

Differentiating Incretin Therapies Based on Structure, Activity, and Metabolism: Focus on Liraglutide

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The incretin effect, mediated by glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), plays an important role in the regulation of insulin secretion in response to oral glucose. The discovery of deficiencies in incretin pathways associated with development of type 2 diabetes mellitus has propelled the growth of incretin-based therapies in patients with this disease. The basic rationale for incretin-based therapies, including both GLP-1-receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors is reviewed, focusing on their roles in glucose regulation and potential therapeutic benefits. Increased awareness of the differences among incretin mimetics, GLP-1 analogs, and DPP-4 inhibitors, including their structures, half-lives, dosages, hemoglobin A_{1c}-lowering capacities, effects on weight, and adverse events will help shape the future of these therapeutic agents. Improved understanding of the mechanism of action and clinical effects of incretin-based therapies will help advance their appropriate use within clinical practice.

Key Words: liraglutide, incretin therapies, type 2 diabetes mellitus.
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Maintenance of normoglycemia is a complicated process that involves signaling by means of many regulatory hormones throughout the body. In particular, a balanced relationship between the actions of insulin and glucagon need to be maintained through β -cell production of insulin and α -cell production of glucagon in response to plasma glucose levels.¹ The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), are released in response to food ingestion to stimulate insulin secretion and, in the case of GLP-1, to inhibit glucagon secretion, thereby decreasing glucose production by the liver in a counterregulatory manner.^{2,3}

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Pancreatic islet dysfunction associated with type 2 diabetes mellitus results in failure of β cells to secrete an adequate quantity of insulin to maintain normoglycemia. At the same time, inappropriately high hepatic glucose output results from continued glucagon production by α cells, which contributes to fasting hyperglycemia.¹ In patients with type 2 diabetes, the incretin effects of GLP-1 and GIP are greatly diminished, as demonstrated by decreased secretion of GLP-1 and impaired insulintropic action of GIP. The discovery of deficiencies associated with the incretin pathways in type 2 diabetes led to the development of incretin-based therapies, including GLP-1-receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. The incretin mimetic, exenatide, and the human GLP-1 analog, liraglutide (as well as others in clinical development), interact with the GLP-1 receptor to promote insulin and block glucagon secretion. The DPP-4 inhibitors block degradation of native GLP-1 and GIP resulting in increased half-lives of GLP-1 and GIP.^{4,5}

Physiologic Actions of Incretins

Components of the Incretin System

Described in 1964, the incretin effect involves release of gastrointestinal hormones with the ability to stimulate insulin secretion as observed in response to glucose.⁶ This glucose-dependent insulin secretion by intestinally derived hormones was found to be more effective at releasing insulin in response to oral glucose compared with intravenously infused glucose.⁶ Subsequently, most of the incretin effect has been found to be mediated by two incretin hormones, GLP-1 and GIP. Glucagon-like peptide-1 is transcribed from the proglucagon gene that is expressed in the α cells of the pancreas and L cells of the intestine. In the intestine, this gene produces proglucagon that is then cleaved to produce GLP-1 and GLP-2.⁴ Glucose-dependent insulinotropic polypeptide is a 42-amino acid peptide that is secreted from specific endocrine cells (K cells) found throughout the small intestine.⁴

Although not specifically classified as an incretin, DPP-4 plays an important role within the incretin system by actively degrading both GLP-1 and GIP, resulting in relatively short half-

lives (~2 min) of both molecules. Dipeptidyl peptidase-4 is a serine peptidase that can be found in multiple sites, including the kidneys, intestinal membranes, hepatocytes, and vascular endothelium, and circulating in plasma and leukocytes.^{7,8} The presence of alanine at position 2 in the structure of both molecules makes them excellent substrates for DPP-4.⁵ Inhibition of DPP-4 results in increased levels of active GLP-1, which enhances insulin secretion and improves glucose tolerance.^{7,9}

Involvement of Incretins in Glucose Metabolism

Normal glucose metabolism is maintained by the two counterregulatory hormones, insulin and glucagon.¹ The incretins, GIP and GLP-1, are released in response to oral glucose and act together to promote the insulin response and decrease glucagon. Insulinogenic activity of GLP-1 and GIP is due to interaction with their respective receptors.⁴ The GLP-1 receptor is expressed on α and β cells of the pancreas, as well as in peripheral tissues such as the nervous system, heart, kidney, lung, and gastrointestinal tract, whereas the GIP receptor is predominantly expressed on islet β cells and to some extent in

