gain.

4.1 | Secretion and action of incretin hormones in obese, non-diabetic subjects

Some studies suggest that there is hypersecretion of GIP in obesity,[120] which might be related to compensatory insulin hypersecretion that may occur as an attempt to overcome the metabolic consequences of insulin resistance.[121] Regarding the secretion of GLP-1 in obesity, reduced increments in meal-related GLP-1 responses have been described with increasing body mass index,[122–124] in particular in the presence of hepatic steatosis.[125] The incretin effect has been reported to be decreased in obesity,[123] even in the absence of impaired glucose tolerance or diabetes mellitus. This may be explained by a reduced responsiveness to GIP or by a reduced contribution of GLP-1 (achieving lower concentrations after physiological nutrient stimulation) to insulin secretory responses.[123] Details have not been studied.

4.2 | Role of GIP and/or GLP-1 in the etiology of obesity

A role for GIP as an obesigenic signal from the gut is mainly based on animal studies looking at the consequences of GIP receptor knock-out: GIP receptor knock-out mice do not become obese when fed a high-fat diet.[48] This may be functionally related to increased hexose absorption from the gut[68] and accelerated lipolysis of chylomicron triglycerides[50] through enhanced adipose tissue lipoprotein lipase activity.[49] Overall, this may lead to more triglycerides being taken up and stored in adipose tissue. Some human GIP receptor polymorphisms are associated with differences in body weight.[126] In contrast, exogenous GLP-1 reduces appetite, increases satiety, and reduces food intake,[53] perhaps even at physiological concentrations.[127] This, together with the reduced secretion of GLP-1 in obese subjects, suggests a significant role of GLP-1 in the pathogenesis of obesity. However, it is unclear what drives the reduced secretion of GLP-1 in obesity and when in the course of the development of obesity these abnormalities occur.

5 | ROLE OF GLP-1 IN MEDIATING EFFECTS OF BARIATRIC SURGERY ON WEIGHT LOSS AND ON GLYCAEMIC CONTROL (DIABETES REMISSION)

Surgery is used to achieve significant reductions in body weight in obese subjects, and to induce diabetes remission, if obesity is associated with type 2 diabetes. The most frequently performed procedures are Roux-en-Y gastric bypass and sleeve gastrectomy. Bariatric surgery results in major changes in the pattern of gastrointestinal hormone secretion, including the secretion of GIP and GLP-1, as well as of other gut hormones produced in the lower small intestines (e.g., peptide YY, PYY, produced in L cells like GLP-1). The most striking change is in the secretion of GLP-1: GLP-1 concentrations reach levels far above the physiological range, most likely because nutrients are rapidly delivered into distal areas of the gut characterized by a high L-cell density.[128] Studies employing the GLP-1 receptor antagonist exendin [9–39] suggest that GLP-1 plays a role in the reduction of energy intake typically following gastric bypass. In fact, the typically increased concentrations of both GLP-1 and PYY seem to reduce appetite and food intake synergistically.[129] GLP-1 and GIP appear to be the factors that best explain the improvement in glycaemic control following gastric bypass.[130] However, weight loss after gastric bypass also occurs in GLP-1 receptor knock-out animals.[131] These findings argue against an absolutely essential role of GLP-1 as a mediator of the benefits of bariatric surgery like gastric bypass. Less information is available on other surgical procedures (e.g., sleeve gastrectomy).

A rare but severe adverse event after bariatric surgery is reactive hypoglycaemia, which has been observed in patients hypersecreting GLP-1 after, for example, gastric bypass.[132,133] Based on findings of studies with young rodents, a proliferative effect of GLP-1 on ß cells was documented.[134] Thus, ß-cell hyperplasia ("nesidioblastosis") has been viewed as a consequence of exaggerated GLP-1 responses. However, careful studies have ruled out ß-cell hyperplasia in such patients.[135] Therefore, GLP-1 is rather unlikely to be the primary cause of hypoglycaemia as a consequence of increased ß-cell mass.

6 | INCRETIN HORMONES IN TYPE 2 DIABETES

Type 2 diabetes is caused by insulin resistance and the inability of the endocrine pancreas to secrete enough insulin to match the increased demand. Hyperglucagonaemia is another facet in the pathophysiology of type 2 diabetes.[136] Given the potential of incretin hormones to augment insulin secretor responses and of GLP-1 to

lower glucagon concentrations, there has been considerable interest to elucidate the role of incretin hormones in the pathophysiology of type 2 diabetes.

6.1 | Secretion of incretin hormones in type 2 diabetic subjects

Incretin hormones are secreted in subjects with type 2 diabetes much like in healthy and obese subjects.[137–139] Initial studies indicated a slightly increased secretion of GIP in type 2 diabetes at the population level[140] and a reduced GLP-1 response following mixed-meal stimulation.[21,141] Moreover, subjects with impaired glucose tolerance had an intermediate GLP-1 response.[141] Thus, it was hypothesized that there is a progressive loss of GLP-1 secretion with advancing stages of type 2 diabetes. Since these findings were generated during the time when incretin-derived glucose-lowering medications were first developed, this was considered a justification for "replacing" GLP-1 under circumstances where there appeared to be a lack of GLP-1. The secretion of GIP and GLP-1 after oral glucose loads and mixed meals has been compared many times between healthy subjects and type 2 diabetic patients. Some studies confirmed slight differences (lower in type 2 diabetes), whereas others did not. Meta-analyses suggest that there are no systematic differences in the nutrient-induced secretion of GIP and GLP-1 between healthy and type 2 diabetic subjects,[137–139] against a background of substantial inter-individual variation in secretory responses (vide supra). In type 2 diabetic patients, a significant correlation of GIP and GLP-1 secretory responses has been noted as well.[4,22]

6.2 | Insulinotropic activitiy of incretin hormones in type 2 diabetic subjects

While the secretion of incretin hormones is more or less normal in type 2 diabetes, the characteristic abnormalities are in the insulinotropic activities of GIP and GLP-1. As an insulinotropic agent, GIP was originally considered a drug candidate for the development of glucose-lowering medications. While the description of insulinotropic effects in healthy human subjects was published in 1973,[10] only in 1988 the first study reported much reduced insulinotropic effectiveness in both type 1 and type 2 diabetic patients.[142] The original report was based on work performed with GIP of the porcine amino acid sequence, leaving some questions regarding the correspondence of GIP concentrations generated by endogenous secretion from human L cells versus exogenous administration of the porcine sequence peptide. Later studies employing synthetic human GIP fully confirmed the inability of GIP to elicit significant insulinotropic responses in subjects with type 2 diabetes.[19,143,144] There may be a residual "early" response lasting 30 min or so,[144] but certainly longer lasting exposures to elevated GIP concentrations do not lead to a significant stimulation of insulin secretion, even though the GIP concentrations achieved in these experiments clearly were far higher than physiological concentrations.

