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REVIEW

Molecular Pharmacology of Glucagon-Like Peptide 1-Based Therapies in the Management of Type Two Diabetes Mellitus and Obesity

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Background: The global increase in type 2 diabetes mellitus (DM2) and obesity presents a significant public health challenge, as these interconnected conditions contribute to severe complications, including cardiovascular disease, stroke, and certain cancers. The incretin system, particularly glucagon-like peptide-1 (GLP-1), has emerged as a promising therapeutic target due to its role in glycemic control and weight management.

Objective: This review explores the molecular pharmacology of GLP-1 and its receptor agonists, evaluating their therapeutic efficacy in managing DM2 and obesity.

Methods: A comprehensive literature review was conducted, analyzing recent advancements in GLP-1-based therapies, their mechanisms of action, and their clinical applications. The review also highlights the pharmacokinetic modifications developed to enhance the stability and efficacy of GLP-1 receptor agonists.

Results: GLP-1 receptor agonists have demonstrated significant benefits in improving glycemic control, reducing body weight, and addressing metabolic complications. Novel therapeutic approaches, including dual and triple incretin receptor agonists, are showing enhanced efficacy in both diabetes and obesity management. However, challenges remain in optimizing treatment outcomes, addressing patient variability, and improving long-term adherence.

Conclusion: GLP-1-based therapies have revolutionized the management of DM2 and obesity. Continued research is essential to refine these treatments, overcome existing limitations, and develop personalized approaches to maximize patient outcomes.

Keywords: GLP-1 receptor agonists, type 2 diabetes mellitus, obesity management, incretin hormones, molecular pharmacology

Introduction

The increasing global prevalence of type two diabetes mellitus (DM2) and obesity has brought them to the forefront of public health challenges. These conditions share overlapping pathophysiological mechanisms, including insulin resistance, inflammation, and dysregulated energy balance. These two conditions are interlinked, often coexisting within individuals, and can lead to serious health complications, which include cardiovascular disease, stroke, and certain types of cancer.[1] The search for effective therapeutic strategies to manage DM2 and obesity has led researchers to explore the incretin system, a metabolic hormone that reduces blood glucose levels. Among these, glucagon-like peptide 1 (GLP-1) has emerged as a particularly promising target. GLP-1 is a powerful incretin hormone that has been shown to stimulate insulin secretion and inhibit glucagon release.

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Beyond its hypoglycemic effect, the equally significant role of GLP-1 in obesity management. GLP-1 receptors in the hypothalamus are widely expressed and play key roles in regulating appetite and food intake by enhancing satiety signals. GLP-1 slows gastric emptying with prolonged postprandial satiety and modulates energy balance by reducing overall caloric intake. Conventional weight loss approaches are primarily caloric restriction, but GLP-1 mimetics offer a new pharmacological strategy that addresses the neuroendocrine mechanisms underlying obesity.[2]

GLP-1-based therapies, including GLP-1 receptor agonists (GLP-1RA), have shown considerable efficacy in the management of DM2 and obesity.[3] In diabetics, GLP-1 primarily enhances β-cell activity and insulin sensitivity. However, in non-diabetic obese individuals, its predominant action is appetite suppression and weight reduction. Furthermore, GLP-1 secretion is defective in obesity, leading to high caloric intake and subsequent weight gain. This heterogeneity again points to the necessity for personalized therapeutic approaches with GLP-1-based therapy.[4] A deeper understanding of the molecular pharmacology of the GLP-1 system is crucial to employ its potential and develop more effective therapeutic strategies. This review provides a comprehensive overview of the molecular pharmacology of GLP-1 and its role in treating type 2 diabetes and obesity, highlighting recent advancements in novel therapies and addressing key challenges in the field.