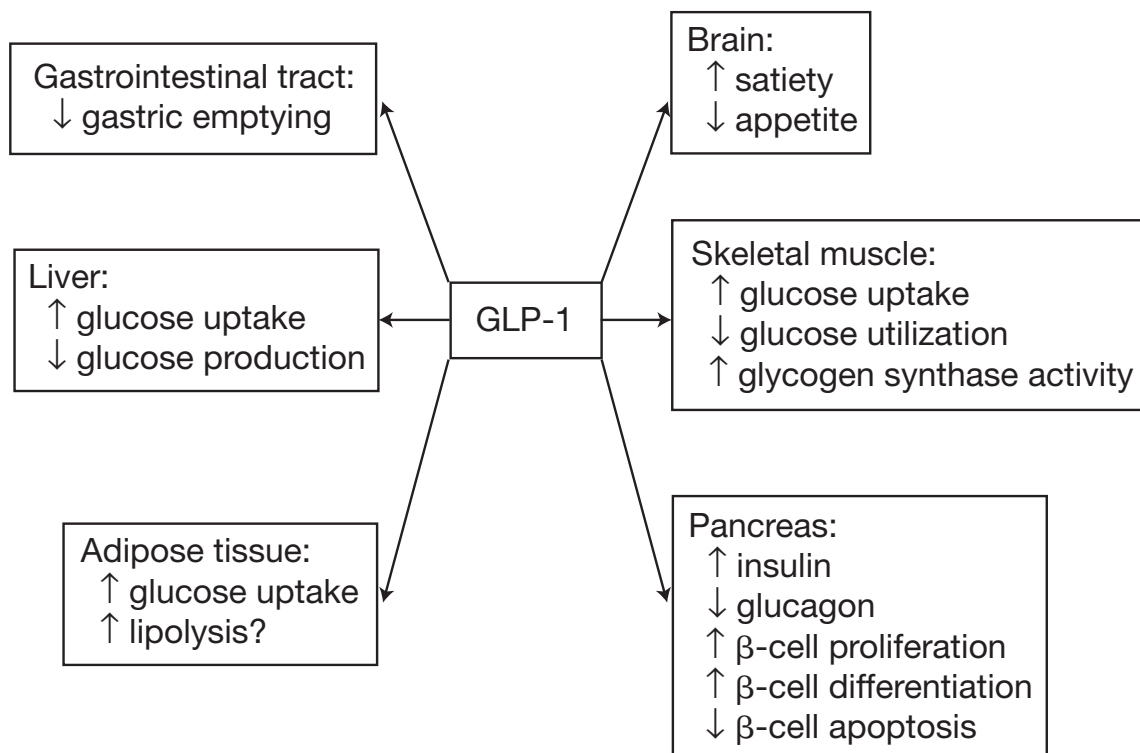


Figure 1. Glucose-lowering actions of glucagon-like peptide-1 (GLP-1) in pancreatic and extrapancreatic tissues. (Adapted with permission from reference 14.)

adipose tissue and the central nervous system.⁵

Signaling pathways following GLP-1- and GIP-receptor activation have been described and include elevation of cyclic adenosine monophosphate (cAMP) and intracellular calcium levels, resulting in exocytosis of insulin-containing granules.¹⁰⁻¹² Activation of the GLP-1 receptor alone may account for up to 70% of insulin secretion.⁴ Although the mechanisms have not all been clearly defined, several other effects mediated by GLP-1 have been characterized, including increased β -cell protection, decreased levels of plasma glucagon, delayed gastric emptying, and enhanced satiety and reduced food intake (Figure 1).^{2, 13, 14}

Effects of Incretins on β Cells

The incretins have been found to play an important role in maintaining β -cell mass by stimulating growth and proliferation of pancreatic β cells as well as by preventing β -cell apoptosis in a variety of animal models and in vitro systems.^{2, 14} Both GLP-1 and GIP have the potential to promote β -cell replication and differentiation according to evidence demonstrating receptor activity during embryonic development and from in vitro studies.¹⁴ Both GLP-1 and GIP were found to act as growth factors for β -cell replication by means of cAMP-protein kinase A, p42 mitogen-activated protein kinase, and phosphoinositol 3-kinase signaling pathways, as identified using the β -cell line INS-1 and primary islet cultures.¹⁵⁻¹⁷ The antiapoptotic action of GLP-1 has been demonstrated in various animal models and in cultured human islets.^{18, 19} The role of GLP-1 in the prevention of β -cell apoptosis has clinical implications for the preservation of β -cell mass and function in the context of patients with type 2 diabetes, as they experience progressive deterioration of β -cell function through the course of their disease.¹⁸

