Current Proteomics 22 (2025) 100014

Contents lists available at ScienceDirect

Current Proteomics

journal homepage: http://www.keaipublishing.com/en/journals/current-proteomics/

Incretin Hormones: Mechanisms, Therapeutic Implications, and Future Directions in Glucose Regulation and Diabetes Management

Abrar Ahmad Zargar[a], Vipasha Mehta[a], Rishikesh Gupta[b], Kishwor Bhandari[c], Mahesh Kumar Posa[d], T. Sri Ramya[e], D. Snigdha[e], Vijayakumar B[f], Mukesh Chandra Sharma[g], P. Balaji[h], Sudhanshu Kumar Jha[b,*]

[a] Department of Pharmacy, SVS Paramedical College, Sunderbani, Rajouri 185153, Jammu and Kashmir, India
[b] Institute of Pharmacy, Bundelkhand University, Jhansi 284128, Uttar Pradesh, India
[c] Department of Anatomy, Shree Narayan Medical Institute and Hospital, Saharsa 852201, Bihar, India
[d] Department of Pharmacology, School of Pharmaceutical Sciences, Jaipur National University, Jagatpur, Jaipur 302017, Rajasthan
[e] Care College of Pharmacy, affiliated to Kakatiya University, Warangal 506001
[f] Department of Pharmaceutical Chemistry, Grace College of Pharmacy, Palakkad 678004
[g] School of Pharmacy, Devi Ahilya Vishwavidalaya, Indore 452001
[h] Department of Pharmacology, School of Pharmaceutical Sciences, Vels Institute of Science, Technology & Advanced Studies (VISTAS), Pallavaram, Chennai, 600117

ARTICLE INFO

Keywords:
Incretins
GLP-1
GIP
Type 2 diabetes
DPP-4 inhibitors
β-cell resistance

ABSTRACT

Background: Type 2 diabetes (T2D) is a global health crisis, currently affecting over 540 million individuals. Its prevalence continues to rise due to aging populations, sedentary lifestyles, and unhealthy diets. T2D accounts for approximately 90–95% of all diabetes cases and is a leading cause of cardiovascular and metabolic morbidity. Incretin hormones—glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP)—play essential roles in glucose homeostasis, insulin secretion, and metabolic regulation. Their dysfunction significantly contributes to the pathophysiology of T2D.

Objective: This review aims to provide an updated synthesis of incretin hormone biology, emphasizing GLP-1 and GIP mechanisms in glucose regulation, β-cell function, and their therapeutic potential in T2D.

Methods: Relevant studies from 2000 to 2024 were reviewed from databases including PubMed and Scopus, focusing on incretin physiology, receptor signaling, therapeutic applications, and mechanisms of secretion.

Results: GLP-1 and GIP stimulate glucose-dependent insulin release, reduce glucagon levels, delay gastric emptying, and contribute to satiety and cardiovascular benefits. Incretin-based therapies—including GLP-1 receptor agonists and DPP-4 inhibitors—demonstrate significant benefits in glycemic control, though limitations such as β-cell resistance and modest cardiovascular outcomes in some agents persist. Dual receptor agonists like tirzepatide show improved metabolic effects. Recent insights into nutrient sensing pathways and enteroendocrine activation offer promising therapeutic directions.

* Corresponding author.
E-mail addresses: abrarnazir578@gmail.com (A.A. Zargar), mehtavipasha04@gmail.com (V. Mehta), rishikeshgupt@gmail.com (R. Gupta), kishworbhandari11@gmail.com (K. Bhandari), posamaheshkumarbabu@gmail.com (M.K. Posa), ramyatotakura1@gmail.com (T.S. Ramya), sudhanshujh121997@gmail.com (S.K. Jha).

https://doi.org/10.1016/j.curpro.2025.100014
Received 27 June 2025; Received in revised form 27 June 2025; Accepted 5 July 2025

Conclusion: Advancements in incretin therapy have transformed T2D treatment. Future strategies should target β-cell resistance, leverage dual agonists, personalize therapies, and develop pharmacologic methods to mimic the hormonal profile of bariatric surgery.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a global health challenge, affecting over 540 million adults worldwide and accounting for nearly 90–95% of all diabetes cases. The International Diabetes Federation (IDF) projects that this number will rise significantly in the coming decades, driven by urbanization, sedentary lifestyles, and unhealthy dietary habits.[1] T2DM is not only associated with chronic hyperglycaemia but also contributes to a wide array of complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy, imposing a significant socio-economic burden.[2] T2DM is characterized by a range of dysfunctions, including insulin resistance, diminished insulin action in the liver, impaired adipocyte function, impaired glucose absorption in muscle, and finally, complete dysfunction of the pancreatic β-cells.[3] A plethora of new drug classes have emerged in the past two decades to treat high blood sugar in T2DM.[4] The multi-targeted strategy to managing this worldwide health crisis has also made room for a number of novel agents, some of which have the ability to rehabilitate diabetes. The term "incretin" is currently used in the field of gastrointestinal endocrinology to describe two specific gut hormones: GIP (formerly "gastric inhibitory polypeptide," later renamed "glucose-dependent insulinotropic polypeptide") and GLP-1 (formerly "glucagon-like peptide 1," now in its compressed form).[5] The creation of incretins, hormones secreted by enteroendocrine cells after the consumption of vitamins and minerals, initiates the production of glucose-dependent insulin from β-cells.[6] One is glucose-dependent insulinotropic polypeptide (GIP), while the other is glucagon-like peptide-1 (GLP-1). More specifically, glucagon-like peptide-1 (GLP-1) has been in the spotlight as a possible building block for medications that lower blood sugar and encourage weight loss. GLP-1RA was approved for the treatment and prevention of type 2 diabetes and obesity because of its effects on increasing insulin secretion, decreasing hunger, and cutting calorie consumption.[7] Additionally, GLP-1 reduces hunger, slows stomach emptying, and inhibits glucagon synthesis via its links to the central nervous system. Because it triggers a glucose-dependent drop in blood sugar, the incretin effect is helpful in controlling type 2 diabetes in both cases. The incretin hormone family includes the glucagon-like peptides GLP-1 and GLP-2, as well as the glucose-dependent insulinotropic polypeptide (GIP).[8] These incretin hormones are secreted from the gut in response to nutrient intake and enhance insulin secretion in a glucose-dependent manner, helping to lower postprandial blood glucose levels. GLP-1 also slows gastric emptying, suppresses glucagon secretion, promotes satiety, and exhibits cardioprotective effects. GIP primarily stimulates insulin release and plays a role in lipid metabolism. Together, these hormones are critical regulators of glucose homeostasis and energy balance, making them key targets in the management of T2D (10.1016/j.cmet.2016.06.009. 10.1111/jdi.12466.) . Many physiological processes rely on these peptides, which are secreted by enteroendocrine L and K cells. These functions include glucose homeostasis regulation, lipoprotein breakdown, and fat buildup.[9] In addition to helping with blood sugar levels, there is some evidence that they may also reduce inflammation. One possible way people can protect themselves against diabetes-related complications is by lowering the body's inflammatory response.[10] Xenatide QW (Bydureon), Lixisenatide (Lyxumia), Albiglutide (Eperzam), Dulaglutide (Trulicity), Liraglutide (Victoza), and a variety of other GLP-1 receptor agonists are currently available for use. Crucial to glucose control, insulin secretion, and general metabolic health are incretin hormones, especially glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). The role of incretins in glucose homeostasis and the development of type 2 diabetes (T2D) has become increasingly important since their discovery.[11] With a focus on their many functions in glucose metabolism, beta-cell function, and cardiometabolic health, this overview delves deeply into the history of incretin research. We talk about the therapeutic potential of GLP-1 and GIP for the management of type 2 diabetes, as well as their physiological mechanisms in controlling appetite, insulin secretion, and cardio-protection.[12] Our attention is particularly drawn to the processes of incretin secretion, the difficulties of β-cell resistance, and the potential therapeutic uses of incretin-based medicines such as GLP-1 receptor agonists and DPP-4 (Dipeptidyl Peptidase-4) inhibitors, which prevent enzymatic degradation of incretins to prolong their action. Also discussed are the receptors' roles in incretin release, the luminal components, and the several sensing pathways.[12,13] In recent years, dual incretin receptor agonists targeting both GLP-1 and GIP receptors have emerged as a promising therapeutic strategy for Type 2 diabetes (10.1038/nrneph.2017.123.). Tirzepatide, the first-in-class dual GIP/GLP-1 receptor agonist, has demonstrated superior glycaemic control and weight loss compared to GLP-1 receptor agonists alone. It mimics the effects of both incretins, enhancing insulin secretion, suppressing glucagon, delaying gastric emptying, and improving metabolic flexibility(10.1016/j.neuropharm.2017.12.031.) . Clinical trials such as the SURPASS series have reported significant reductions in HbA1c and body weight with tirzepatide, making it a major advancement in incretin-based therapy (10.1016/j.eclinm.2024.102782.). Its ability to harness the complementary actions of GIP and GLP-1 represents a novel approach in overcoming limitations of monotherapy and β-cell resistance in T2D management (10.1159/000475731. 10.1007/164_2015_9.) . A comprehensive literature search was conducted using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. This review study concludes by outlining the most recent therapeutic options that aim to target the incretin axis. These include employing GLP-1 mimetics, mimicking bariatric surgery, and developing new methods to overcome β-cell resistance. Through a comprehensive analysis of existing research, this review sheds light on the successes and setbacks of incretin-based therapeutics, offering guidance for where the field may go from here. Fig. 1 shows the PRISMA flowchart.