The situation is different in the case of GLP-1. There is no doubt that physiological, and certainly pharmacological, concentrations of GLP-1 elicit insulinotropic (and glucagonostatic) effect in subjects with type 2 diabetes.[19] However, the effects are reduced in magnitude as compared to healthy subjects. Under hyperglycaemic clamp conditions, only slightly reduced insulin and C-peptide responses to exogenous GLP-1 have been found between type 2 diabetic and healthy subjects.[19] In a careful dose–response study, Kjems et al. studied type 2 diabetic and healthy subjects with increasing intravenous infusion rates of GLP-1.[145] At each GLP-1 dose, the insulin secretory responses to increasing glucose concentrations were determined and were described as the slope relating insulin secretion to the degree of hyperglycaemia. GLP-1 augmented the relationship between glucose and insulin secretory responses much less (approximately 25%) compared to healthy subjects.[145] In addition, GLP-1 reduces glucagon concentrations.[19] Taken together, the stimulation of insulin secretion as well as suppression of glucagon secretion with GLP-1 is sufficient to lead to a meaningful reduction in plasma glucose, however, at pharmacological concentrations.[146] A detailed account of actions of GIP and GLP-1 on insulin and glucagon secretion, and of the important dependence on ambient glucose concentrations, in healthy as well as type 2 diabetic subjects is provided in Table 2.

Co-administration of GLP-1 and GIP in subjects with type 2 diabetes does not stimulate insulin secretion more than does GLP-1 alone.[143] Rather, the glucagon suppression seen with GLP-1 alone is no longer there when GIP is administered as well.[143]

6.3 | Role of incretin hormones in the pathophysiology of type 2 diabetes (reduced incretin effect)

When the incretin effect is quantified in subjects with type 2 diabetes, it is found much reduced or absent in comparison to healthy subjects (Figure 1).[3,39,147] The most likely explanation is the inability to respond appropriately to GIP[19,144] (which in healthy subjects mediates the major proportion of the incretin effect, vide supra) and the rather minor role GLP-1 plays in the mediation of the incretin effect in healthy subject (so that even the relatively preserved effectiveness of GLP-1 in type 2 diabetic patients does not really matter much).[31] Thus, in type 2 diabetic patients, a mechanism, which in healthy subjects contributes approximately two-thirds to the insulin secretory response after oral glucose, is largely impaired or even no longer operative. This is likely to have functional consequences. One question arises: Does the inability to respond to GIP with an insulin secretory response represent a defect preceding (and potentially driving) the development of diabetes? Or is it a consequence of the diabetic state? Numerous studies have suggested that this defect (the inability to respond to GIP with a substantially augmented release of insulin) and a reduced incretin effect occur after the diagnosis of diabetes is established, suggesting these consequences to be secondary.[148] In particular, a reduced incretin effect is seen only in those patients with chronic pancreatitis, who also develop diabetes, but not in those who have normal glucose tolerance. This indicates that it is the diabetic state itself that is associated with the reduced incretin effect, and not the disease process characterizing chronic pancreatitis.[147] It is not known which facets of type 2 diabetes (hyperglycaemia, islet lipid overload, inflammatory

TABLE 2 Effects of physiological and pharmacological concentrations of the incretin hormones glucose-dependent insulinotropic hormone (GIP) and glucagon-like peptide-1 (GLP-1) on insulin secretion and glucagon secretion and on plasma glucose concentrations in human subjects with normal glucose tolerance or type 2 diabetes

Parameter	Incretin hormone	Glucose-dependent insulinotropic polypeptide		Glucagon-like peptide-1/ GLP-1 receptor agonists	
	Glucose tolerance Condition	Normal	Type 2 diabetes	Normal	Type 2 diabetes
Insulin secretion	Normal fasting plasma glucose[a]	• Minor and transient stimulation[7,31]	• Not studied[b]	• GLP-1: Minor and transient stimulation[7,27,31,149] • Exenatide, liraglutide: Minor and transient stimulation[150]	• Stimulation lasting until normalization of fasting glucose concentrations, especially at pharmacological concentrations of GLP-1[146]
	Hyperglycaemia	• Major stimulation (2-3-fold at post-meal glycaemic excursions)[7,31] or during hyperglycaemic clamp experiments[19]	• No effect or minor stimulation (borderline significance),[19,151] event at pharmacological concentrations[143]	• GLP-1 (physiological concentrations): Stimulation[7,31] • GLP-1 (pharmacological concentrations): Major stimulation[19]	• GLP-1 (physiological concentrations): Minor stimulation[19] • GLP-1 (pharmacological concentrations): Major stimulation[19] • GLP-1 RA: Major stimulation[2]
	Hypoglycaemia[c]	• Rats: No effect[152]	• Most likely no effect	• GLP-1 (pharmacological concentrations): No effect[24]	• Exenatide (GLP-1 RA): Little if any effect[150]
Glucagon secretion	Normal fasting plasma glucose[a]	• Rats: Stimulation[152]; human subjects: Stimulation[26]	• No effect in addition to GLP-1; prevention of suppression by GLP-1[143]	• GLP-1: Minor and transient suppression[24,27]	• GLP-1: No effect in previously hyperglycaemic subjects reaching normoglycaemia[146,153]
	Hyperglycaemia	• Mo major effect[19]	• Minor stimulation[19]	• GLP-1: Minor suppression[19] • GLP-1 RA: Suppression[1,2]	• GLP-1: Suppression[19] • GLP-1 RA: Suppression[1,2]
	Hypoglycaemia	• Enhanced counter-regulatory glucagon response (type 1-diabetic subjects)[154]	• Not studied	• No effect on counter-regulatory glucagon response[24]	• Exenatide (GLP-1 RA): No effect on counter-regulatory glucagon response[150]
Plasma glucose	Normal fasting plasma glucose[a]	• At most minor reduction (no hypoglycaemia)[7]	• Not studied	• At most minor reduction (no hypoglycaemia)[7,27,149]	• Minor reduction at most[d]; no further reduction after achieving normoglycaemia with exogenous GLP-1[146]
	Hyperglycaemia	• Reduction (by inference: Stimulation of insulin secretion)[155] • Increased glucose infusion necessary to maintain hyper-glycaemic clamp level)	• At most minor reduction[143] • Almost no change in glucose infusion necessary to maintain hyper-glycaemic clamp level[19]	• Reduction (by inference: Stimulation of insulin secretion)[7,19,155] • Increased glucose infusion necessary to maintain hyper-glycaemic clamp level[19,155]	• Reduction[143,146,156] • Increased glucose infusion necessary to maintain hyper-glycaemic clamp level)[143]
	Hypoglycaemia	• Not studied	• Not studied	• Not studied	• Not studied

[a] Approximately 4–5.5 mmol L^{-1} (80–100 mg dL^{-1}).

[b] In type 2 diabetic patients, fasting hyperglycaemia is a typical finding.

[c] Below 3.8 mmol L^{-1} (66 mg dL^{-1}).