The Rising Challenge of DM2 and Obesity

The global burden of DM2 presented a significant concern in 2019, with an estimated 9.3% prevalence, equating to 463 million individuals affected. Projections suggest an escalating trend, with the prevalence anticipated to reach 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045.[5] Notably, the Arab Gulf Cooperation Council (GCC) is identified as a zone with an exceptionally high prevalence of DM2. According to the International Diabetes Federation's (IDF) regional data, in countries within the Gulf region, the observed incidence of diabetes in the adult population, specifically individuals aged between 20 and 79 years, exhibits a range from 8% to 22%.[6] Furthermore, a meta-analysis elucidated a pooled prevalence of DM2 in Saudi Arabia of 16.4%, with evidence suggesting a dominant trajectory of DM2 prevalence in the region.[7] Moreover, obesity prevalence, a key risk factor for DM, has seen a substantial rise globally and in Saudi Arabia. Globally, it has experienced almost a threefold increase since 1975, as reported by the World Health Organization (WHO). Currently, the population of adults characterized as obese exceeds 650 million individuals. In Saudi Arabia, the trend is more alarming. Based on projections, the overall prevalence of obesity has increased from approximately 12% in 1992 to 41% in 2022 among men and from 21% in 1992 to 78% in 2022 among women. This escalating trend of obesity presents a significant public health concern and is likely to contribute further to the increasing prevalence of DM2 in the country.[8] A crucial approach to managing obesity includes the utilization of bariatric surgical procedures. In 2019, Saudi Arabia reported over 27,000 such operations, marking one of the highest per capita procedure rates globally. It is important to note that this figure only represents the public sector data. It is estimated that an equivalent number of procedures were likely performed within the private healthcare sector, thereby doubling the total number of bariatric surgeries in the country[9].

The Physiological Roles of Incretin Hormones

Food intake stimulates the postprandial release of incretin hormones, particularly GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), from enteroendocrine cells located in the epithelial mucosa of the small intestine.[10] Known for more than 40 years,[11] the "incretin effect" explains the increased insulin secretion from β-cells after taking glucose orally compared to via IV. The interaction between the pancreas and the intestine contributes to 50–70% of the overall insulin response to glucose intake orally. This phenomenon is attributed to the signaling process between these two organs. GLP-1 and GIP are the key incretin hormones, cumulatively boosting insulin secretion in non-diabetic individuals. GIP originates from K cells in the small intestine, while GLP-1, secreted in response to gut nutrients, from L cells primarily in the distal ileum. These cells also produce glicentin and Glucagon-like peptide 2 (GLP-2), which influence intestinal growth and health.[12] After eating, GLP-1 levels rise, peaking at 30 minutes and staying high for hours.[13] Overall, the incretin hormones intensify post-meal insulin release, stabilize blood sugar, and reduce appetite. The peripheral effects of GLP-1 include interacting with its binding site in β-cells receptors, promoting glucose-dependent insulin release without initiating it. GLP-1 also reduces the secretion of glucagon from pancreatic alpha cells, slows

gastric emptying, and may influence the cardiovascular and neural systems. On the other hand, central effects involve regulating appetite through GLP-1 receptors in the hypothalamus and potentially other areas of the CNS. GLP-1 reduces appetite, and research has demonstrated that when GLP-1 is administered into the cerebrovascular system of fasting rats, it suppresses their feeding behavior.[14] Its impact extends beyond the hypothalamus, possibly including the brain stem. Additionally, by slowing gastric emptying, it increases feelings of fullness. In general, incretin hormones control appetite and digestion, justifying the use of GLP-1-based treatments for DM2 and obesity.[15,16]

Overview of the GLP-1 System

GLP-1 initiates from the enzymatic breakdown of proglucagon, predominantly observed in enteroendocrine cells, pancreatic α cells, and the nucleus of the solitary tract (NTS) within the brainstem. Proglucagon's enzymatic cleavage varies depending on the tissue and is modulated by specific prohormone convertase enzymes. Within the pancreas, proglucagon undergoes a transformation into glucagon, glicentin-related pancreatic polypeptide (GRPP), and the main proglucagon fragment (MPGF). This MPGF, which includes both GLP-1 and GLP-2, undergoes further breakdown to produce GLP-1. Peripheral GLP-1 is released mainly from the enteroendocrine cells of the small intestine and colon, which process proglucagon using prohormone convertase 1/3 to yield compounds like glicentin, GLP-1, and GLP-2. The brain also synthesizes GLP-1 in a similar manner. GLP-1 can undergo post-translational modifications, resulting in four different forms. The predominant circulating in humans is GLP-1(7–36) NH2. GLP-1 secretion is initiated by the carbohydrates, proteins, and fats present in the meal. GLP-1 release is regulated primarily by glucose uptake into specialized cells called enteroendocrine GLP-1-producing cells (EECs of GLP-1) via sodium-coupled glucose transporters (SGLT). The rate of gastric emptying is strongly correlated with GLP-1 secretion. The primary objective of pharmacological treatments for diabetes and obesity is to enhance and increase the release of GLP-1.[17]