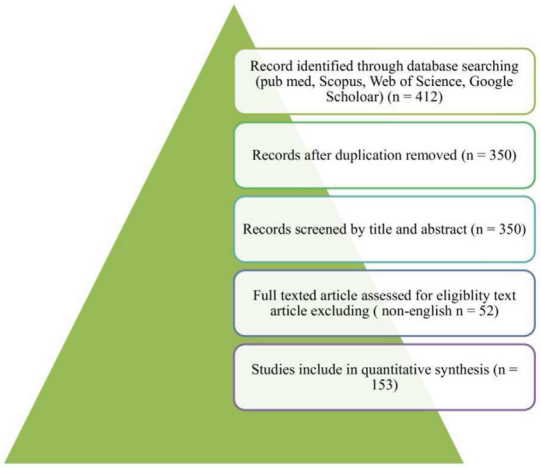

Fig. 1. PRISMA flowchart.

2. The Role of Incretins in Glucose Homeostasis

2.1. Discovering Incretins to Insulinotropic Insights

Bayliss and Starling found secretin in 1902; it was the first hormone found to regulate exocrine production from the pancreas. Hormones were thought to regulate metabolism as well. After insulin was discovered, researchers began to speculate that incretins could play a role in regulating insulin production, similar to how excretins regulate exocrine function. However, it was discovered by von Mering and Minkowski in 1889 that intestinal factors regulated pancreatic endocrine secretion. Along with other researchers, they looked at how intestine extracts and secretin formulations affected blood sugar levels[1,2]. In 1932, Belgian scientist Jean La Barre was the first to discover the hormone called "incretin" in the digestive tract. It stimulates the pancreatic endocrine glands to release insulin and other hormone-like substances. He also mentioned that these incretins could be used to treat diabetes mellitus[3,4]. The year 1960 saw the greatest leap forward in biomedicine, especially in endocrinology. It changed everything and reignited people's interest in incretin. It was Yalow and Berson's creation of the radioimmunoassay (RIA)[5]. In 1932, the term "incretin" was initially used to describe chemicals secreted by the intestinal mucosa in reaction to eating that were found to reduce blood glucose levels. John C. Brown was the first to identify GIP in dogs in 1970. Originally called "gastric inhibitory polypeptide," this hormone blocks the secretion of stomach acid. After the insulinotropic function of the protein was shown in humans three years later, a suggestion was made to rename the acronym GIP to glucose-dependent insulinotropic polypeptide[6].

2.2. GLP-1 and GIP Regulate Glucose, Beta Cell Function, and Cardiometabolic Health

Both GIP and GLP-1, the two primary incretins, have distinct yet complementary biological roles. Both GLP-1 and GIP stimulate insulin release from pancreatic beta cells through a glucose-dependent mechanism. Their ability to prevent hypoglycemia is enhanced when blood glucose levels are higher, suggesting that they have a stronger insulinotropic effect. This reaction is crucial for keeping blood sugar levels stable after eating.[7] GLP-1 inhibits glucagon secretion by pancreatic alpha cells. Hormone glucagon typically raises blood glucose levels by promoting glucose production in the liver. GLP-1 reduces glucagon levels, which in turn lowers blood glucose levels; this effect is most pronounced after eating.[8] Reduced gastric emptying due to GLP-1 controls the rate of glucose release into the bloodstream. One way to control one's weight is to wait eating until after a meal. This helps with glycaemic regulation and making you feel full.[9] People report feeling better and eating less after taking GLP-1 because of its effects on the central nervous system. A positive side effect of GLP-1 receptor agonists used to treat obesity and type 2 diabetes is their anorectic effect, which aids in weight control.[10] Proof that GLP-1 promotes beta cell proliferation and inhibits cell death has been found. This has the potential to improve the number and function of beta cells in type 2 diabetics, which might help with blood glucose control in the long run. New evidence suggests that GLP-1 can improve endothelial function, reduce blood pressure, and reduce inflammation, all of which contribute to its cardioprotective effects. Managing cardiovascular disease in people with type 2 diabetes is greatly impacted by these impacts.[11]

2.3. Glucose Regulation, Appetite Control, and Cardioprotection: GLP-1 Physiology

A key function of GLP-1 is to increase glucose-dependent insulin synthesis from pancreatic beta cells. This reduces hypoglycaemia risk since GLP-1 only boosts insulin release in response to high blood glucose[12]. GLP-1 inhibits pancreatic alpha cell glucagon secretion. Glucagon increases blood sugar via stimulating hepatic gluconeogenesis and glycogenolysis[13]. GLP-1 prolongs stomach emptying, allowing nutrients to enter the circulation. Satiety decreases food intake and regulates postprandial blood glucose levels[14].

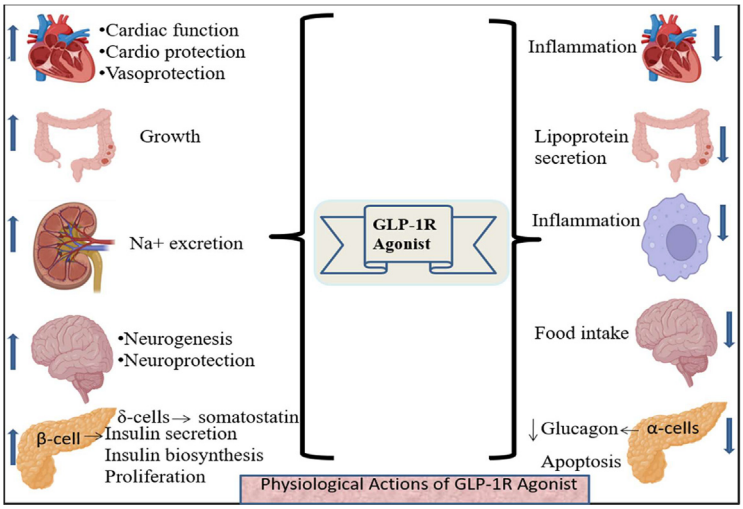

Fig. 2. Physiological Actions of GLP-1R Agonist.

Increased transit time for nutrients from the stomach to the bloodstream is a result of GLP-1's ability to postpone emptying. Postprandial (after meal) blood glucose levels are helped to regulate by this effect, which also promotes satiety, which reduces food intake[15]. For people with type 2 diabetes, who are at increased risk for cardiovascular disease, the increasing body of research suggesting that GLP-1 has cardioprotective effects is very encouraging. Inflammation is reduced, endothelial function is enhanced, and heart function is improved as a result of these benefits[16]. Fig. 2 shows the physiology of the GLP-1R agonist.

3. Physiological Functions and Mechanisms of Incretin Hormones in Glucose Regulation

3.1. Mechanisms, Therapeutic Potential, and the Incretin Effect in Glucose Homeostasis

Two major peptides that have been identified as incretin hormones are GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1). Although GLP-1 shows non-incretin properties, previous studies on glucoregulatory responses in receptor deletion mice models show that GIP solely works as an incretin. Investigating genetically modified mice may be complicated, though, by compensatory adaptive changes. To disprove this, we tested GIP and GLP-1 in wild-type mice for incretin and non-incretin activity, respectively, by blocking their effects using antibodies against GIP receptors and exendin, an antagonist for GLP-1 receptors.[17] The incretin hormone glucose-dependent insulinotropic polypeptide (GIP) is mostly produced by K-enteroendocrine cells found in the duodenum and proximal jejunum; it consists of 42 amino acids.[18] However, studies using genetically modified mice can be obstructed by compensatory adaption modifications. To rule out this possibility, we tested the incretin and non-incretin activities of GIP and GLP-1 in wild-type mice. We used the GLP-1 receptor antagonist exendin to block GLP-1 action and immunopurified anti-GIP receptor antisera to test GIP. We found that GLP-1, but not GIP, significantly regulates blood glucose levels in mice even when they don't eat by mouth. Research on the possible therapeutic advantages of GLP-1 in the treatment of diabetes is currently underway since this incretin decreases blood glucose via a variety of additional channels.[30] Incretin mimetics are a new family of medications developed for the treatment of type 2 diabetes. Incretin mimetics are peptide hormones that function by imitating the activities of incretins, which are produced in the gastrointestinal system. The generation of incretins is boosted during food absorption, which in turn enhances insulin secretion. The effects of incretins on insulin and glucagon levels are glucose dependent. In contrast to sulfonylureas, incretins can decrease glucagon suppression and increase insulin in hypoglycaemic conditions, rather than having an insulin-boosting action. Consequently, this inhibition may reduce the frequency of hypoglycemia in individuals with type 2 diabetes.[19] The role of the intestines in glucose homeostasis can be better understood by comparing the results of oral and intravenous glucose infusions. Using the same amount of glucose (25 g, or around half the sugar in a can of soda) may not provide very unusual outcomes, especially considering how small the quantities of glucose are. Since the amount of insulin secreted (as determined by C-peptide responses) may be almost same, changes in peripheral insulin concentrations could be seen as an indication of changes in hepatic insulin clearance. The incretin effect refers to the dramatic rise in insulin secretion that happens when oral or enteral glucose administration is timed to coincide with plasma glucose concentrations achieved by oral or small intestinal glucose administration, and the intravenous glucose infusion is adjusted accordingly. Common wisdom holds that the incretin effect indicates that insulinotropic substances (also known as incretin hormones) are secreted by the stomach.[20,21] In the 1930s, Belgian doctor Dr. Jean La Barre used the term "incretin" to describe a substance present in the intestinal mucosa that, when administered intravenously to non-pancreatectomy mice, induced hypoglycemia. Dr. Hans Heller of Austria put forth a comparable proposal a few years after that, although he referred to this experimental substance as "duodenin." It was suggested by La Barre and Heller that the substance(s) under research could be