[d] Difficult to be studied since normoglycaemia is not a typical finding in type 2 diabetic subjects.

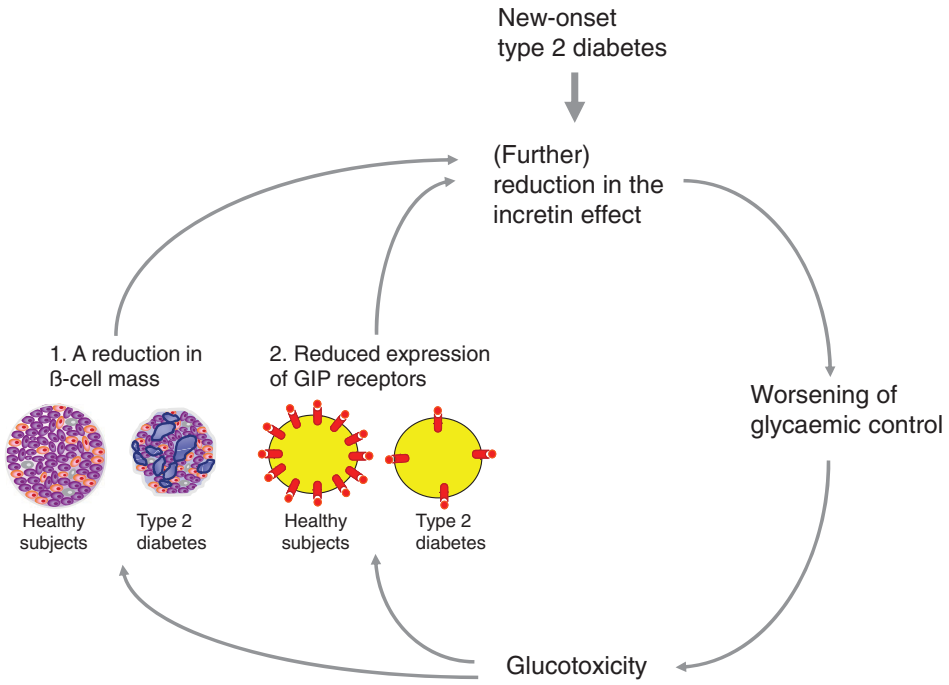

FIGURE 4 Vicious cycle illustrating the role of reduced effectiveness of GIP on insulin secretion in established type 2 diabetes and, potentially, in the progressive deterioration of glycaemic control in advancing type 2 diabetes. Two hypotheses may explain the reduced responsiveness of insulin secretion from endocrine pancreatic ß cells to endogenous (pathophysiology) and exogenous (potentially therapeutic administration of) GIP in type 2 diabetes: a reduced ß-cell mass or a reduced expression of GIP receptors on ß cells in patients with type 2 diabetes

infiltration of ß cells, etc.) trigger this development. Studies using intensive insulin treatment for optimal glycaemic control suggest that reducing hyperglycaemia into the near-normal range of glucose concentrations will improve, yet not normalize, the insulinotropic activity of both GIP and GLP-1 in type 2 diabetic subjects and glucose excursions after a mixed meal, perhaps indicating an improvement in their incretin effect.[157,158]

Another question is whether the inability to secrete insulin in response to GIP is related specifically to abnormalities in the stimulus–secretion coupling for the GIP pathway, such as a reduced expression of GIP receptors or other components of the signal-transduction pathway,[159] or may rather be related to more general features of the type 2 diabetic endocrine pancreas, namely reductions in ß-cell mass and functional insulin secretory capacity.[4,148] A reduced expression of GIP receptors has been described in animals with diabetic hyperglycaemia[159] but, so far, not in human pancreas specimens. A reduction in ß-cell mass and functional insulin secretory capacity can be assumed to lead to a reduced incretin effect, since oral glucose is a strong stimulus to insulin secretion, while "isoglycaemic" intravenous glucose is a weak stimulus. One can speculate that the insulin response to this weak stimulus is already close to the upper limit of the overall secretory capacity, such that a stronger stimulus can hardly elicit an even greater response.[148]

While the abnormalities in the incretin system, foremost the inability of the endocrine pancreas to respond to GIP, do not seem to be involved in the progression from pre-diabetic states to manifest diabetes mellitus,[148] they may well contribute to the progression that is typical for this disease. It is likely that the loss of a major physiological mechanism stimulating insulin secretion will further deteriorate glycaemic control, leading to a vicious cycle by worsening glucose toxicity, which in turn may reduce ß-cell mass and functional capacity and the expression of GIP receptors and a progressive reduction in the incretin effect (Figure 4).

7 | THERAPEUTIC POTENTIAL OF INCRETIN HORMONES IN TYPE 2 DIABETES (GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS)

Based on the physiological effects described above in great detail, there is no obvious therapeutic potential for GIP in type 2 diabetes, because it has only negligible effects on insulin secretion in such patients, because it rather increases glucagon secretion, and because there are no measurable effects of even supra-physiological doses/concentrations on plasma glucose concentrations. Still research is being conducted to identify conditions under which GIP may have greater beneficial effects, for example, after DPP-4 inhibitor treatment.[160] Based on findings suggesting a role for GIP in the enhanced triglyceride deposition during hypercaloric feeding (based mainly on animal studies), GIP receptor antagonists have been suggested for the treatment of the metabolic syndrome and pre-diabetes.[161] However, this has never led to clinical trials substantiating these claims.

On the contrary, the therapeutic potential of GLP-1 for the treatment of obesity and type 2 diabetes is obvious, since the parent compound itself is able to reduce hyperglycaemia both in the fasting and postprandial state.[1,2] GLP-1 receptor agonists had to be developed to derive agents with slower elimination than GLP-1 itself, which has a half-life of 1–2 min and needs to be administered continuously to fully elicit its therapeutic potential. Properties of GLP-1 receptor agonists will be described in more detail elsewhere in this volume. The other development that originated from the characterization of in vivo degradation and inactivation of GLP-1 was that of DPP-4 inhibitors, which mainly preserve GLP-1 (and, potentially, other insulinotropic peptides) in its (their) intact, biologically active state (addressed in another article in this volume). Especially, the latter therapy employs incretin hormone concentrations that closely resemble the physiological range and emphasizes the important

physiological role of incretin hormones in the maintenance of glucose homeostasis.

ACKNOWLEDGEMENTS

We thank Ms. Laura Kupfer for help with retrieving literature and secretarial assistance and Dr. Sandra Ueberberg for providing microphotographs of human gut and endocrine pancreatic tissue.

Author contributions

Both authors drafted the manuscript and contributed to designing figures and tables and to writing the text. Both authors were involved in revising the manuscript for critical intellectual content and jointly made the decision to publish the final version. MAN takes full responsibility for the integrity of the information compiled and is the guarantor for the manuscript as a whole.