The release of GLP-1 from the brain's NTS is regulated by the firing of neurons that express preproglucagon. GLP-1 secretion from peripheral tissues can also stimulate additional GLP-1 secretion in the brain despite its very short half-life. This plays a vital role in GLP-1-mediated anorexia and GLP-1 enhancement of insulin sensitivity. These findings highlight variations in the signals that stimulate GLP-1 release from GLP-1 EECs and NTS neurons expressing preproglucagon. The first responds to nutrient-related signals, while the second is activated by hormonal signals and vagal nerve activity.[17,18]

In individuals with DM2, the ability to respond to GIP, a primary component of the incretin hormones, is significantly decreased or lost. Additionally, the response to GLP-1 is only partially preserved. Consequently, the insulin response to physiological GLP-1 in diabetic patients is diminished. However, the administration of GLP-1 in pharmacological doses can normalize insulin secretion and lower plasma glucose levels. Although exogenous GIP does not lower glucose in diabetic patients, making it unsuitable for DM2 treatment alone, new GLP-1-GIP co-agonists show promising antidiabetic and weight-reducing effects.[19–21]

At the same time, increased body weight is associated with a lowered level of GLP-1 secretion and a diminished incretin effect. The incretin effect is markedly affected in obese individuals with DM2 compared to lean ones. Furthermore, GLP-1 response to glucose is reduced in obesity. This could be due to "functional deficits in GLP-1 signaling caused by leptin resistance, impaired ghrelin secretion, and hyperinsulinemia associated with obesity".[19,22]

Mechanism of Action of GLP-1

GLP-1 Receptor Activation/Deactivation Signaling Cascades

In pancreatic β cells, GLP-1 binds to its receptor (GLP-1R), a G-protein coupled receptor that signals via Gαs to activate adenylate cyclase and increase cyclic AMP (cAMP). This stimulates downstream pathways, including protein kinase A (PKA) and exchange protein activated by cAMP (EPAC). Through these cAMP-dependent mechanisms, GLP-1 inhibits Adenosine triphosphate (ATP)-sensitive potassium channels, enhances L-type calcium channel activity, and opens cation channels. The overall effect is an increase in calcium influx that triggers insulin secretion. GLP-1 signaling also increases β cell proliferation and neogenesis while decreasing apoptosis. The sensitivity to glucose is heightened by GLP-1 inhibition of potassium channels and resulting membrane depolarization. Similar cAMP-mediated mechanisms may occur in GLP-1 receptive neurons, but more research is needed Figure 1.[23,24]