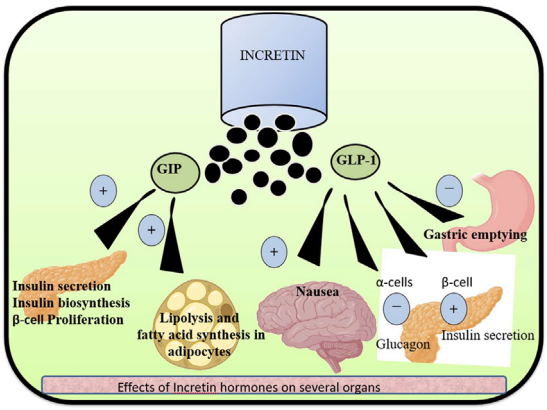

Fig. 3. Effects of Incretin hormones on several organs.

Table 1
Summary of Incretin Hormone-Based Therapeutics and Their Clinical Status.

Ssr. No.	Drug Name	Class	Mechanism of Action	Approval Status	Key Clinical Outcomes	Ref. (s)
1	Exenatide	GLP-1 receptor agonist	Activates GLP-1 receptor, increases insulin secretion, delays gastric emptying	FDA-approved for T2D & weight loss	Reduces HbA1c by ~1%; modest weight loss	doi: 10.1152/physrev.00013.2014.
2	Liraglutide	GLP-1 receptor agonist	Enhances glucose-dependent insulin secretion, suppresses glucagon	FDA-approved for T2D & obesity	HbA1c reduction ~1.5%; significant weight loss; cardioprotective	doi: 10.1016/j.jdiacomp.2014.12.006.
3	Dulaglutide	GLP-1 receptor agonist	Same as above; long-acting formulation	FDA-approved	Weekly dosing; effective glycaemic control	doi: 10.1007/s00125-016-3899-2.
4	Semaglutide	GLP-1 receptor agonist	Long-acting GLP-1RA; improves glycaemic control and reduces appetite	FDA-approved for T2D & obesity	Up to 2% HbA1c reduction; notable weight loss	doi: 10.1111/obr.12917.
5	Sitagliptin	DPP-4 inhibitor	Inhibits DPP-4 enzyme, prolongs endogenous GLP-1 and GIP activity	FDA-approved	HbA1c reduction ~0.7–1%; weight-neutral	doi: 10.1016/j.peptides.2017.11.023.
	Vildagliptin	DPP-4 inhibitor	Same as above	Approved in Europe & Asia	Mild HbA1c reduction; low hypoglycemia risk	doi: 10.2337/dc16-0351.
	Tirzepatide	Dual GIP/GLP-1 receptor agonist	Activates both GIP and GLP-1 receptors; enhances insulin secretion and reduces appetite	FDA-approved (2022)	HbA1c ↓ >2%; weight loss up to 22% in some trials	doi: 10.3389/fendo.2018.00754.

used to treat diabetes.[22] The effects of incretin hormones are shown in Fig. 3 and Table 1 shows summary of incretin hormone-based therapeutics.

3.2. GLP-1's Effect on Glucose Metabolism and Type 2 Diabetes Treatment

The expression of GLP-1 occurs in the distal small intestine by L-cells in reaction to food consumption. Important roles it plays in glucose metabolism include stimulating insulin secretion, inhibiting glucagon secretion, postponing gastric emptying, and improving satiety. Individuals afflicted with type 2 diabetes exhibit a significant reduction in GLP-1 synthesis in reaction to dietary intake.[23] Reduced insulin release after meals is another consequence of impaired GLP-1 insulinotropic action. Notwithstanding these dysfunctions, GLP-1 can still be given externally to restore glycaemic control in type 2 diabetes (T2DM) and retains some of its ability to boost insulin production. The development of GLP-1-based medications that target the incretin system has led to improved glycaemic control for type 2 diabetes patients.[24]

3.3. Type 2 Diabetes: Glucose-Dependent Insulinotropic Polypeptide (GIP) Challenges and Therapeutic Limitations Due to β-Cell Resistance

When given orally to healthy individuals, GIP causes an increase in insulin secretion in response to glucose. The insulinotropic effect of GIP is greatly diminished in type 2 diabetics, even though GIP levels are normal or even high. The lower postprandial insulin response observed in type 2 diabetes is likely caused by the pancreatic β-cells' resistance to GIP's activity.[25] GIP has less therapeutic

promise in type 2 diabetes due to its reduced insulinotropic activity compared to GLP-1. There has been little research on how to overcome GIP resistance in people with type 2 diabetes, and GIP mimics have only shown modest efficacy in improving glycaemic management.[26]

3.4. Release of GLP-1 and GIP: Glucose Sensing Pathways and SGLT1 in Incretin Secretion

The release of incretin can be strongly stimulated by glucose, and various routes for glucose sensing have been put up. Brush border sodium glucose cotransporter 1 (SGLT1) mediates Na+ coupled glucose uptake in the upper small intestine, which is thought to stimulate GLP-1 and GIP release. Membrane depolarisation, which initiates electrical activity, voltage-gated calcium entry, and peptide release, seems to be driven by small transporter-associated currents.[27] This theory is backed by evidence that pharmacological SGLT1 inhibitors can limit glucose-dependent GLP-1 and GIP secretion in vitro[28] and that SGLT1 knockout animals release less GIP and GLP-1 early after glucose gavage.[29] On the other hand, mice deficient in SGLT1 had significantly higher plasma GLP-1 levels when tested later after glucose administration. This could indicate that more glucose is delivered to the L-cell rich distal gut, where other sensing pathways may be activated, due to reduced glucose absorption in the upper small intestine.[30] According to one theory, L-cell activation occurs via different signalling pathways when the distal glucose load is high enough to promote microbial fermentation and the formation of short chain fatty acids.[31] One possible explanation for the delayed elevation of GLP-1 levels in SGLT1 mutant animals is the existence of glucose-sensing mechanisms independent of SGLT1 in enteroendocrine cells. It is the job of glucokinase and ATP sensitive potassium (KATP) channel subunits expressed by L-cells and K-cells to relate electrical activity with glucose metabolism. There was no change in peak incretin levels seen in patients treated with KATP channel inhibitors, suggesting that this route is not responsible for these levels.[32] Concentrations of glucose within L-cells were measured, and while the SGLT1-mediated Na+ flow was big enough to cause membrane depolarisation, the monosaccharide flux that accompanied it was not adequate to change the concentrations of glucose within the cells. On the other hand, L-cells have a high phloretin-sensitive glucose flux, which means that facilitative glucose transporters could manage the balance between cytoplasmic and basolateral glucose levels. This would mean that glucose entering L-cells from the plasma, rather than luminal glucose, would mainly impact their metabolism. Problematically, the relationship between GLP-1 production, metabolism, and plasma glucose is still not well understood. Enteroendocrine secretion activates sweet taste receptors via a third, contentious mechanism. A G protein coupled receptor heterodimer (T1R2/T1R3) is used in this pathway to detect glucose and other sweets, and it couples with the G protein α-gustducin. α-gustducin and T1R3 have been identified in the intestines and have been observed in association with GLP-1 and GIP in certain research.[33-35] However, there are indications from many discoveries that they might not function as the L-cell glucose sensor on their own. Evidence from many studies showings that glucose, but not artificial sweeteners, causes an increase in plasma incretin levels in both rats[36] and humans[37] provides convincing evidence against the importance of sweet taste receptors.

4. Therapeutic Applications of Incretin-Based Agents in Type 2 Diabetes Management

4.1. Diabetic Treatments Based on Incretin: GLP-1 Receptor Agonists and DPP-4 Inhibitors for Blood Sugar Management

The digestive tract secretes two crucial incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), into the bloodstream following food consumption. It has recently been proven that GLP-1 and GIP are responsible for 50-70% of the insulin released by healthy individuals after oral glucose consumption. The result is a decrease in average blood glucose levels and an increase in insulin release that is glucose dependant.[38] Since GLP-1 receptor agonists only trigger insulin secretion in response to elevated blood glucose levels, exenatide does pose a small risk of hypoglycemia. No cases of severe hypoglycemia (i.e., episodes requiring assistance from another person) were recorded, however 4% to 11% of patients had hypoglycemia when receiving either combination or solo medication.[39] Currently, there are two types of incretin-based medications available: GLP-1 receptor agonists (exenatide, 1-2 times daily) and DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin, and linagliptin).[40] The pharmacological profiles of GLP-1 receptor agonists and DPP-4 inhibitors are given in Table 2.