Conflict of interest

MAN has received compensation for lectures or advisory boards from AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., Fractyl, GlaxoSmithKline, Intarcia/Servier, Menarini/Berlin Chemie, Merck, Sharp & Dohme, and NovoNordisk. He has received grant support from AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co., GlaxoSmithKline, Menarini/Berlin-Chemie, Merck, Sharp & Dohme, and Novartis. JJM has received compensation for lectures or advisory boards from Astra Zeneca, Boehringer-Ingelheim, BristolMyersSquibb, Eli Lilly, Merck, Sharp & Dohme, Novo Nordisk, Servier and Sanofi. He has received research support from Boehringer-Ingelheim, Merck, Sharp & Dohme, Novo Nordisk, and Sanofi.

ORCID

Michael A. Nauck http://orcid.org/0000-0002-5749-6954
Juris J. Meier http://orcid.org/0000-0002-5835-8019

REFERENCES

1. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368:1696-1705.
2. Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab*. 2016;18:203-216.
3. Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in Type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 1986;29:46-54.
4. Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. *Lancet Diabetes Endocrinol*. 2016;4:525-536.
5. Creutzfeldt W. The incretin concept today. *Diabetologia*. 1979;16:75-85.
6. Meier JJ, Deacon CF, Schmidt WE, Holst JJ, Nauck MA. Suppression of glucagon secretion is lower after oral glucose administration than during intravenous glucose administration in human subjects. *Diabetologia*. 2007;50:806-813.
7. Kreymann B, Williams G, Ghatei MA, Bloom SR. Glucagon-like peptide-1 [7-36]: a physiological incretin in man. *Lancet*. 1987;2:1300-1304.
8. Shuster LT, Go VLW, Rizza RA, O'Brien PC, Service FJ. Incretin effect due to increased secretion and decreased clearance of insulin in normal humans. *Diabetes*. 1988;37:200-203.
9. Brown JC. Gastric Inhibitory Polypeptide. Heidelberg, Germany: Springer-Verlag; 1982.
10. Dupré J, Ross SA, Watson D, Brown JC. Stimulation of insulin secretion by gastric inhibitory polypeptide in man. *J Clin Endocrinol Metab*. 1973;37:826-828.
11. Drucker DJ. The biology of incretin hormones. *Cell Metab*. 2006;3:153-165.
12. Bell GI, Sanchez-Pescador R, Laybourn PJ, Najarian RC. Exon duplication and divergence in the human preproglucagon gene. *Nature*. 1983;304:368-371.
13. Eissele R, Göke R, Willemer S, et al. Glucagon-like peptide-1 cells in the gastrointestinal tract and pancreas of rat, pig and man. *Eur J Clin Invest*. 1992;22:283-291.
14. Holst JJ, Ørskov C, Vagn-Nielsen O, Schwartz TW. Truncated glucagon-like peptide 1, an insulin-releasing hormone from the distal gut. *FEBS Lett*. 1987;211:169-174.
15. Mojsov S, Weir GC, Habener JF. Insulinotropin: glucagon-like peptide I (7-37) co-encoded in the glucagon gene is a potent stimulator of insulin release in the perfused rat pancreas. *J Clin Invest*. 1987;79:616-619.
16. Parker HE, Reimann F, Gribble FM. Molecular mechanisms underlying nutrient-stimulated incretin secretion. *Expert Rev Mol Med*. 2010;12:e1.
17. Schirra J, Katschinski M, Weidmann C, et al. Gastric emptying and release of incretin hormones after glucose ingestion in humans. *J Clin Invest*. 1996;97:92-103.
18. Brubaker PL. Regulation of intestinal proglucagon-derived peptide secretion by intestinal regulatory peptides. *Endocrinol*. 1991;128:3175-3182.
19. Nauck MA, Heimesaat MM, Ørskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J Clin Invest*. 1993;91:301-307.
20. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Host JJ. Both subcutaneously and intravenously administered glucagon-like peptide 1 are rapidly degraded from the NH_2-terminus in type 2-diabetic patients and in healthy subjects. *Diabetes*. 1995;44:1126-1131.
21. Vilsbøll T, Krarup T, Deacon CF, Madsbad S, Holst JJ. Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. *Diabetes*. 2001;50:609-613.
22. Nauck MA, El-Ouaghlidi A, Gabrys B, et al. Secretion of incretin hormones (GIP and GLP-1) and incretin effect after oral glucose in first-degree relatives of patients with type 2 diabetes. *Regul Pept*. 2004;122:209-217.
23. Mortensen K, Petersen LL, Orskov C. Colocalization of GLP-1 and GIP in human and porcine intestine. *Ann N Y Acad Sci*. 2000;921:469-472.
24. Nauck MA, Heimesaat MM, Behle K, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. *J Clin Endocrinol Metab*. 2002;87:1239-1246.
25. Holst JJ, Gromada J. Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *Am J Physiol (Endocrinol Metab)*. 2004;287:E199-E206.
26. Meier JJ, Gallwitz B, Siepmann N, et al. Gastric inhibitory polypeptide (GIP) dose-dependently stimulates glucagon secretion in healthy human subjects at euglycaemia. *Diabetologia*. 2003;46:798-801.
27. Hvidberg A, Nielsen MT, Hilsted J, Ørskov C, Holst JJ. Effect of glucagon-like peptide-1 (proglucagon 78-107amide) on hepatic glucose production in healthy man. *Metab: Clin Exp*. 1994;43:104-108.