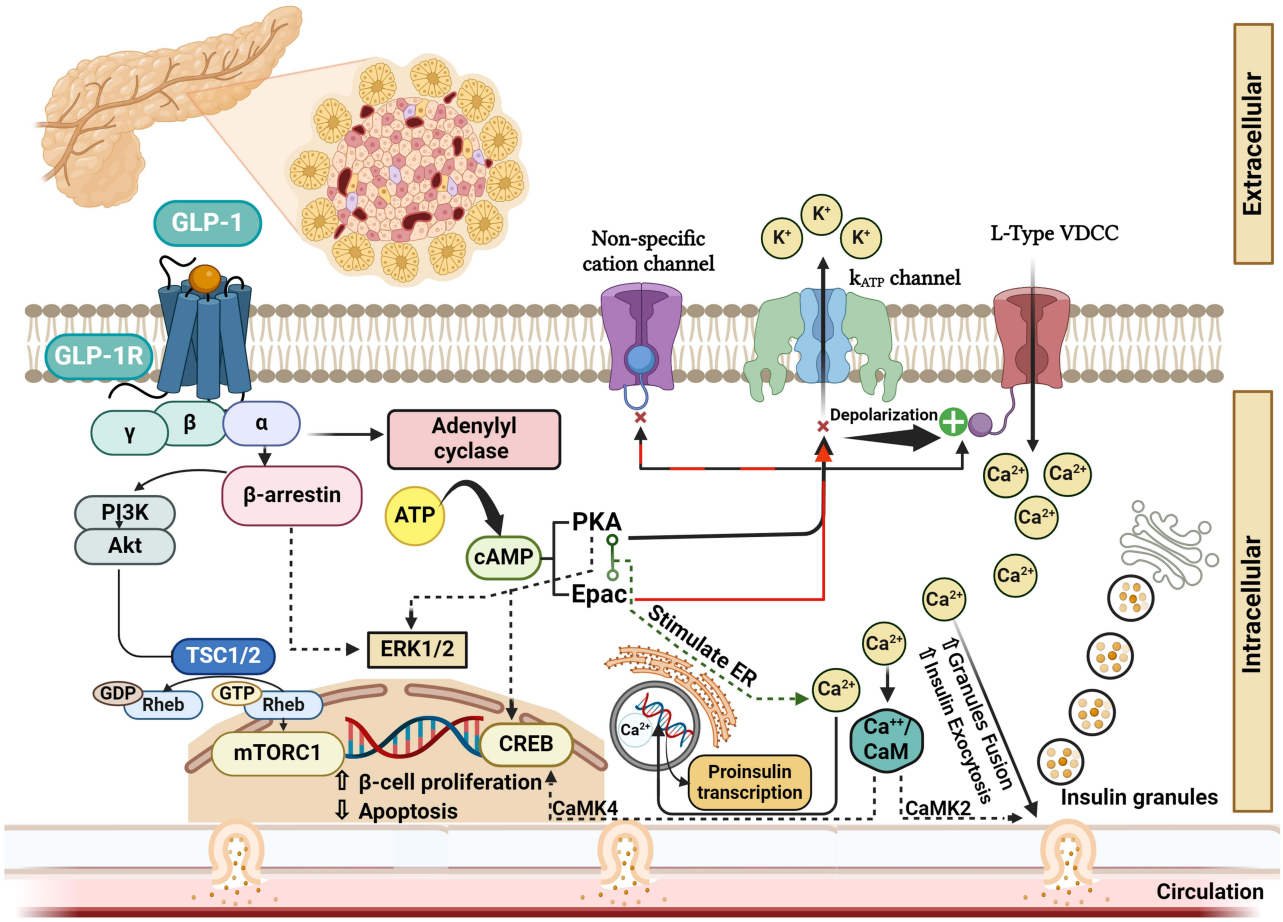

Figure 1 Signaling Pathways of the GLP-1 Receptor: Activation via Gαs and Downstream Mediators Including cAMP, PKA, and β-Arrestin for Varied Cellular Outcomes. Created with Biorender.com.

The GLP-1R, like other G protein-coupled receptors (GPCRs), undergoes inactivation following stimulation. When GLP-1R signals in β-cells, it recruits β-arrestin and signals via extracellular signal-regulated kinases (ERK1/2). After being stimulated by GLP-1 or various agonists, GLP-1R in pancreatic cells internalizes and is eventually recycled back to the cell surface. However, the exact internalization mechanism remains unclear. In cell cultures, evidence has suggested both a clathrin-dependent and a caveolin-dependent mechanism. Based on further evidence found in HEK cells, it appears that a mechanism that depends on Gαq might trigger the activation of protein kinase C (PKC) and ERK 1/2. This mechanism involves the activation of Gαq, which leads to an increase in inositol triphosphate (IP3). This increase then elevates the levels of intracellular calcium by mobilizing the calcium stores found in the endoplasmic reticulum. This elevation activates PKC, which then causes phosphorylation ERK 1/2. ERK 1/2 subsequently will do phosphorylation of the C terminal of GLP-1R, leading to internalization through an unknown mechanism. The exact mechanism may vary depending on the specific context where GLP-1R is expressed.[18,25]