4.2. Comparison of GLP-1 Receptor Agonists with DPP-4 Inhibitors for Type 2 Diabetes Management and Cardiovascular Safety

Compared to subcutaneous injections of GLP-1 agonists once, twice, or, more recently, once a week, DPP-4 inhibitors are taken orally once a day. While DPP-4 inhibitors do not appear to have these effects, GLP-1 agonists appear to reduce hunger and slow down stomach emptying.[45] There are no statistically significant or clinically significant differences between DPP4 and placebo in terms of the incidence of serious cardiovascular events, such as stroke, myocardial infarction, or cardiovascular mortality, according to recent randomised controlled studies. Similarly, the risk of serious adverse cardiovascular events with GLP-1RA lixisenatide compared to placebo did not change, according to the results of the recent cardiovascular outcome study ELIXA.[46] With both administered in addition to background medication consisting of metformin and sulfonylureas, the purpose of the LEAD-6 study was to evaluate the safety and effectiveness of once-daily liraglutide administration vs twice-daily exenatide injection. When 1.8 mg of liraglutide was injected once day instead of twice a day, there was a significant decrease in fasting plasma glucose and HbA1c.[47] When comparing GLP-1RA medication to metformin, two trials included data on cardiovascular risk factors; however, neither study found any clinically meaningful variations in cardiovascular risk variables between the groups.[48]Fig. 4 depicting mechanisms and cellular dynamics in Incretin Action.

Table 2
How GLP-1 receptor agonists and DPP-4 inhibitors work pharmacologically.[41-44]

S.No.	Parameter	GLP-1 receptor agonists	DPP-4 inhibitors
1.	**Mechanism of Action**	Delay stomach emptying, increase insulin secretion, suppress glucagon, and activate GLP-1 receptors to mimic the activity of endogenous GLP-1.	Prevent the breakdown of endogenous GLP-1 and GIP by inhibiting the dipeptidyl peptidase-4 enzyme, which in turn enhances their effect.
2.	**Insulin Secretion**	The secretion of insulin is enhanced when glucose is present.	Improving glucose-dependent insulin secretion to a moderate degree
3.	**Glucagon Secretion**	Limit the release of glucagon after eating	Subtle reduction in glucagon secretion
4.	**Gastric Emptying**	Reduce the occurrence of postprandial glucose increases by delaying stomach emptying.	The rate of stomach emptying is unaffected.
5.	**Weight Effect**	As a result of delayed stomach emptying and enhanced satiety, promote weight loss.	Weight-neutral
6.	**Risk of Hypoglycaemia**	Insufficient on its own because of its effect on glucose levels	Low when used alone, as it enhances insulin secretion in a glucose-dependent manner
7.	**Administration**	Subcutaneous injection	Oral tablets
8.	**Duration of Action**	Long-acting (once daily or weekly formulations)	Shorter duration, requiring daily administration
9.	**Common Side Effects**	Nausea, vomiting, diarrhoea	Nasopharyngitis, headache, mild gastrointestinal symptoms
10.	**Effect on HbA1c**	Significant reduction (1-1.5%)	Moderate reduction (0.5-1%)

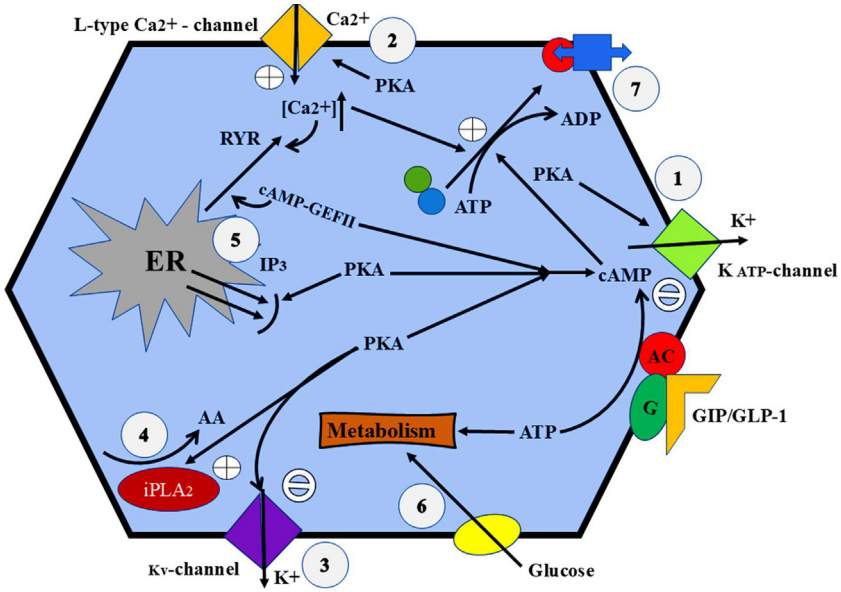

Fig. 4. GLP-1 and GIP connect to their receptors, activate adenylate cyclase, and increase cAMP, which activates PKA and cAMP-GEFII to secrete insulin. With glucose, this cascade closes KATP channels, depolarising the membrane and starting electrical activity. Extended action potentials increase Ca^{2+} influx, while Kv channel antagonism and iPLA2 activation boost excitability and arachidonic acid synthesis. Ca^{2+}- induced release increases intracellular Ca^{2+} reserves, promoting mitochondrial ATP production for exocytosis. Elevated cAMP promotes granule mobilisation, making more insulin available for release, accounting for most insulinotropic activity.[49]

5. Sensing Pathways and Activation Mechanisms

5.1. L-cell activation via lipid and SCFA sensing pathways: importance of GPCRs on GLP-1 secretion

Although dietary lipid byproducts are believed to be detected by G protein coupled receptors (GPCRs), there is no evidence that they affect L-cell electrical activity. Lipid signalling in L-cells has been associated with many GPCRs, including GPR120,[50] GPR119, and FFAR1 (GPR40).[51] In response to medium-chain and long-chain fatty[52,53] acids, FFAR1 and GPR120 activate phospholipase C, which in turn triggers IP3-mediated Ca2+ release and peptide secretion.[54] These receptors are believed to be Gq-coupled. Lipases convert triglycerides into 2-monoacylglycerols, which are another type of lipid that accumulates in the intestine after a meal. These ligands bind to the GPR119 receptor, which is present in both K-cells and L-cells.[55-57] The Gs-coupled GPR119 is activated by ligand binding, which raises cAMP levels, activates adenylyl cyclase, and improves L-cell secretion.[58] There are alternative lipid sensing routes that have been discovered that are involved in GLP-1 secretion. These pathways include fatty acid transport protein

(FATP4) absorption[59] and activation of atypical protein kinase C.[60] Colon bacterial fermentation of dietary fibre or, less commonly, of non-absorbed carbohydrates produces short-chain fatty acids (SCFA). Through two GPCRs, FFAR2 and FFAR3, they may mediate a connection between fibre intake, the gut microbiome, and L-cells.[61,62] A Gq component appears to be absent from FFAR3, although FFAR2 can couple to both the Gq-signalling and Gi/o-signalling pathways.[63] It was found that SCFA generated Ca2+ transients in primary L-cells and that circulating GLP-1 levels and SCFA-dependent GLP-1 release in vitro were decreased in animals lacking FFAR2,[64] suggesting a role for FFAR2 in GLP-1 secretion.

5.2. Protein and amino acid digestion-induced GLP-1 release: mechanisms and receptors

Optimal digestion product size for secretion stimulation is unknown, despite the fact that protein digestion is a potent GLP-1 release stimulant. Experiments in vitro have demonstrated that a number of amino acids can increase GLP-1 secretion. One theory puts L-Gln's efficacy down to its capacity to increase cytoplasmic cAMP concentrations, possibly through activation of an as-yet-unidentified Gs-coupled GPCR,[65,66] while another suggests that it triggers membrane depolarisation via electrogenic Na+-dependent amino acid absorption. Whether a person is healthy, overweight, or diabetic, taking L-Gln with food will cause their bodies to secrete more GLP-1.[67] The sense of other luminal amino acids by enteroendocrine cells has been associated with GPCRs: phenylalanine by the CaSR and ornithine by GPRC6A.[68,69] There is less consensus regarding the receptors involved in the sensing of bigger protein digestion products, such as beef hydrolysate, however activation of mitogen-activated protein (MAP) kinases has been associated with this phenomenon.[70,71]