28. Seghieri M, Rebelos E, Gastaldelli A, et al. Direct effect of GLP-1 infusion on endogenous glucose production in humans. *Diabetologia*. 2013;56:156-161.
29. Knop FK, Vilsbøll T, Madsbad S, Holst JJ, Krarup T. Inappropriate suppression of glucagon during OGTT but not during isoglycaemic i. v. glucose infusion contributes to the reduced incretin effect in type 2 diabetes mellitus. *Diabetologia*. 2007;50:797-805.
30. Meier JJ, Nauck MA, Pott A, et al. Glucagon-like peptide 2 stimulates glucagon secretion, enhances lipid absorption, and inhibits gastric acid secretion in humans. *Gastroenterology*. 2006;130:44-54.
31. Nauck MA, Bartels E, Ørskov C, Ebert R, Creutzfeldt W. Additive insulinotropic effects of exogenous synthetic human gastric inhibitory polypeptide and glucagon-like peptide-1-(7-36) amide infused at near-physiological insulinotropic hormone and glucose concentrations. *J Clin Endocrinol Metab*. 1993;76:912-917.
32. Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. *Dig Dis Sci*. 1993;38: 665-673.
33. Nauck MA, Niedereichholz U, Ettler R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol (Endocrinol Metab)*. 1997;273: E981-E988.
34. Vilsbøll T, Krarup T, Madsbad S, Holst JJ. Both GLP-1 and GIP are insulinotropic at basal and postprandial glucose levels and contribute nearly equally to the incretin effect of a meal in healthy subjects. *Regul Pept*. 2003;114:115-121.
35. Asmar M, Asmar A, Simonsen L, et al. The gluco- and liporegulatory and vasodilatory effects of glucose-dependent insulinotropic polypeptide (GIP) are abolished by an antagonist of the human GIP receptor. *Diabetes*. 2017;66:2363-2371.
36. Ensinck JW, Vogel RE, Laschansky EC, et al. Endogenous somatostatin-28 modulates postprandial insulin secretion. Immunoneutralization studies in baboons. *J Clin Invest*. 1997;100:2295-3202.
37. Ramos AC, Galvao Neto MP, de Souza YM, et al. Laparoscopic duodenal-jejunal exclusion in the treatment of type 2 diabetes mellitus in patients with BMI<30 kg/m2 (LBMI). *Obes Surg*. 2009;19: 307-312.
38. Nauck MA, Homberger E, Siegel EG, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab*. 1986;63:492-498.
39. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsbøll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011;96:737-745.
40. Lund A, Bagger JI, Wewer Albrechtsen NJ, et al. Evidence of extrapancreatic glucagon secretion in man. *Diabetes*. 2016;65:585-597.
41. Marchetti P, Lupi R, Bugliani M, et al. A local glucagon-like peptide 1 (GLP-1) system in human pancreatic islets. *Diabetologia*. 2012;55: 3262-3272.
42. Chambers AP, Sorrell JE, Haller A, et al. The role of pancreatic preproglucagon in glucose homeostasis in mice. *Cell Metab*. 2017;25: 927-934.e3.
43. Turton MD, O'Shea D, Gunn I, et al. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature*. 1996;379:69-72.
44. Flint A, Raben A, Astrup A, Holst JJ. Glucagon-like peptide-1 promotes satiety and suppresses energy intake in humans. *J Clin Invest*. 1998;101:515-520.
45. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest*. 2014;124:4473-4488.
46. Sanchez-Garrido MA, Brandt SJ, Clemmensen C, Muller TD, DiMarchi RD, Tschöp MH. GLP-1/glucagon receptor co-agonism for treatment of obesity. *Diabetologia*. 2017;60:1851-1861
47. Finan B, Yang B, Ottaway N, et al. A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. *Nat Med*. 2015;21:27-36.
48. Miyawaki K, Yamada Y, Ban N, et al. Inhibition of gastric inhibitory polypeptide signaling prevents obesity. *Nat Med*. 2002;8:738-742.
49. Eckel RH, Fujimoto WY, Brunzell JD. Gastric inhibitory polypeptide enhance lipoprotein lipase activity in cultured preadipocytes. *Diabetes*. 1979;28:1141-1142.
50. Wasada T, McCorkle K, Harris V, Kawai K, Howard B, Unger RH. Effect of gastric inhibitory polypeptide on plasma levels of chylomicron triglycerides in dogs. *J Clin Invest*. 1981;68:1107-1110.
51. Meier JJ, Goetze O, Anstipp J, et al. Gastric inhibitory polypeptide does not inhibit gastric emptying in humans. *Am J Physiol (Endocrinol Metab)*. 2004;286:E621-E625.
52. Scrocchi LA, Brown TJ, MaClusky N, et al. Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide 1 receptor gene. *Nat Med*. 1996;2:1254-1258.
53. Verdich C, Flint A, Gutzwiller JP, et al. A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans. *J Clin Endocrinol Metab*. 2001;86:4382-4389.
54. Meeran K, O'Shea D, Edwards CM, et al. Repeated intracerebroventricular administration of glucagon-like peptide-1-(7-36) amide or exendin-(9-39) alters body weight in the rat. *Endocrinology*. 1999; 140:244-250.
55. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Circulation*. 2017;136:849-870.
56. Nikolaidis LA, Elahi D, Hentosz T, et al. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing-induced dilated cardiomyopathy. *Circulation*. 2004;110:955-961.
57. Lønborg J, Vejlstrup N, Kelbaek H, et al. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J*. 2012;33:1491-1499.
58. Fehmann H-C, Habener JF. Insulinotropic hormone glucagon-like peptide-I(7-37) stimulation of proinsulin gene expression and proinsulin biosynthesis in insulinoma ßTC-1 cells. *Endocrinology*. 1992; 130:159-166.
59. Campbell JE, Ussher JR, Mulvihill EE, et al. TCF1 links GIPR signaling to the control of beta cell function and survival. *Nat Med*. 2016;22: 84-90.
60. Brubaker PL, Drucker DJ. Minireview: glucagon-like peptides regulate cell proliferation and apoptosis in the pancreas, gut, and central nervous system. *Endocrinology*. 2004;145:2653-2659.
61. Wei Q, Sun YQ, Zhang J. Exendin-4, a glucagon-like peptide-1 receptor agonist, inhibits cell apoptosis induced by lipotoxicity in pancreatic beta-cell line. *Peptides*. 2012;37:18-24.
62. Tourrel C, Bailbe D, Meile MJ, Kergoat M, Portha B. Glucagon-like peptide-1 and exendin-4 stimulate beta-cell neogenesis in streptozotocin-treated newborn rats resulting in persistently improved glucose homeostasis at adult age. *Diabetes*. 2001;50:1562-1570.
63. Tschen SI, Dhawan S, Gurlo T, Bhushan A. Age-dependent decline in beta-cell proliferation restricts the capacity of beta-cell regeneration in mice. *Diabetes*. 2009;58:1312-1320.
64. Deane AM, Nguyen NQ, Stevens JE, et al. Endogenous glucagon-like peptide-1 slows gastric emptying in healthy subjects, attenuating postprandial glycemia. *J Clin Endocrinol Metab*. 2010;95: 215-221.
65. Nicolaus M, Brodl J, Linke R, Woerle HJ, Göke B, Schirra J. Endogenous GLP-1 regulates postprandial glycemia in humans: relative contributions of insulin, glucagon, and gastric emptying. *J Clin Endocrinol Metab*. 2011;96:229-236.
66. Nauck MA, Bartels E, Ørskov C, Ebert R, Creutzfeldt W. Lack of effect of synthetic human gastric inhibitory polypeptide and glucagon-like peptide 1 [7-36 amide] infused at near-physiological concentrations on pentagastrin-stimulated gastric acid secretion in normal human subjects. *Digestion*. 1992;52:214-221.
67. Schjoldager BT, Mortensen PE, Christiansen J, Ørskov C, Holst JJ. GLP-1 (glucagon-like peptide 1) and truncated GLP-1, fragments of human proglucagon, inhibit gastric acid secretion in humans. *Dig Dis Sci*. 1989;34:703-708.
68. Cheeseman CI, Tsang R. The effect of GIP and glucagon-like peptides on intestinal basolateral membrane hexose transport. *Am J Physiol (Gastrointest Liver Physiol)*. 1996;271:G477-G482.
69. Singh SK, Bartoo AC, Krishnan S, Boylan MO, Schwartz JH, Michael Wolfe M. Glucose-dependent insulinotropic polypeptide (GIP) stimulates transepithelial glucose transport. *Obesity (Silver Spring)*. 2008; 16:2412-2416.