GLP-1 Agonists: Molecular Design and Pharmacokinetics

Evolution of GLP-1 Agonist Structures

The potential benefits of natural GLP-1 is constrained by its rapid breakdown by serum enzymes proteases, primarily dipeptidyl peptidase IV (DPP-IV), along with neutral endopeptidase (NEP), plasma kallikrein, and plasmin. This results in an extremely short half-life of only 2 minutes after intravenous administration.[26,27] To overcome this limitation and extend the activity of GLP-1 receptor agonists with subcutaneous dosing, different stabilization strategies have been explored. Two approaches have been successful so far in mitigating the fast deactivation of GLP-1. The first approach involves creating

GLP-1 receptor agonist peptides (also known as GLP-1 mimetics), which are not easily broken down by DPP-IV due to their low affinity for this enzyme, thus providing a longer circulation time. The second approach focuses on inhibiting DPP-IV, preventing GLP-1 from being degraded, and allowing for an increase in GLP-1 levels with each meal. However, in this review, we will not delve into the inhibition of DPP-4 but rather concentrate on modifications of GLP-1.[3,28]

One approach is to prevent degradation by DPP-IV through amino acid substitutions, as this enzyme preferentially cleaves N-terminal Xaa-Pro or Xaa-Ala sequences. Modifying the N-terminal amino acid, particularly the second residue, has been shown to reduce cleavage by DPP-IV. For example, replacing the alanine at position 2 with amino acids like glycine, serine, or alpha-aminoisobutyric acid generates analogs more resistant to DPP-IV-mediated proteolysis. This stabilization technique helps prolong the duration of action of GLP-1 receptor agonists after subcutaneous injection.[17]

Exenatide is a synthetic analog of exendin-4, a peptide found in the saliva of the Gila monster "Heloderma suspectum". It contains glycine rather than alanine at position 2, making it resistant to degradation by DPP-IV. Additionally, its compact Trp-cage tertiary structure enhances stability. Exenatide was the first GLP-1 receptor agonist approved in 2005 as Byetta (Amylin/BMS) for DM2. With a t½ of only 2.4 hours after subcutaneous dosing, exenatide is administered twice daily (BID) at 10 μg. In 30-week trials as monotherapy or combined with oral antidiabetics, it reduced hemoglobin A1c (HbA1c) by 0.8–0.9% and body weight by 1.8–2.6 kg. An 82-week open-label extension with metformin showed greater reductions of 1.1% in HbA1c and 4.4 kg in weight. Exenatide BID demonstrated similar HbA1c improvement as insulin glargine over 26 weeks (1.25% vs 1.26%) but led to weight loss rather than weight gain of 3 kg with insulin.[29] Overall, exenatide BID was the first incretin mimetic approved for DM2, providing glucose control along with the benefit of weight reduction.[18]

Lixisenatide (Sanofi/Zealand) is a synthetic analog of exendin-4. In comparison to exendin-4, lixisenatide has six additional Lys residues at the C-terminus, while one Pro in the C-terminal region has been removed. It has an average t½ of roughly 3 hours. In a study involving patients with DM2 who were not responding adequately to metformin, lixisenatide demonstrated the most effective efficacy-to-tolerance ratio at a dose of 20 μg administered once daily. In the Phase 3 trials, lixisenatide (20 μg) was administered once daily and showed effectiveness as monotherapy when used in combination with oral antidiabetic medications and as an add-on to basal insulin. It was particularly effective in reducing postprandial glucose excursion, resulting in a reduction of up to 0.9% in HbA1c. When used with other oral antidiabetic drugs, lixisenatide led to a sustained weight reduction ranging from 1.8 to 3 kg over a period of 24 weeks. A comparative study of lixisenatide and exenatide BID as supplemental treatments to metformin revealed a similar reduction in HbA1c, but lixisenatide caused less hypoglycemia, slightly less weight loss, and had a more favorable gastrointestinal tolerance profile after 24 weeks. One notable feature of lixisenatide is its significant delay of gastric emptying, which is accompanied by robust post-prandial glucose lowering. This trait is particularly advantageous when used in conjunction with basal insulins like insulin glargine. In this combinatorial therapy, lixisenatide exhibited substantial decreases in HbA1C (0.7–0.8%) and body weight (1.8 kg). In February 2013, the European Medicines Agency (EMA) granted marketing authorization for lixisenatide for the treatment of adults with DM2.[18]

Molecular Modifications for Improved Stability and Half-Life

While modifying GLP-1 receptor agonists to resist DPP-IV can extend their half-life, renal clearance still limits the duration of most peptidic agonists like exenatide and lixisenatide. To further prolong activity, researchers have developed strategies for sustained peptide release from a subcutaneous depot or reducing renal clearance through conjugation with carrier molecules.