5.3. Effects of Progesterone, Bile Acids, and Bariatric Surgery on GLP-1 Secretion by Luminal Components

In addition to nutrition, other luminal components can promote GLP-1 production. It has been suggested that incretin secretion may be influenced by enteral progesterone, which activates receptors on plasma membranes.[72] One metabolic signal that bile acids help integrate is the secretion of fibroblast growth factor 15/19 from the distal intestines, which occurs downstream of the well-studied nuclear hormone receptor FXR.[73] However, it seems that bile acids activate the Gs-coupled receptor TGR5 (GPBAR) in L-cells, which in turn stimulates GLP-1 secretion.[74,75] Recent studies in humans have demonstrated that bile acid treatment improves glucose homeostasis and plasma GLP-1 levels.[76,77] The rise in plasma bile acid levels following bariatric surgery is intriguing, and the concomitant improvements in metabolic control may be due, in part, to bile acid driven GLP-1 production.[78]

6. Regulation and Therapeutic Strategies

6.1. Somatostatin and Gi-Coupled GPCRs Regulate Incretin Secretion in Enteroendocrine Cells

Not only do enteroendocrine cells have stimulatory pathways that enhance incretin secretion, but they also express GPCRs connected to inhibitory Gi proteins. For instance, somatostatin receptors that are Gi-coupled are expressed by K-cells and L-cells. In keeping with the involvement of a Gi-coupled signalling cascade, somatostatin reduces GLP-1 and GIP production and blocks forskolin-stimulated cAMP transients in enteroendocrine cell lines.[79] Patients treated with GLP-1 mimetics showed a suppression of GLP-1 secretion, which is likely explained by an enhanced somatostatin release route.[80] Evidence suggests that the Gi-coupled endocannabinoid receptor Cnr1 may have a role in controlling the release of incretin hormones. The secretion of GIP is specifically inhibited by Cnr1, a protein that is more highly expressed in K-cells compared to L-cells.[81] More and more evidence points to the fact that enteroendocrine cells get signals from a variety of sources, including nutrients eaten, components of the gut lumen, and other cells and tissues within the same kind of cell. Electrogenic pathways, which include the co-transport of Na+, and GPCRs and classical downstream G protein coupled pathways are both involved in these inputs. It is believed that by learning more about the physiological signalling mechanisms used by enteroendocrine cells in living organisms, we can find approaches to cure type 2 diabetes and obesity by targeting these cells specifically.

6.2. GLP-1 Mimetics, Endogenous Enteroendocrine Cell Activation, and Bariatric Surgery Mimicry for T2DM

The incretin axis is crucial for glucose homeostasis, and treatments that target this axis have shown great promise in the treatment of type 2 diabetes. Additional benefits, such as weight loss and cardioprotection, are offered by GLP-1 mimetics, which are licensed for the treatment of type 2 diabetes mellitus (T2DM), in contrast to inhibitors of dipeptidyl peptidase 4 (DPP4), which quickly deactivates circulating GLP-1.[82,83] On the other hand, therapies that aim to stimulate the body's own endogenous enteroendocrine cells may have the added advantage of stimulating multiple peptide release, which could lead to the activation of both insulinotropic and appetite suppressant pathways. The FFAR1, GPR119, and GPR120 are among the possible enteroendocrine targets that are presently being studied. One of these medications, TAK-875, which is an FFAR1 agonist, targets both pancreatic β-cells and L-cells. It effectively lowers blood sugar levels in people with type 2 diabetes, although GLP-1 may have a little role. For reasons that are still up for debate, GPR119 agonists shown promising efficacy in animal models but failed to exert their full incretin and glucose-lowering potential in humans.[84,85] Contrary to expectations, a dual-acting SGLT1/2 inhibitor has been demonstrated to increase GLP-1 and PYY levels in both diabetic rats and humans.[86] This action is similar to that of SGLT1 knockout and may be due to the fact that it feeds the gut microbiome and boosts SCFA production in the L-cell rich distal gut. Following certain types of bariatric surgery, there is a noticeable increase in post-prandial GLP-1 and PYY levels.[87] This is likely related to the enhanced supply of nutrients to the distal

intestine and has a significant impact on appetite and the resolution of type 2 diabetes.[88-90] A huge step forward in medicine would be to find a way to make medical treatments work like bariatric surgery.

6.3. Secretion, metabolism, and additive effects on insulin secretion of the incretin hormones GIP and GLP-1

Hence, it is quite probable that both of these hormone's function as incretin hormones. We have two hormones; why? While the density of the L-cells responsible for secreting GLP-1 is largest in the lower small intestine, it is likely that GIP is mostly secreted from the upper small intestine. Hence, the higher incretin hormone, GIP, would be preferentially activated by smaller loads of quickly absorbable nutrients, whereas the distal incretin, GLP-1, would also be activated by bigger meals containing more complex nutrients that require more digestive processing. This is in line with the results of experiments using alpha-glycosidase inhibitors, such acarbose, which push back the digestion and absorption of carbs in the upper intestines and shift nutrient transport to the lower parts of the gut. Because acarbose decreases GIP secretion while increasing GLP-1 secretion,[91] it may help diabetic people improve their glucose tolerance. In our study, we tested the effects of incretin hormone selectivity by intubating participants with either long (ileal) or short (duodenal) catheters and then injecting them with little amounts of glucose. Interestingly, investigations that did not appear in the published literature found that the GIP and GLP-1 responses to glucose instillation were nearly same whether it was administered proximally or distally. Reasons for this could include the widespread presence of cells that produce both GLP-1 and GIP in the small intestine and, more recently, the discovery that many endocrine cells in the gut of mammals, including humans, synthesise both hormones.[92] That being said, while GIP concentrations can rise to hundreds of picomoles per litre, GLP-1 concentrations seldom go over 50 pmol/l, even though a mixed meal would typically trigger the production of both peptides.[93] The concentrations of the physiologically active hormones GLP-1 and postprandial GIP are absent from the majority of published studies on the topic. The pervasive enzyme dipeptidyl-peptidase IV, or DPP-IV, is known to metabolise GIP and GLP-1 extensively and quickly, according to recent studies.[94,95] Enzyme inactivation occurs when the N-terminus of the molecule is cleaved by this enzyme. Actually, the metabolites (GLP-1 9-36 amide and GIP 3-42) may function as receptor antagonists.[96] Conversion may take place both within the blood vessels and when organs and tissues pass through them because the enzyme is present in both soluble plasma form and bound to endothelial surfaces.[97] The N-terminal degradation of the peptides should be easily detected by GLP-1 and GIP tests. However, the majority of published data comes from assays that do not distinguish between the intact and degraded versions, meaning that the results do not represent the quantities of bioactive hormones. In addition, the two hormones' sensitivity to DPP-IV is very different from one another. About half of the GIP that is injected survives, compared to just 10 to 20% of the exogenous GLP-1.[98] The clearance of intact GLP-1 from plasma surpasses cardiac output, suggesting that the peptide is destroyed at a rate that prevents steady state estimations of its metabolism, in contrast to intact GIP, which has a half-life of around 7 minutes. Similarly, compared to what was previously reported using non-discriminating assays, the postprandial plasma concentrations of both intact hormones are significantly lower.[99,100] When comparing intact GLP-1 (10-20 pmol/l) to intact GIP (up to 100 pmol/l), the former is significantly lower. Thus, substantially more physiologically active GIP than GLP-1 is present in plasma after a meal. However, it should be mentioned that the most accurate way to determine the hormone secretion rate is to use assays that respond with both the intact hormones and the products of DPP-IV degradation. This is because assays designed to detect intact hormones will miss the digested hormone molecules, which constitute a clearly variable fraction of the total secreted hormones, whereas non-discriminating assays will capture both forms thus capture the overall secretion rate. As a result of fast elimination from the body, especially in the kidneys, the half-lives of GIP metabolites are around 17 minutes and those of GLP-1 metabolites are 4 to 5 minutes.[101] Although it has a small function in the removal of the metabolites, the liver is primarily involved in the hormones' DPP-IV mediated metabolism.[102] As plasma glucose concentrations rise before and after a meal, the question of which hormone stimulates insulin release the most naturally emerges. While some studies indicated no difference in potency between the two hormones, others indicated that GLP-1 was three to five times stronger than GIP.[103,104] Multiple studies indicated that GIP did not stimulate insulin secretion at fasting glucose concentrations and had no effect at glucose concentrations below 8 mmol/l[105]. It was for this reason that we have now resolved to investigate the insulinotropic effects of the two hormones administered at doses that would elevate their physiological concentrations when they are undiluted. The infusions were administered with glucose concentrations clamped at fasting or slightly elevated levels to replicate the prandial condition as closely as feasible[106]. Both hormones demonstrated comparable and statistically significant insulinotropic effects at fasting glucose concentrations and 6 mmol/l in their physiological concentrations; however, GLP-1 was marginally more effective at 7 mmol/l. Since increases in their concentrations are observed as early as 5-10 minutes after a meal begins, it was shown that both hormones typically contribute to the incretin effect in humans. It appears that the two hormones have an additive effect when taken together. Therefore, the combined insulin response from GIP and GLP-1 infusions was around equal to the total of the two individual responses, even though they each produced around the same amount of insulin when administered alone. There has been recent success in creating mice that lack both the GIP and GLP-1 receptors. Initial findings in these animals also support the idea that the two hormones had additive effects; specifically, the combination deletion had additive effects on glucose tolerance when compared to the individual receptor knockouts[107].