70. Ogawa E, Hosokawa M, Harada N, et al. The effect of gastric inhibitory polypeptide on intestinal glucose absorption and intestinal motility in mice. *Biochem Biophys Res Commun*. 2011;404:115-120.
71. Helman CA, Barbezat GO. The effect of gastric inhibitory polypeptide on human jejunal water and electrolyte transport. *Gastroenterology*. 1977;72:376-379.
72. Qin X, Shen H, Liu M, et al. GLP-1 reduces intestinal lymph flow, triglyceride absorption, and apolipoprotein production in rats. *Am J Physiol Gastrointest Liver Physiol*. 2005;288:G943-G949.
73. Hsieh J, Longuet C, Baker CL, et al. The glucagon-like peptide 1 receptor is essential for postprandial lipoprotein synthesis and secretion in hamsters and mice. *Diabetologia*. 2010;53:552-561.
74. Meier JJ, Gethmann A, Gotze O, et al. Glucagon-like peptide 1 abolishes the postprandial rise in triglyceride concentrations and lowers levels of non-esterified fatty acids in humans. *Diabetologia*. 2006;1-7.
75. Thazhath SS, Marathe CS, Wu T, et al. The glucagon-like peptide 1 receptor agonist exenatide inhibits small intestinal motility, flow, transit, and absorption of glucose in healthy subjects and patients with Type 2 diabetes: a randomized controlled trial. *Diabetes*. 2016;65:269-275.
76. Song DH, Getty-Kaushik L, Tseng E, Simon J, Corkey BE, Wolfe MM. Glucose-dependent insulinotropic polypeptide enhances adipocyte development and glucose uptake in part through Akt activation. *Gastroenterology*. 2007;133:1796-1805.
77. Sancho V, Nuche B, Arnes L, et al. The action of GLP-1 and exendins upon glucose transport in normal human adipocytes, and on kinase activity as compared to morbidly obese patients. *Int J Mol Med*. 2007;19:961-966.
78. Bertin E, Arner P, Bolinder J, Hagstrom-Toft E. Action of glucagon and glucagon-like peptide-1-(7-36) amide on lipolysis in human subcutaneous adipose tissue and skeletal muscle in vivo. *J Clin Endocrinol Metab*. 2001;86:1229-1234.
79. Asmar M, Arngrim N, Simonsen L, et al. The blunted effect of glucose-dependent insulinotropic polypeptide in subcutaneous abdominal adipose tissue in obese subjects is partly reversed by weight loss. *Nutr Diabetes*. 2016;6:e208.
80. Asmar M, Simonsen L, Arngrim N, Holst JJ, Dela F, Bulow J. Glucose-dependent insulinotropic polypeptide has impaired effect on abdominal, subcutaneous adipose tissue metabolism in obese subjects. *Int J Obes (Lond)*. 2014;38:259-265.
81. Chen S, Okahara F, Osaki N, Shimotoyodome A. Increased GIP signaling induces adipose inflammation via a HIF-1alpha-dependent pathway and impairs insulin sensitivity in mice. *Am J Physiol Endocrinol Metab*. 2015;308:E414-E425.
82. Varol C, Zvibel I, Spektor L, et al. Long-acting glucose-dependent insulinotropic polypeptide ameliorates obesity-induced adipose tissue inflammation. *J Immunol*. 2014;193:4002-4009.
83. Lee YS, Park MS, Choung JS, et al. Glucagon-like peptide-1 inhibits adipose tissue macrophage infiltration and inflammation in an obese mouse model of diabetes. *Diabetologia*. 2012;55:2456-2468.
84. Kim SJ, Nian C, McIntosh CH. Resistin is a key mediator of glucose-dependent insulinotropic polypeptide (GIP) stimulation of lipoprotein lipase (LPL) activity in adipocytes. *J Biol Chem*. 2007;282:34139-34147.
85. Kim SJ, Nian C, McIntosh CH. GIP increases human adipocyte LPL expression through CREB and TORC2-mediated trans-activation of the LPL gene. *J Lipid Res*. 2010;51:3145-3157.
86. Ohneda A, Kobayashi T, Nihei J. Effect of endogenous gastric inhibitory polypeptide (GIP) on the removal of triacylglycerol in dogs. *Regul Pept*. 1983;6:25-32.
87. Heppner KM, Marks S, Holland J, et al. Contribution of brown adipose tissue activity to the control of energy balance by GLP-1 receptor signalling in mice. *Diabetologia*. 2015;58:2124-2132.
88. Lockie SH, Heppner KM, Chaudhary N, et al. Direct control of brown adipose tissue thermogenesis by central nervous system glucagon-like peptide-1 receptor signaling. *Diabetes*. 2012;61:2753-2762.
89. Xu F, Lin B, Zheng X, et al. GLP-1 receptor agonist promotes brown remodelling in mouse white adipose tissue through SIRT1. *Diabetologia*. 2016;59:1059-1069.
90. Mantelmacher FD, Fishman S, Cohen K, et al. Glucose-dependent Insulinotropic polypeptide receptor deficiency leads to impaired bone marrow Hematopoiesis. *J Immunol*. 2017;198:3089-3098.
91. Tsukiyama K, Yamada Y, Yamada C, et al. Gastric inhibitory polypeptide as an endogenous factor promoting new bone formation after food ingestion. *Mol Endocrinol*. 2006;20:1644-1651.
92. Mieczkowska A, Bouvard B, Chappard D, Mabilleau G. Glucose-dependent insulinotropic polypeptide (GIP) directly affects collagen fibril diameter and collagen cross-linking in osteoblast cultures. *Bone*. 2015;74:29-36.
93. Yamada C, Yamada Y, Tsukiyama K, et al. The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. *Endocrinology*. 2008;149:574-779.
94. Iepsen EW, Lundgren JR, Hartmann B, et al. GLP-1 receptor agonist treatment increases bone formation and prevents bone loss in weight-reduced obese women. *J Clin Endocrinol Metab*. 2015;100:2909-2917.
95. Lu N, Sun H, Yu J, et al. Glucagon-like peptide-1 receptor agonist liraglutide has anabolic bone effects in ovariectomized rats without diabetes. *PLoS One*. 2015;10:e0132744.
96. Pereira M, Jeyabalan J, Jorgensen CS, et al. Chronic administration of glucagon-like peptide-1 receptor agonists improves trabecular bone mass and architecture in ovariectomised mice. *Bone*. 2015;81:459-467.
97. Ding KH, Shi XM, Zhong Q, et al. Impact of glucose-dependent insulinotropic peptide on age-induced bone loss. *J Bone Miner Res*. 2008;23:536-543.
98. Mabilleau G, Perrot R, Mieczkowska A, et al. Glucose-dependent insulinotropic polypeptide (GIP) dose-dependently reduces osteoclast differentiation and resorption. *Bone*. 2016;91:102-112.
99. Nissen A, Christensen M, Knop FK, Vilsboll T, Holst JJ, Hartmann B. Glucose-dependent insulinotropic polypeptide inhibits bone resorption in humans. *J Clin Endocrinol Metab*. 2014;99:E2325-E2329.
100. Garg G, McGuigan FE, Kumar J, Luthman H, Lyssenko V, Akesson K. Glucose-dependent insulinotropic polypeptide (GIP) and GIP receptor (GIPR) genes: an association analysis of polymorphisms and bone in young and elderly women. *Bone Rep*. 2016;4:23-27.
101. Gaudin-Audrain C, Irwin N, Mansur S, et al. Glucose-dependent insulinotropic polypeptide receptor deficiency leads to modifications of trabecular bone volume and quality in mice. *Bone*. 2013;53:221-230.
102. Mieczkowska A, Irwin N, Flatt PR, Chappard D, Mabilleau G. Glucose-dependent insulinotropic polypeptide (GIP) receptor deletion leads to reduced bone strength and quality. *Bone*. 2013;56:337-342.
103. Xie D, Zhong Q, Ding KH, et al. Glucose-dependent insulinotropic peptide-overexpressing transgenic mice have increased bone mass. *Bone*. 2007;40:1352-1360.
104. Torekov SS, Harslof T, Rejnmark L, et al. A functional amino acid substitution in the glucose-dependent insulinotropic polypeptide receptor (GIPR) gene is associated with lower bone mineral density and increased fracture risk. *J Clin Endocrinol Metab*. 2014;99:E729-E733.
105. Driessen JH, Henry RM, van Onzenoort HA, et al. Bone fracture risk is not associated with the use of glucagon-like peptide-1 receptor agonists: a population-based cohort analysis. *Calcif Tissue Int*. 2015;97:104-112.
106. Mabilleau G, Mieczkowska A, Chappard D. Use of glucagon-like peptide-1 receptor agonists and bone fractures: a meta-analysis of randomized clinical trials. *J Diabetes*. 2014;6:260-266.
107. Su B, Sheng H, Zhang M, et al. Risk of bone fractures associated with glucagon-like peptide-1 receptor agonists' treatment: a meta-analysis of randomized controlled trials. *Endocrine*. 2015;48:107-115.
108. Snook LA, Nelson EM, Dyck DJ, Wright DC, Holloway GP. Glucose-dependent insulinotropic polypeptide directly induces glucose transport in rat skeletal muscle. *Am J Physiol Regul Integr Comp Physiol*. 2015;309:R295-R303.
109. Egan JM, Meneilly GS, Habener JF, Elahi D. Glucagon-like peptide-1 augments insulin-mediated glucose uptake in the obese state. *J Clin Endocrinol Metab*. 2002;87:3768-3773.
110. Meneilly GS, McIntosh CH, Pederson RA, et al. Effect of glucagon-like peptide 1 (7-36 amide) on insulin-mediated glucose