Exenatide LAR "Bydureon, developed by Amylin/Lilly/Alkermes (now BMS)", represents a new approach to slow down the release of exenatide using a polymeric matrix. This formulation of exenatide, which is delivered once weekly, entraps exenatide non-covalently within a biodegradable polymeric matrix composed of poly(D, L-lactide-co-glycolide) (PLG) to form microspheres. The gradual liberation of exenatide from the matrix occurs through the processes of diffusion and the degradation of microspheres. In humans, Exenatide LAR has a t½ of 5–6 days. A steady state of plasma exendin-4 levels typically occurs after 6–10 weeks following a 2 mg subcutaneous injection. This dosage has been associated with reductions in HbA1c levels of 1.3–1.9%. Compared to BID exenatide, Exenatide LAR demonstrated a more significant decrease in HbA1c (1.9% versus 1.5%), accompanied by a comparable reduction in body weight

(3.6 kg versus 3.7 kg). However, in a head-to-head comparison with liraglutide, the latter demonstrated superior glycemic control and greater weight reduction after 26 weeks (HbA1c reduction of 1.5% vs 1.3% and weight loss of 3.6 kg vs 2.7 kg). A disadvantage of Exenatide LAR is the requirement for a relatively large injection needle (23 gauge), required by the thick consistency of the polymeric suspension. In addition to this, the pre-injection preparation procedure can be somewhat complex.[18]

The conjugation of peptides to fatty acids is a strategy used to extend their half-life and duration of action. Fatty acid promotes binding to albumin, resulting in a reduction in renal clearance of the peptide. This approach has been successfully applied in developing long-acting insulin analogs like insulin detemir and insulin glargine. The fatty acid chain, typically around 14–16 carbons, binds reversibly to albumin in the bloodstream. This albumin binding results in the peptide being released slowly over time rather than undergoing rapid renal filtration and excretion. The peak action is blunted, and the overall time of activity is prolonged.[30]

Liraglutide, marketed as Victoza and developed by Novo Nordisk, closely resembles the structure of GLP-1(7–37), sharing a 97% chain similarity to the natural hormone. In liraglutide, a crucial alteration includes replacing Lys at the 34th position with Arg and joining a palmitic acid to Lys at the 26th position using a glutamate linker. This unique arrangement of the linker and fatty acid chain has shown superior results, both in laboratory tests and with prolonged efficacy within porcine models. The mechanisms that ensure this extended effect vary. When liraglutide is administered via a subcutaneous route, the dispersion of the peptide from the site is gradual, which is attributed to its inherent tendency to self-bind. Upon entering systemic circulation, liraglutide demonstrates a notable affinity to bind to serum albumin (around 99%), leading to increased resistance to enzymatic breakdown by DPP-IV and NEP and a subsequent decrease in kidney-based elimination. The plasma t½ is estimated to be 13 hours. Liraglutide was approved for the treatment of DM2 in 2009. The standard therapeutic dose is 1.2 mg once daily, which can be increased to 1.8 mg to further enhance glycemic control. In Phase 3 trials, these dosing regimens achieved HbA1c reductions of 1.1–1.8% and weight loss of approximately 2–3 kg over a 26-week treatment period. When evaluated head-to-head, liraglutide administered once a day showed marked improvements in blood sugar management compared to exenatide administered twice a day, resulting in a decrease in HbA1c by 1.12% compared to 0.79%. Furthermore, increased doses of liraglutide (3 mg) were evaluated in Phase 3, and the result showed that overweight to obese participants experienced a weight decrease of 6% when treated with 3 mg of liraglutide, compared to those on a placebo. Within the GLP-1 RA category, liraglutide emerged as the top-performing medication for the management of overweight and obesity.[18,30]