7. Conclusion

Our knowledge of glucose control and the therapeutic potential of incretin hormones, especially GLP-1 and GIP, in the management of type 2 diabetes has been greatly enhanced by the research of these hormones. Insulin secretion, hunger regulation, and cardioprotection are just a few of the many functions performed by these hormones. Treatments based on incretins, like those that

bind to the GLP-1 receptor and those that block the dipeptidyl peptidase-4, are showing great promise in the quest for improved glucose management and cardiovascular safety. Even though β-cell resistance is a hurdle, improving therapy outcomes can be achieved by delving further into the pathways that control incretin release, such as glucose, lipid, and amino acid sensing. Key approaches in this review based on treating and resolving the difficulties of Type 2 diabetes include innovative pharmaceutical strategies targeting the incretin axis, such as GLP-1 mimetics and bariatric surgery mimics.

8. Future Directions

To enhance the clinical utility of incretin-based therapies, it is imperative to address several pressing challenges in the field of T2D management (10.3803/EnM.2024.1940.). First, persistent β-cell resistance remains a central issue. Although GLP-1 and GIP can potentiate insulin secretion in healthy individuals, studies show that up to 70% of T2D patients exhibit impaired β-cell responsiveness to GIP, and partial resistance to GLP-1 increases with disease progression. This reduces the efficacy of incretin-based agents over time and necessitates strategies that improve or bypass this resistance (10.1084/jem.20171965.). Second, while GLP-1 receptor agonists (GLP-1RAs) have demonstrated cardiovascular benefits in large outcome trials such as LEADER (liraglutide) and SUSTAIN-6 (semaglutide), DPP-4 inhibitors have consistently failed to show significant reductions in major adverse cardiovascular events (MACE). For example, the TECOS trial on sitagliptin showed no superiority over placebo in reducing MACE. This highlights the need for more metabolically comprehensive agents (10.3389/fendo.2018.00324.). Third, there is growing evidence of heterogeneous patient responses to incretin therapies, influenced by genetic polymorphisms (e.g., TCF7L2 variants), gut microbiota composition, and obesity-related metabolic dysfunction (10.1111/dom.13869.). This reinforces the need for precision medicine approaches that can predict and tailor incretin response, thereby maximizing therapeutic benefit and minimizing cost. Fourth, mimicking the effects of bariatric surgery pharmacologically remains a critical unmet goal. Bariatric procedures (e.g., Roux-en-Y gastric bypass) result in 3–5-fold increases in GLP-1 and PYY levels and achieve T2D remission in up to 80% of patients, according to the STAMPEDE trial (10.1177/1932296818778607.). However, current drugs do not fully replicate this hormonal environment. Dual (e.g., tirzepatide) and triple receptor agonists (targeting GLP-1, GIP, and glucagon) are being investigated to fill this translational gap (10.1080/00325481.2022.2147326.).

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Abrar Ahmad Zargar contributed to research conceptualization, writing, and revision. Vipasha Mehta was responsible for literature collection and screening. Rishikesh Gupta conducted data analysis and interpretation. Kishwor Bhandari undertook article design. Mahesh Kumar Posa provided guidance on key arguments. T. Sri Ramya performed academic review. D. Snigdha participated in data analysis. Vijayakumar B assisted in literature collection. Mukesh Chandra Sharma contributed to research conceptualization. P. Balaji was involved in article revision. Sudhanshu Kumar Jha was responsible for article conceptualization and overall supervision. All authors read and approved the final manuscript.

Data availability statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgement

None.

References

1. Drucker DJ, Holst JJ. The expanding incretin universe: from basic biology to clinical translation. *Diabetologia*. 2023;66(10):1765–1779.
2. Holst JJ, Gasbjerg LS, Rosenkilde MM. The role of incretins on insulin function and glucose homeostasis. *Endocrinology*. 2021;162(7) bqab065.
3. https://en.wikipedia.org/wiki/Incretin. Assessed on 13 April, 2024.
4. Tandon N. Incretins: An Introduction.
5. Rehfeld JF. The origin and understanding of the incretin concept. *Front Endocrinol*. 2018;9:398523.
6. Michałowska J, Miller-Kasprzak E, Bogdański P. Incretin hormones in obesity and related cardiometabolic disorders: the clinical perspective. *Nutrients*. 2021;13(2):351.

7. Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. *Diabetes, Obesity Metab*. 2018;20:5–21.
8. Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. *Cell Metab*. 2018;27(4):740–756.
9. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev*. 2007;87(4):1409–1439.
10. Vilsbøll T, Holst JJ. Incretins, insulin secretion and type 2 diabetes mellitus. *Diabetologia*. 2004;47:357–366.
11. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834–1844.
12. 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(9548):1696–1705.
13. Hayes MR, De Jonghe BC, Kanoski SE. Role of the glucagon-like-peptide-1 receptor in the control of energy balance. *Physiol Behav*. 2010;100(5):503–510.
14. Meier JJ, Nauck MA. Incretins and the development of type 2 diabetes. *Current Diabetes Rep*. 2006;6(3):194–201.
15. Hayes MR, Skibicka KP, Grill HJ. Caudal brainstem processing is sufficient for behavioral, sympathetic, and parasympathetic responses driven by peripheral and hindbrain glucagon-like-peptide-1 receptor stimulation. *Endocrinology*. 2008;149(8):4059–4068.
16. Ussher JR, Drucker DJ. Cardiovascular actions of incretin-based therapies. *Circ Res*. 2014;114(11):1788–1803.
17. Baggio LL. *The role of incretin hormones in glucose homeostasis* (Doctoral dissertation).
18. Sanusi H. The role of incretin on diabetes mellitus. *Acta Med Indones*. 2009;41(4):205–212.
19. Freeman JS. The pathophysiologic role of incretins. *J Osteopathic Med*. 2007;107(s3):6–9.
20. Holst JJ, Gribble F, Horowitz M, Rayner CK. Roles of the gut in glucose homeostasis. *Diabetes care*. 2016;39(6):884–892.
21. Ahrén B. Incretin dysfunction in type 2 diabetes: clinical impact and future perspectives. *Diabetes Metab*. 2013;39(3):195–201.
22. Toft-Nielsen MB, Damholt MB, Madsbad S, Hilsted LM, Hughes TE, Michelsen BK, Holst JJ. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2001;86(8):3717–3723.
23. Vilsbøll T, Krarup T, Madsbad S, Holst J. Defective amplification of the late phase insulin response to glucose by GIP in obese Type II diabetic patients. *Diabetologia*. 2002;45:1111–1119.
24. Nauck MA, Heimesaat MM, Behle KA, Holst JJ, Nauck MS, Ritzel R, Hüfner M, Schmiegel WH. 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(3):1239–1246.
25. Baggio LL, Drucker DJ. Therapeutic approaches to preserve islet mass in type 2 diabetes. *Annu Rev Med*. 2006;57(1):265–281.
26. Gribble FM, Williams L, Simpson AK, Reimann F. A novel glucose-sensing mechanism contributing to glucagon-like peptide-1 secretion from the GLUTag cell line. *Diabetes*. 2003;52:1147–1154 [DOI] [PubMed] [Google Scholar]; This study uses pharmacological and genetic approaches to show that SGLT1 is required for glucose-stimulated GLP-1 secretion and Ca^{2+} transients in L-cells. The study suggests that glucose-mediated GLP-1 secretion is mediated by electrogenic Na^{+}-coupled pathways rather than metabolic pathways. doi:10.2337/diabetes.52.5.1147.
27. Parker HE, Adriaenssens A, Rogers G, Richards P, Koepsell H, Reimann F. Predominant role of active versus facilitative glucose transport for glucagon-like peptide-1 secretion. *Diabetologia*. 2012;55:2445–2455 [DOI] [PMC free article] [PubMed] [Google Scholar]; This study characterises the role of SGLT1 in glucose absorption and incretin release using *Sglt1−/−* mice. The study shows that SGLT1 is expressed in K-cells and L-cells that SGLT1 is required for glucose-stimulated incretin release, confirming the role of electrogenic pathways in incretin secretion. doi:10.1007/s00125-012-2585-2.
28. Gorboulev V, Schurmann A, Vallon V, Kipp H, Jaschke A, Klessen D. Na(+)-d-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. *Diabetes*. 2012;61:187–196 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.2337/db11-1029.
29. Powell DR, Smith M, Greer J, Harris A, Zhao S, DaCosta C. LX4211 increases serum glucagon-like peptide 1 and peptide YY levels by reducing sodium/glucose cotransporter 1 (SGLT1)-mediated absorption of intestinal glucose. *J Pharmacol Exp Ther*. 2013;345:250–259 [DOI] [PubMed] [Google Scholar]. doi:10.1124/jpet.113.203364.
30. Powell DR, DaCosta CM, Gay J, Ding ZM, Smith M, Greer J. Improved glycemic control in mice lacking Sglt1 and Sglt2. *Am J Physiol Endocrinol Metab*. 2013;304:E117–E130 [DOI] [PubMed] [Google Scholar]. doi:10.1152/ajpendo.00439.2012.
31. Stephens JW, Bodvarsdottir TB, Wareham K, Prior SL, Bracken RM, Lowe GD. Effects of short-term therapy with glibenclamide and repaglinide on incretin hormones and oxidative damage associated with postprandial hyperglycaemia in people with type 2 diabetes mellitus. *Diabetes Res Clin Pract*. 2011;94:199–206 [DOI] [PubMed] [Google Scholar]. doi:10.1016/j.diabres.2011.07.014.
32. Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proc Natl Acad Sci U S A*. 2007;104:15069–15074 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.1073/pnas.0706890104.
33. Margolskee RF, Dyer J, Kokrashvili Z, Salmon KS, Ilegems E, Daly K. T1R3 and gustducin in gut sense sugars to regulate expression of Na+-glucose cotransporter 1. *Proc Natl Acad Sci U S A*. 2007;104:15075–15080 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.1073/pnas.0706678104.
34. Young RL, Chia B, Isaacs NJ, Ma J, Khoo J, Wu T. Disordered control of intestinal sweet taste receptor expression and glucose absorption in type 2 diabetes. *Diabetes*. 2013;62:3532–3541 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.2337/db13-0581.
35. Fujita Y, Wideman RD, Speck M, Asadi A, King DS, Webber TD. Incretin release from gut is acutely enhanced by sugar but not by sweeteners in vivo. *Am J Physiol Endocrinol Metab*. 2009;296:E473–E479 [DOI] [PubMed] [Google Scholar]. doi:10.1152/ajpendo.90636.2008.
36. Ma J, Bellon M, Wishart JM, Young R, Blackshaw LA, Jones KL. Effect of the artificial sweetener, sucralose, on gastric emptying and incretin hormone release in healthy subjects. *Am J Physiol Gastrointest Liver Physiol*. 2009;296:G735–G739 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.1152/ajpgi.90708.2008.
37. Petrie JR. The cardiovascular safety of incretin-based therapies: a review of the evidence. *Cardiovasc Diabetology*. 2013;12:1–2.
38. White J. Efficacy and safety of incretin-based therapies: clinical trial data. *J Am Pharm Assoc*. 2009;49(5):S30–S40.
39. Russell S. Incretin-based therapies for type 2 diabetes mellitus: a review of direct comparisons of efficacy, safety and patient satisfaction. *Int J Clin Pharm*. 2013;35:159–172.
40. Drucker DJ. The biology of incretin hormones. *Cell Metab*. 2006;3(3):153–165.
41. Ahrén B. DPP-4 inhibitors—clinical data and clinical implications. *Diabetes care*. 2007;30(6):1344–1350.
42. Nauck MA. Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. *Am j med*. 2011;124(1):S3–18.
43. Neumiller JJ, Wood L, Campbell RK. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes mellitus. *Pharmacother: J Hu Pharmacol Drug Ther*. 2010;30(5):463–484.
44. Nisal K, Kela R, Khunti K, Davies MJ. Comparison of efficacy between incretin-based therapies for type 2 diabetes mellitus. *BMC med*. 2012;10.
45. Gamble JM, Thomas JM, Twells LK, Midodzi WK, Majumdar SR. Comparative effectiveness of incretin-based therapies and the risk of death and cardiovascular events in 38,233 metformin monotherapy users. *Medicine*. 2016;95(26):e3995.
46. Rigato M, Fadini GP. Comparative effectiveness of liraglutide in the treatment of type 2 diabetes. *Diabetes, Metab Syndr Obes: Targets Ther*. 2014:107–120.
47. Levin PA, Nguyen H, Wittbrodt ET, Kim SC. Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research. *Diabetes, Metab Syndr Obes: Targets Ther*. 2017;4:123–139.
48. Gromada J, Holst JJ, and Rorsman P. Cellular regulation of islethormone secretion by the incretin hormone glucagon-like peptide 1.Pflu¨gers Arch 435: 583–594, 1998.
49. Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, Yamada M. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nat Med*. 2005;11:90–94 [DOI] [PubMed] [Google Scholar]. doi:10.1038/nm1168.
50. Edfalk S, Steneberg P, Edlund H. Gpr40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. *Diabetes*. 2008;57:2280–2287 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.2337/db08-0307.
51. Lauffer LM, Iakoubov R, Brubaker PL. GPR119 is essential for oleoylethanolamide-induced glucagon-like peptide-1 secretion from the intestinal enteroendocrine L-cell. *Diabetes*. 2009;58:1058–1066 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.2337/db08-1237.
52. Chu ZL, Carroll C, Alfonso J, Gutierrez V, He H, Lucman A. A role for intestinal endocrine cell-expressed g protein-coupled receptor 119 in glycemic control by