uptake in patients with type 1 diabetes. *Diabetes Care*. 2003;26:837-842.
111. Ryan AS, Egan JM, Habener JF, Elahi D. Insulinotropic hormone glucagon-like peptide-1-(7-37) appears not to augment insulin-mediated glucose uptake in young men during euglycemia. *J Clin Endocrinol Metab*. 1998;83:2399-2404.
112. Gutzwiller JP, Tschopp S, Bock A, et al. Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men. *J Clin Endocrinol Metab*. 2004;89:3055-3061.
113. Mann JFE, Orsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:839-848.
114. Nyström T, Gutniak MK, Zhang Q, et al. Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. *Am J Physiol (Endocrinol Metab)*. 2004;287:E1209-E1215.
115. Tolessa T, Gutniak M, Holst JJ, Efendic S, Hellström PM. Glucagon-like peptide-1 retards gastric emptying and small bowel transit in the rat: effect mediated through central or enteric nervous mechanisms. *Dig Dis Sci*. 1998;43:2284-2290.
116. Schirra J, Göke B. The physiological role of GLP-1 in human: incretin, ileal brake or more? *Regul Pept*. 2005;128:109-115.
117. Yamada Y, Seino Y. Physiology of GIP – a lesson from GIP receptor knockout mice. *Horm Metab Res*. 2004;36:771-774.
118. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. *Cell Metab*. 2016;24:15-30.
119. Gros R, You X, Baggio LL, et al. Cardiac function in mice lacking the glucagon-like peptide-1 receptor. *Endocrinology*. 2003;144:2242-2252.
120. Creutzfeldt W, Ebert R, Willms B, Frerichs H, Brown JC. Gastric inhibitory polypeptide (GIP) and insulin in obesity: increased response to stimulation and defective feedback control of serum levels. *Diabetologia*. 1978;14:15-24.
121. Roust LR, Stesin M, Go VLW, O'Brien PC, Rizza RA, Service FJ. Role of gastric inhibitory polypeptide in postprandial hyperinsulinemia of Obesity 1988:
122. Ranganath LR, Beety JM, Morgan LM, Wright JW, Howland R, Marks V. Attenuated GLP-1 secretion in obesity: cause or consequence? *Gut*. 1996;38:916-919.
123. Muscelli E, Mari A, Casolaro A, et al. Separate impact of obesity and glucose tolerance on the incretin effect in normal subjects and type 2 diabetic patients. *Diabetes*. 2008;57:1340-1348.
124. Faerch K, Torekov SS, Vistisen D, et al. GLP-1 response to oral glucose is reduced in prediabetes, screen-detected type 2 diabetes, and obesity and influenced by sex: the ADDITION-PRO Study. *Diabetes*. 2015;64:2513-2525.
125. Matikainen N, Bogl LH, Hakkarainen A, et al. GLP-1 responses are heritable and blunted in acquired obesity with high liver fat and insulin resistance. *Diabetes Care*. 2014;37:242-251.
126. Vogel CI, Scherag A, Bronner G, et al. Gastric inhibitory polypeptide receptor: association analyses for obesity of several polymorphisms in large study groups. *BMC Med Genet*. 2009;10:19.
127. Flint A, Raben A, Ersboll AK, Holst JJ, Astrup A. The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. *Int J Obes Relat Metab Disord*. 2001;25:781-792.
128. Laferrere B. Effect of gastric bypass surgery on the incretins. *Diabetes Metab*. 2009;35:513-517.
129. Svane MS, Jorgensen NB, Bojsen-Moller KN, et al. Peptide YY and glucagon-like peptide-1 contribute to decreased food intake after Roux-en-Y gastric bypass surgery. *Int J Obes (Lond)*. 2016;40:1699-1706.
130. Svane MS, Bojsen-Moller KN, Nielsen S, et al. Effects of endogenous GLP-1 and GIP on glucose tolerance after Roux-en-Y gastric bypass surgery. *Am J Physiol (Endocrinol Metab)*. 2016;310:E505-E514.
131. Mokadem M, Zechner JF, Margolskee RF, Drucker DJ, Aguirre V. Effects of Roux-en-Y gastric bypass on energy and glucose homeostasis are preserved in two mouse models of functional glucagon-like peptide-1 deficiency. *Mol Metab*. 2014;3:191-201.
132. Service FJ, Thompson GB, Service FJ, Andrews JC, Collazo-Clavell ML, Lloyd RV. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. *N Engl J Med*. 2005;353:249-254.
133. Patti ME, McMahon G, Mun EC, et al. Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. *Diabetologia*. 2005;48:2236-2240.
134. Perfetti R, Zhou J, Doyle ME, Egan JM. Glucagon-like peptide-1 induces cell proliferation and pancreatic-duodenum homeobox-1 expression and increases endocrine cell mass in the pancreas of old, glucose-intolerant rats. *Endocrinology*. 2000;141:4600-4605.
135. Meier JJ, Butler AE, Galasso R, Butler PC. Hyperinsulinemic hypoglycemia after gastric bypass surgery is not accompanied by islet hyperplasia or increased beta-cell turnover. *Diabetes Care*. 2006;29:1554-1559.
136. DeFronzo RA. Banting lecture from the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58:773-795.
137. Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? *Diabetologia*. 2011;54:10-18.
138. Calanna S, Christensen M, Holst JJ, et al. Secretion of glucagon-like peptide-1 in patients with type 2 diabetes mellitus: systematic review and meta-analyses of clinical studies. *Diabetologia*. 2013;56:965-972.
139. Calanna S, Christensen M, Holst JJ, et al. Secretion of glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes: systematic review and meta-analysis of clinical studies. *Diabetes Care*. 2013;36:3346-3352.
140. Jones IR, Owens DR, Luzio S, Williams S, Hayes TM. The glucose dependent insulinotropic polypeptide response to oral glucose and mixed meals is increased in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia*. 1989;32:668-677.
141. Toft-Nielsen MB, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2001;86:3717-3723.
142. Krarup T, Saurbrey N, Moody AJ, Kühl C, Madsbad S. Effect of porcine gastric inhibitory polypeptide on ß-cell function in Type 1 and Type II diabetes mellitus. *Metabolism*. 1988;36:677-682.
143. Mentis N, Vardarli I, Köthe LD, et al. GIP does not potentiate the antidiabetic effects of GLP-1 in hyperglycemic patients with type 2 diabetes. *Diabetes*. 2011;60:1270-1276.
144. Vilsbøll T, Krarup T, Madsbad S, Holst JJ. Defective amplification of the late phase insulin response to glucose by GIP in obese Type II diabetic patients. *Diabetologia*. 2002;45:1111-1119.
145. Kjems LL, Holst JJ, Vølund A, Madsbad S. The influence of GLP-1 on glucose-stimulated insulin secretion: effects on beta-cell sensitivity in type 2 and nondiabetic subjects. *Diabetes*. 2003;52:380-386.
146. Nauck MA, Kleine N, Ørskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*. 1993;36:741-744.
147. Knop FK, Vilsbøll T, Højberg PV, et al. Reduced incretin effect in type 2 diabetes: cause or consequence of the diabetic state? *Diabetes*. 2007;56:1951-1959.
148. Meier JJ, Nauck MA. Is the diminished incretin effect in type 2 diabetes just an epi-phenomenon of impaired beta-cell function? *Diabetes*. 2010;59:1117-1125.
149. Qualmann C, Nauck MA, Holst JJ, Ørskov C, Creutzfeldt W. Insulinotropic actions of intravenous glucagon-like peptide-1 (GLP-1) [7-36 amide] in the fasting state in healthy subjects. *Acta Diabetol*. 1995;32:13-16.
150. Degn KB, Brock B, Juhl CB, et al. Effect of intravenous infusion of exenatide (synthetic exendin-4) on glucose-dependent insulin secretion and counterregulation during hypoglycemia. *Diabetes*. 2004;53:2397-2403.
151. Amland PF, Jorde R, Aanderup S, Burhol PG, Gierckskiy K-E. Effects of intravenously infused porcine GIP on serum insulin, plasma C-peptide, and pancreatic polypeptide in non-insulin-dependent diabetes in the fasting state. *Scand J Gastroenterol*. 1985;20:315-320.