Role of the Incretin System in Type 2 Diabetes

Common physiologic defects associated with the progression of type 2 diabetes include development of insulin resistance and ultimate β -cell failure. These defects coupled with impaired incretin effects observed in patients with type 2 diabetes may contribute to glucose intolerance and hyperglycemia. Early studies found that the incretin effect was decreased in patients with type 2 diabetes compared with healthy controls.²⁰ However, this could not be correlated with GIP

levels in response to oral glucose, which were generally found to be similar to healthy controls.^{20, 21} In contrast, it was found that meal-stimulated GLP-1 secretion is severely impaired in patients with type 2 diabetes.²¹

Defects in the activity of the hormones may also explain the observed impaired incretin activity. One study found that GIP does not stimulate insulin secretion in patients with type 2 diabetes at the same level as in healthy controls.²² In the same study, the insulinotropic effects of GLP-1 were observed to be similar in healthy controls and patients with type 2 diabetes. In addition, GLP-1 demonstrated the ability to lower pancreatic glucagon levels in a dose-dependent manner in patients with type 2 diabetes.²² The finding that GLP-1 effects on insulin secretion and glucagon remain intact in patients with type 2 diabetes makes this hormone a key target for pharmacologic development.

Development of Incretin-Based Therapies for Type 2 Diabetes

Glucagon-Like Peptide-1-Receptor Agonists

In response to the physiologic loss of incretin activity associated with type 2 diabetes, administration of exogenous GLP-1 has been shown to significantly lower both fasting and postprandial glucose levels in patients with type 2 diabetes.² However, due to its rapid degradation by DPP-4, this native molecule has limited use as a long-term therapeutic option. The development of the GLP-1-receptor agonists, including incretin mimetics (e.g., exenatide) and human GLP-1 analogs (e.g., liraglutide), offer incretin-based therapies with built-in modifications to provide resistance to DPP-4 degradation.

Liraglutide is 97% homologous to native GLP-1 with a substitution at residue 34 of arginine for lysine and addition of a C16 fatty acid chain on the ϵ -amino group of lysine at position 26 (Figure 2).^{5, 23} Addition of the fatty acid chain to the structure of liraglutide allows for binding to albumin, which results in an extended half-life and prevents degradation by DPP-4, allowing for once-daily dosing.²³ Exenatide is a synthetic construct of the exendin-4 peptide, which was originally isolated from Gila monster venom, that acts as a potent GLP-1-receptor agonist.²⁴ The amino acid sequence of exenatide is only 53% identical to native GLP-1 with a significant substitution of glycine in position 2 that provides resistance to DPP-4.²³ Both of these molecules

are administered through subcutaneous injections and can be distinguished from each other by their respective structure and activity profiles.²⁵ With observation of a longer half-life in the range of 10–14 hours, liraglutide can be administered once/day, whereas the 2.5-hour half-life observed with exenatide allows for twice-daily administration before meals in patients with type 2 diabetes.²⁶

The metabolic actions of the GLP-1–receptor agonists have been shown to closely mimic many of the glucoregulatory effects mediated by native GLP-1. Both liraglutide and exenatide have demonstrated glucose-dependent insulin secretion, decreased glucagon secretion, improvements in β -cell function, deceleration of gastric emptying, and promotion of early satiety leading to weight loss.^{23, 27} The most common adverse effects noted with these GLP-1–receptor agonists were mild nausea and minor hypoglycemia. As exenatide is extensively cleared by the kidneys, it is not recommended in patients with a creatinine clearance below 30 ml/minute or in those with end-stage renal disease.^{28, 29} In contrast, the pharmacokinetics of liraglutide are unchanged in patients with different stages of renal impairment, and treatment with liraglutide was not associated with an increased risk of adverse events.³⁰ As the effects of liraglutide and exenatide on insulin secretion are glucose dependent, this generally results only in mild, transient hypoglycemia.²³