enhancing glucagon-like Peptide-1 and glucose-dependent insulinotropic Peptide release. *Endocrinology*. 2008;149:2038–2047 [DOI] [PubMed] [Google Scholar]. doi:10.1210/en.2007-0966.
53. Hara T, Hirasawa A, Ichimura A, Kimura I, Tsujimoto G. Free fatty acid receptors FFAR1 and GPR120 as novel therapeutic targets for metabolic disorders. *J Pharm Sci*. 2011;100:3594–3601 [DOI] [PubMed] [Google Scholar]; First demonstration that GPR119 is activated by monoacyl-glycerol, thus providing a possible direct link between triglyceride digestion and GLP-1 secretion independent of free fatty acids. doi:10.1002/jps.22639.
54. Reimann F, Habib AM, Tolhurst G, Parker HE, Rogers GJ, Gribble FM. Glucose sensing in L cells: a primary cell study. *Cell Metab*. 2008;8:532–539 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.1016/j.cmet.2008.11.002.
55. Parker HE, Habib AM, Rogers GJ, Gribble FM, Reimann F. Nutrient-dependent secretion of glucose-dependent insulinotropic polypeptide from primary murine K cells. *Diabetologia*. 2009;52:289–298 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.1007/s00125-008-1202-x.
56. Cox HM, Tough IR, Woolston AM, Zhang L, Nguyen AD, Sainsbury A. Peptide YY is critical for acylethanolamine receptor Gpr119-induced activation of gastrointestinal mucosal responses. *Cell Metab*. 2010;11:532–542 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.1016/j.cmet.2010.04.014.
57. Poreba MA, Dong CX, Li SK, Stahl A, Miner JH, Brubaker PL. Role of fatty acid transport protein 4 in oleic acid-induced glucagon-like peptide-1 secretion from murine intestinal L cells. *Am J Physiol Endocrinol Metab*. 2012;303:E899–E907 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.1152/ajpendo.00116.2012.
58. Iakoubov R, Ahmed A, Lauffer LM, Bazinet RP, Brubaker PL. Essential role for protein kinase Cζ in oleic acid-induced glucagon-like peptide-1 secretion in vivo in the rat. *Endocrinology*. 2011;152:1244–1252 [DOI] [PubMed] [Google Scholar]. doi:10.1210/en.2010-1352.
59. Freeland KR, Wilson C, Wolever TM. Adaptation of colonic fermentation and glucagon-like peptide-1 secretion with increased wheat fibre intake for 1 year in hyperinsulinaemic human subjects. *Br J Nutr*. 2010;103:82–90 [DOI] [PubMed] [Google Scholar]. doi:10.1017/S0007114509991462.
60. Everard A, Lazarevic V, Derrien M, Girard M, Muccioli GG, Muccioli GM. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice. *Diabetes*. 2011;60:2775–2786 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.2337/db11-0227.
61. Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D. The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J Biol Chem*. 2003;278:11312–11319 [DOI] [PubMed] [Google Scholar]; This study shows that SCFA stimulate GLP-1 release through the GPCR FFAR2 and triggers elevations in intracellular Ca^{2+} levels in L-cells. This report reveals a mechanism by which gut microbiota may influence food intake and metabolism. doi:10.1074/jbc.M211609200.
62. Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E. Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes*. 2012;61:364–371 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.2337/db11-1019.
63. Reimann F, Williams L, da Silva, Xavier G, Rutter GA, Gribble FM. Glutamine potently stimulates glucagon-like peptide-1 secretion from GLUTag cells. *Diabetologia*. 2004;47:1592–1601 [DOI] [PubMed] [Google Scholar]. doi:10.1007/s00125-004-1498-0.
64. Tolhurst G, Zheng Y, Parker HE, Habib AM, Reimann F, Gribble FM. Glutamine triggers and potentiates glucagon-like peptide-1 secretion by raising cytosolic Ca2+ and cAMP. *Endocrinology*. 2011;152:405–413 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.1210/en.2010-0956.
65. Greenfield JR, Farooqi IS, Keogh JM, Henning E, Habib AM, Blackwood A. Oral glutamine increases circulating glucagon-like peptide 1, glucagon, and insulin concentrations in lean, obese, and type 2 diabetic subjects. *Am J Clin Nutr*. 2009;89:106–113 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.3945/ajcn.2008.26362.
66. Oya M, Kitaguchi T, Pais R, Reimann F, Gribble F, Tsuboi T. The G protein-coupled receptor family C Group 6 Subtype A (GPRC6A) receptor is involved in amino acid-induced glucagon-like Peptide-1 secretion from GLUTag cells. *J Biol Chem*. 2013;288:4513–4521 [DOI] [PMC free article] [PubMed] [Google Scholar]. doi:10.1074/jbc.M112.402677.
67. Mace OJ, Schindler M, Patel S. The regulation of K- and L-cell activity by GLUT2 and the calcium-sensing receptor CasR in rat small intestine. *J Physiol*. 2012;590:2917–2936 [DOI] [PMC free article] [PubMed. doi:10.1113/jphysiol.2011.223800.
68. Reimer RA, Darimont C, Gremlich S, Nicolas-Metral V, Ruegg UT, Mace K. A human cellular model for studying the regulation of glucagon-like peptide-1 secretion. *Endocrinology*. 2001;142:4522–4528. doi:10.1210/endo.142.10.8415.
69. Cordier-Bussat M, Bernard C, Levenez F, Klages N, Laser-Ritz B, Philippe J. Peptones stimulate both the secretion of the incretin hormone glucagon-like peptide 1 and the transcription of the proglucagon gene. *Diabetes*. 1998;47:1038–1045. doi:10.2337/diabetes.47.7.1038.
70. Flock GB, Cao X, Maziarz M, Drucker DJ. Activation of enteroendocrine membrane progesterone receptors promotes incretin secretion and improves glucose tolerance in mice. *Diabetes*. 2013;62:283–290. doi:10.2337/db12-0601.
71. Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. *Cell Metab*. 2005;2:217–225. doi:10.1016/j.cmet.2005.09.001.
72. Parker HE, Wallis K, le Roux CW, Wong KY, Reimann F, Gribble FM. Molecular mechanisms underlying bile acid-stimulated glucagon-like peptide-1 secretion. *Br J Pharmacol*. 2012;165:414–423. doi:10.1111/j.1476-5381.2011.01561.x.
73. Thomas C, Gioiello A, Noriega L, Strehle A, Oury J, Rizzo G. TGR5-mediated bile acid sensing controls glucose homeostasis. *Cell Metab*. 2009;10:167–177. doi:10.1016/j.cmet.2009.08.001.
74. Wu T, Bound MJ, Standfield SD, Jones KL, Horowitz M, Rayner CK. Effects of taurocholic acid on glycemic, glucagon-like peptide-1, and insulin responses to small intestinal glucose infusion in healthy humans. *J Clin Endocrinol Metab*. 2013;98:E718–E722. doi:10.1210/jc.2012-3961.
75. Adrian TE, Gariballa S, Parekh KA, Thomas SA, Saadi H, Al Kaabi J. Rectal taurocholate increases L cell and insulin secretion, and decreases blood glucose and food intake in obese type 2 diabetic volunteers. *Diabetologia*. 2012;55:2343–2347. doi:10.1007/s00125-012-2593-2.
76. Moss CE, Marsh WJ, Parker HE, Ogunnowo-Bada E, Riches CH, Habib AM. Somatostatin receptor 5 and cannabinoid receptor 1 activation inhibit secretion of glucose-dependent insulinotropic polypeptide from intestinal K cells in rodents. *Diabetologia*. 2012;55:3094–3103. doi:10.1007/s00125-012-2663-5.
77. Reimann F, Tolhurst G, Gribble FM. G-protein-coupled receptors in intestinal chemosensation. *Cell Metab*. 2012;15:421–431. doi:10.1016/j.cmet.2011.12.019.
78. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013;381:117–124. doi:10.1016/S0140-6736(12)61267-7.
79. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013;381:117–124. doi:10.1016/S0140-6736(12)61267-7.
80. Gejl M, Sondergaard HM, Stecher C, Bibby BM, Moller N, Botker HE. Exenatide alters myocardial glucose transport and uptake depending on insulin resistance and increases myocardial blood flow in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2012;97:E1165–E1169. doi:10.1210/jc.2011-3456.
81. Habib AM, Richards P, Rogers GJ, Reimann F, Gribble FM. Co-localisation and secretion of glucagon-like peptide 1 and peptide YY from primary cultured human L cells. *Diabetologia*. 2013;56:1413–1416. doi:10.1007/s00125-013-2887-z.
82. Katz LB, Gambale JJ, Rothenberg PL, Vanapalli SR, Vaccaro N, Xi L. Effects of JNJ-38431055, a novel GPR119 receptor agonist, in randomized, double-blind, placebo-controlled studies in subjects with type 2 diabetes. *Diabetes, Obesity Metab.*. 2012;14:709–716. doi:10.1111/j.1463-1326.2012.01587.x.
83. Zambrowicz B, Freiman J, Brown PM, Frazier KS, Turnage A, Bronner J. LX4211, a dual SGLT1/SGLT2 inhibitor, improved glycemic control in patients with type 2 diabetes in a randomized, placebo-controlled trial. *Clin Pharmacol Ther*. 2012;92:158–169. doi:10.1038/clpt.2012.58.
84. Dirksen C, Hansen DL, Madsbad S, Hvolris LE, Naver LS, Holst JJ. Postprandial diabetic glucose tolerance is normalized by gastric bypass feeding as opposed to gastric feeding and is associated with exaggerated GLP-1 secretion: a case report. *Diabetes Care*. 2010;33:375–377. doi:10.2337/dc09-1374.
85. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med*. 2009;122:248–256. doi:10.1016/j.amjmed.2008.09.041.e5.
86. Rizzello M, Abbatini F, Casella G, Alessandri G, Fantini A, Leonetti F. Early postoperative insulin-resistance changes after sleeve gastrectomy. *Obes Surg*. 2010;20:50–55. doi:10.1007/s11695-009-0017-2.
87. Jørgensen NB, Dirksen C, Bojsen-Møller KN, Jacobsen SH, Worm D, Hansen DL. The exaggerated glucagon-like peptide-1 response is important for the improved β-cell function and glucose tolerance after Roux-en-Y gastric bypass in patients with type 2 diabetes. *Diabetes*. 2013. doi:10.2337/db13-0022.
88. Qualmann C, Nauck MA, Holst JJ, Orskov C, Creutzfeldt W. Glucagon-like peptide 1 (7–36 amide) secretion in response to luminal sucrose from the upper and lower gut. A study using alpha-glucosidase inhibition (acarbose). *Scand J Gastroenterol*. 1995;30:892–896.
89. Mortensen K, Christensen LL, Holst JJ, Orskov C. GLP-1 and GIP are colocalized in a subset of endocrine cells in the small intestine. *Regul Pept*. 2003;114:189–196.