152. Pederson RA, Brown JC. The insulinotropic action of gastric inhibitory polypeptide in the perfused rat pancreas. *Endocrinology*. 1976; 99:780-785.
153. Nauck MA, Holst JJ, Willms B. Glucagon-like peptide 1 and its potential in the treatment of non-insulin-dependent diabetes mellitus. *Horm Metab Res*. 1997;29:411-416.
154. Christensen M, Calanna S, Sparre-Ulrich AH, et al. Glucose-dependent insulinotropic polypeptide augments glucagon responses to hypoglycemia in type 1 diabetes. *Diabetes*. 2015;64:72-78.
155. Meier JJ, Hücking K, Holst JJ, Deacon CF, Schmiegel WH, Nauck MA. Reduced insulinotropic effect of gastric inhibitory polypeptide in first-degree relatives of patients with type 2 diabetes. *Diabetes*. 2001;50:2497-2504.
156. Nauck MA. Glucagon-like peptide 1 (GLP-1) in the treatment of diabetes. *Horm Metab Res*. 2004;36:852-858.
157. Højberg PV, Vilsbøll T, Zander M, et al. Four weeks of near-normalization of blood glucose has no effect on postprandial GLP-1 and GIP secretion, but augments pancreatic B-cell responsiveness to a meal in patients with Type 2 diabetes. *Diabet Med*. 2008;25: 1268-1275.
158. Højberg PV, Vilsbøll T, Rabol R, et al. Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. *Diabetologia*. 2009;52:199-207.
159. Xu G, Kaneto H, Laybutt DR, et al. Downregulation of GLP-1 and GIP receptor expression by hyperglycemia: possible contribution to impaired incretin effects in diabetes. *Diabetes*. 2007;56:1551-1558.
160. Aaboe K, Akram S, Deacon CF, Holst JJ, Madsbad S, Krarup T. Restoration of the insulinotropic effect of glucose-dependent insulinotropic polypeptide contributes to the antidiabetic effect of dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab*. 2015;17:74-81.
161. Gault VA, Irwin N, Green BD, et al. Chemical ablation of gastric inhibitory polypeptide receptor action by daily (Pro3)GIP administration improves glucose tolerance and ameliorates insulin resistance and abnormalities of islet structure in obesity-related diabetes. *Diabetes*. 2005;54:2436-2446.

How to cite this article: Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. *Diabetes Obes Metab*. 2018;20:5–21. https://doi.org/10.1111/dom.13129