Dipeptidyl Peptidase-4 Inhibitors

A different mechanism for overcoming the loss of incretin activity in patients with diabetes involves inhibition of the DPP-4 enzyme, thus prolonging the activity of endogenous GLP-1. Several different compounds have been identified that can competitively and reversibly inhibit DPP-4 activity, including sitagliptin and saxagliptin, which are approved for use in the United States, as well as vildagliptin and alogliptin, which are under review.³¹ These agents are all orally administered and rapidly absorbed, as 100% inhibition of enzyme activity can be observed within 30 minutes after administration.³¹ By virtue of their action to prevent the degradation of native GLP-1, the DPP-4 inhibitors have demonstrated an ability to regulate blood glucose levels by promoting increased insulin secretion and decreased glucagon secretion.^{8, 31}

In contrast to the GLP-1 agonists, DPP-4 inhibitors do not appear to mediate all the glucoregulatory actions of native GLP-1. The DPP-4 inhibitors have little or no effect on gastric emptying or satiety. This may partly explain why they are generally found to be weight neutral in the clinical setting.^{31, 32} In addition, less evidence exists on the role that these agents may play in stimulating β -cell function.^{32, 33} Patients with renal insufficiency require a dosage adjustment when receiving sitagliptin as it is primarily eliminated by the kidneys. Studies on the effects

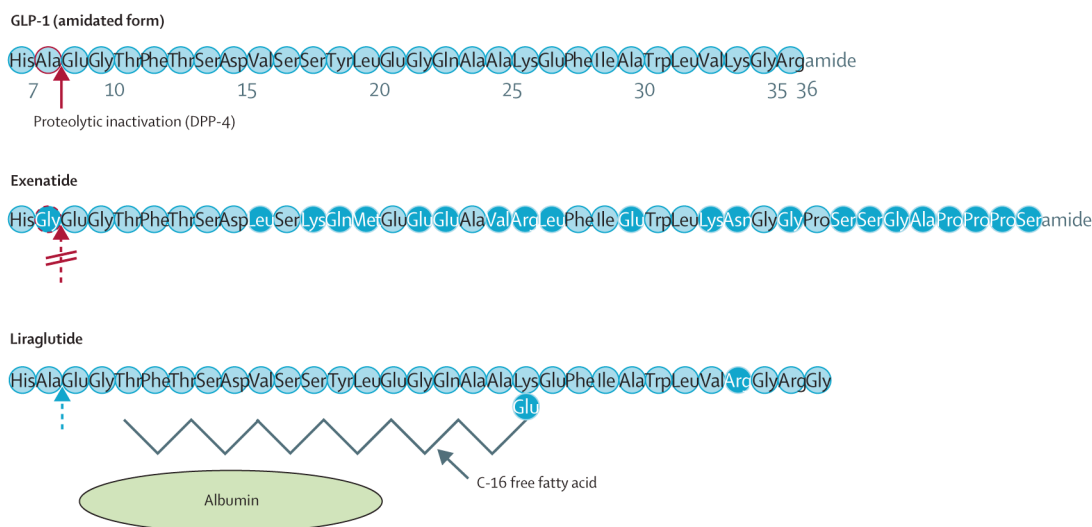


Figure 2. Structures of glucagon-like peptide-1 (GLP-1) and the GLP-1–receptor agonists, exenatide and liraglutide. (Reprinted with permission from reference 5.)

of other DPP-4 inhibitors in patients with renal insufficiency are ongoing.³¹

Differentiation of Liraglutide from Other Incretin-Based Therapies

Physiologic Effects of Liraglutide versus Other GLP-1–Receptor Agonists

Liraglutide can be differentiated from other GLP-1 agonists based on many different characteristics. Liraglutide is an analog of native GLP-1, whereas exenatide is an incretin mimetic. The amino acid sequence of liraglutide is 97% the same as native human GLP-1, with a single substitution of arginine for lysine in position 34, near the NH₂-terminus.^{23,34} Exenatide has a 53% homology to human GLP-1 with a key substitution from alanine to glycine at position 2, making it less susceptible to DPP-4 degradation.^{23,34} The high degree of homology of liraglutide to GLP-1 may in part explain the observation that relatively low levels of antibodies are produced in response to liraglutide. Antibodies to liraglutide were detected in less than 13% of patients,^{35,36} whereas approximately 20% of exenatide-treated patients developed antibodies.²³ However, the clinical relevance of antibodies to either agent is not yet known.