90. Orskov C, Wettergren A, Holst JJ. Secretion of the incretin hormones glucagon-like peptide-1 and gastric inhibitory polypeptide correlates with insulin secretion in normal man throughout the day. *Scand J Gastroenterol*. 1996;31:665–670.
91. Kieffer TJ, McIntosh CH, Pederson RA. Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-like peptide 1 in vitro and in vivo by dipeptidyl peptidase IV. *Endocrinology*. 1995;136:3585–3596.
92. Deacon CF, Nauck MA, Meier J, Hucking K, Holst JJ. Degradation of endogenous and exogenous gastric inhibitory polypeptide in healthy and in type 2 diabetic subjects as revealed using a new assay for the intact peptide. *J Clin Endocrinol Metab*. 2000;85:3575–3581.
93. Gault VA, Parker JC, Harriott P, Flatt PR, O'Harte FP. Evidence that the major degradation product of glucose-dependent insulinotropic polypeptide, GIP(3–42), is a GIP receptor antagonist in vivo. *J Endocrinol*. 2002;175:525–533.
94. Mentlein R. Dipeptidyl-peptidase IV (CD26)—role in the inactivation of regulatory peptides. *Regul Pept*. 1999;85:9–24.
95. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects. *Diabetes*. 1995;44:1126–1131.
96. Vilsboll 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.
97. Vilsboll T, Krarup T, Sonne J, Madsbad S, Volund A, Juul AG, et al. Incretin secretion in relation to meal size and body weight in healthy subjects and people with type 1 and type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2003;88:2706–2713.
98. Vilsboll T, Agersoe H, Krarup T, Holst JJ. Similar elimination rates of GLP-1 in obese type diabetic patients and healthy subjects. *J Clin Endocrinol Metab*. 2003;88:220–224.
99. Deacon CF, Danielsen P, Klarskov L, Olesen M, Holst JJ. Dipeptidyl peptidase IV inhibition reduces the degradation and clearance of GIP and potentiates its insulinotropic and antihyperglycemic effects in anesthetized pigs. *Diabetes*. 2001;50:1588–1597.
100. Nauck MA, Bartels E, Orskov 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.
101. Toft-Nielsen M, Madsbad S, Holst JJ. Exaggerated secretion of glucagon-like peptide-1 (GLP-1) could cause reactive hypoglycaemia. *Diabetologia*. 1998;41:1180–1186.
102. Krarup T, Saurbrey N, Moody AJ, Kuhl C, Madsbad S. Effect of porcine gastric inhibitory polypeptide on beta-cell function in type I and type II diabetes mellitus. *Metabolism*. 1987;36:677–682.
103. Vilsboll 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.
104. Preitner F, Burcelin R, Ibberson M, Hansotia T, Drucker D, Thorens B. Disruption of both GLP-1 and GIP signalling pathways in the mouse leads to glucose intolerance. *Diabetes*. 2002;51:A66 [Suppl 2].