Another distinctive structural feature of liraglutide is the attachment of a 16-carbon moiety (–CO-[CH₂]₁₄CH₃) linked by means of a γ -glutamic acid spacer at the ϵ -amino group of lysine (at position 26), which allows noncovalent binding to albumin and extends its half-life to be longer than that of exenatide.^{23,37} Liraglutide has demonstrated a half-life of 13 hours in healthy subjects³⁸ and has also been shown to be effective for once-daily dosing in patients with type 2 diabetes.^{39,40} This observed increase in protraction is believed to be related to the albumin binding of the C16 fatty acid moiety, which can be specifically correlated to fatty acid chain length, and delayed absorption after injection, which is most likely due to self-association.^{37,41} Alteration of the spacer region did not affect protraction of liraglutide, but it was found to optimize the potency of molecular interaction with GLP-1 receptor.³⁷ Liraglutide metabolism does not depend on one single organ responsible for its elimination. About 89–100% of intact liraglutide is present in plasma, with only two minor metabolites and no intact liraglutide detected in urine or feces.^{23,42}

Exenatide has a peak action of about 2–3 hours, with circulating levels detected for up to 10 hours after dosing when administered 60 minutes before meals.^{26,43} Resistance to DPP-4 degradation and then clearance from the plasma and elimination by the kidney contribute to exenatide's extended half-life of 2.4 hours compared with native GLP-1.^{23,34} An extended-release version of exenatide, which is a polylactic-co-glycolic acid microsphere suspension, has been developed that will allow for once-weekly dosing.^{26,44} When compared with the exenatide formulation administered twice/day, extended-release exenatide (LAR) resulted in greater improvements in glycemic control with no increased risk of hypoglycemia and similar effects on body weight.⁴⁵ Another GLP-1 agonist compound, CJC-1131, has demonstrated an extended half-life of 8.9–14.7 days due to resistance to degradation by DPP-4 and covalent binding to serum albumin. Studies to determine safety and efficacy of this agent in patients with type 2 diabetes are ongoing.^{46,47} Other GLP-1 agonist compounds, including BIM-51077 and CJC-1134, are in various stages of development, and long-term clinical results may be available for these compounds soon.²⁷

Clinical Effects of Liraglutide versus Exenatide

The efficacy and safety of liraglutide and exenatide in clinical trials have been well documented. Recently, a head-to-head study of these two agents was published. The Liraglutide Effect and Action in Diabetes (LEAD)-6 study was a 26-week, randomized, open-label, parallel-group trial conducted within 132 centers in Europe and the United States.⁴⁸ Four hundred sixty-four patients with type 2 diabetes were randomized to receive either liraglutide 1.8 mg once/day or exenatide 10 μ g twice/day for 26 weeks. All patients were maintained with background oral antidiabetic treatment, which included maximally tolerated doses of metformin and/or sulfonylureas. End points included reduction in hemoglobin A_{1c} (A1C) value from baseline (primary outcome), body weight, fasting plasma glucose level, self-measured 7-point plasma glucose profiles, proportion of patients reaching target A1C values (< 7.0% and \leq 6.5%), β -cell function, glucagon level, blood pressure, lipid profiles, hypoglycemic episodes, and other adverse events.

Results from the LEAD-6 study indicate that liraglutide once/day provides significantly

Table 1. Comparison of Efficacy and Safety Outcomes in the LEAD-6 Study⁴⁸

Outcome	Liraglutide Group ^a (n=233)	Exenatide Group ^b (n=231)	p Value
Change in hemoglobin A _{1c}	-1.12%	-0.79%	0.0001
Hemoglobin A _{1c} < 7.0%	54% of patients	43% of patients	0.0015
Hemoglobin A _{1c} ≤ 6.5%	35% of patients	21% of patients	0.0001
Change in fasting plasma glucose level	-29 mg/dl	-11 mg/dl	0.0001
Change in body weight	-3.24 kg	-2.87 kg	NS
HOMA-B	32.12%	2.74%	0.0001
Minor hypoglycemia (no. of events/subject-year)	1.932	2.600	0.0131

Data are mean unless otherwise indicated.

LEAD = Liraglutide Effect and Action in Diabetes; NS = not significant; HOMA-B = homeostatic model assessment.

^aLiraglutide 1.8 mg once/day.

^bExenatide 10 µg twice/day.

improved glycemic control compared with twice-daily exenatide, with only minimal and transient adverse events (Table 1).⁴⁸ Reduction of A1C levels was significantly greater with liraglutide compared with exenatide (-1.12% vs -0.79, $p < 0.0001$). In addition, a significantly greater proportion of patients receiving liraglutide compared with exenatide reached an A1C level below 7.0% (54% vs 43%, $p = 0.0015$) as well as an A1C level of 6.5% or lower (35% vs 21%, $p < 0.0001$). Significant reductions in fasting plasma glucose level from baseline were also observed with liraglutide compared with exenatide (-29 mg/dl vs -11 mg/dl, $p < 0.0001$). However, exenatide significantly reduced postprandial glucose levels after breakfast and dinner compared with baseline; the difference in these levels after lunch was not significant. As assessed by the homeostasis model assessment (HOMA-B), β -cell function was improved significantly more with liraglutide compared with exenatide. Changes in body weight were comparable and clinically meaningful with both drugs. A significantly lower rate of minor hypoglycemia was observed with liraglutide than with exenatide, and levels of nausea were initially comparable, with a trend toward more rapid reduction of patients experiencing nausea when treated with liraglutide.⁴⁸

In a review of clinical studies, exenatide resulted in an average reduction in A1C level of about 1.0%, whereas liraglutide reduced the A1C level about 1–1.5%.^{49, 50} Weight reduction from baseline was approximately 2–3 kg for exenatide and 3–4 kg for liraglutide.^{49, 50} Dose-dependent nausea was observed with exenatide, occurring in as many as 57% of patients. Mild nausea was observed in 10–15% of patients treated with

liraglutide. Overall, significantly fewer episodes of gastrointestinal adverse effects were observed with liraglutide compared with exenatide.^{49, 50}

Liraglutide versus Dipeptidyl Peptidase-4 Inhibitors

Although both liraglutide and DPP-4 inhibitors result in increased insulin secretion, their mechanisms of achieving this clinical effect are different. Liraglutide, as a GLP-1-receptor agonist, provides further incretin activity that is decreased in patients with type 2 diabetes, whereas DPP-4 inhibitors act to prolong the half-life of endogenous GLP-1. Therefore, the clinical effects of DPP-4 inhibitors are dependent on the availability of endogenous GLP-1.⁵ The DPP-4 inhibitors' actions are less specific than those of GLP-1 agonists because this enzyme is ubiquitously expressed and has been shown to be differentially regulated in a variety of disease states and during an inflammatory response.^{8, 51}

Overall, the glucose-lowering effects are similar with both agents, although slightly more pronounced with GLP-1 agonists than with DPP-4 inhibitors (Table 2).^{49, 50, 52} The evidence demonstrates that liraglutide promotes significant weight loss compared with the DPP-4 inhibitors, which are considered to be weight neutral.⁵³ However, DPP-4 inhibitors may be preferred by some patients, as they are administered orally, compared with GLP-1 agonists, which are administered subcutaneously. Both DPP-4 inhibitors and liraglutide have been shown to cause fewer gastrointestinal adverse effects than exenatide.^{49, 50} In a direct comparison study of exenatide and liraglutide, the frequency of nausea was similar initially but then resolved much earlier with liraglutide compared with exenatide.⁴⁸

Table 2. Comparison of GLP-1–Receptor Agonists and DPP-4 Inhibitors^{49, 50}

Characteristic	GLP-1–Receptor Agonists	DPP-4 Inhibitors
Route of administration	Subcutaneous	Oral
Hemoglobin A _{1c} -lowering capacity	1.0–2.0%	0.5–1.0%
Effect on body weight	Promotes satiety and weight loss	Neutral
Adverse-event profile	Some nausea and vomiting	Well tolerated

GLP-1 = glucagon-like peptide-1; DPP-4 = dipeptidyl peptidase-4.

Conclusion

The physiologic, glucose-dependent, mechanism of action of incretin-based therapies promotes glucose homeostasis in patients with type 2 diabetes. Incretin-based therapies, in general, and specifically, the GLP-1 analog, liraglutide, have the potential to improve type 2 diabetes management. Liraglutide is similar to native GLP-1 in structure, exhibits potent effects by means of the GLP-1 receptor, and promotes significant clinical effects.

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