Dulaglutide, marketed as Trulicity, is a long-acting GLP-1 RA developed by Eli Lilly for the once-weekly treatment of DM2. Dulaglutide was approved by the US Food and Drug Administration (FDA) in 2014 and by the European Medicines Agency (EMA) in 2015 for subcutaneous administration once weekly to improve glycemic control in adults with DM2. It consists of two modified GLP-1 analogs covalently linked to a variant human IgG4 immunoglobulin Fc fragment by a small peptide connector. The GLP-1 analogs contain amino acid substitutions, including Ala8→Gly and Arg36→Gly, that protect against DPP-IV degradation and maintain potency. The Fc fusion increases the molecular weight to approximately 60 kDa, thereby reducing renal clearance. This results in a prolonged t½ of around 4 days in humans. Results of Phase 2 trials have demonstrated that dulaglutide causes significant, dose-dependent reductions in HbA1c levels, with up to a 1.5% decrease observed after 12 weeks of treatment with a 1.5 mg dose. It also caused dose-dependent weight loss, although not statistically significant compared to placebo. The completed AWARD phase 3 trials showed that dulaglutide 1.5 mg leads to a superior reduction in HbA1c compared to exenatide and sitagliptin once weekly after 26 weeks. Dulaglutide also provided a greater weight loss of two to three kilograms compared to comparators. The data demonstrate the sustained efficacy of dulaglutide for glycemic control and weight loss in longer-term studies.[18,30]

Semaglutide is a next-generation GLP-1 RA developed by Novo Nordisk for once-weekly treatment of DM2. It was approved in 2018 as Ozempic at doses of 0.5 and 1.0 mg. Structurally, semaglutide is similar to liraglutide but with two key modifications - replacement of glycine at position 8 with alpha-aminoisobutyric acid and optimization of the fatty acid chain for albumin binding. These changes extend the t½ to around 160 hours. A 12-week phase 2 trial involving DM2 patients examined semaglutide administered once weekly at five different doses (0.1–1.6 mg). For doses above 0.2 mg, semaglutide resulted in a dose-dependent reduction in HbA1c up to 1.7% (compared to a 0.5% reduction with placebo). For doses above 0.8 mg, it also led to a weight loss of up to 4.8 kg (compared to a 1.2 kg reduction with

a placebo). Another mechanism for extending the half-life of semaglutide involves the genetic fusion to recombinant albumin. Serum albumin, with a molecular weight of 67 kDa, has a t½ of about 19 days in humans. This elongated half-life is partly due to pH-dependent recycling mediated by the neonatal FC receptor (FcRN). When therapeutic peptides such as GLP-1 RA are fused with albumin, the increased half-life is attributed to a combination of FcRN-mediated recycling and the decreased clearance resulting from the increased molecular weight.[18,30]

Clinical Benefit of GLP-1 RA, GIP, and Glucagon Coadministration

Various techniques have been explored to enhance the effectiveness of GLP-1RAs. One method involves increasing the dose, but this may be restricted by gastrointestinal side effects. Elevated doses of dulaglutide and semaglutide have been shown to augment weight loss and better control glucose levels in DM2 patients, but the additional benefits are modest, particularly in patients with poor control. A groundbreaking and hopeful strategy is the introduction of dual GIP/GLP-1 RA, known as "twincretins". Activating both GIP and GLP-1 receptors could be beneficial for DM2 treatment, as their joint actions can amplify insulin production, reduce energy usage, and enhance insulin sensitivity.[31] This combined action becomes possible as a result of the restored GIP sensitivity with better glycemia and the development of hybrid ligands that show dual actions. Dual activation could significantly impact insulin production, given both receptors are present in pancreatic β cells. Additionally, GIPR's unique activation in the brain and white adipose tissue (WAT) might complement GLP-1R signaling, potentially improving therapeutic outcomes Figure 2.

Tirzepatide is a novel GLP-1 and GIP receptor agonist administered by once-weekly subcutaneous injection. It is effective in the treatment of obesity in patients with and without DM.[32] Tirzepatide, a GLP-1R-GIPR co-agonist, exhibits

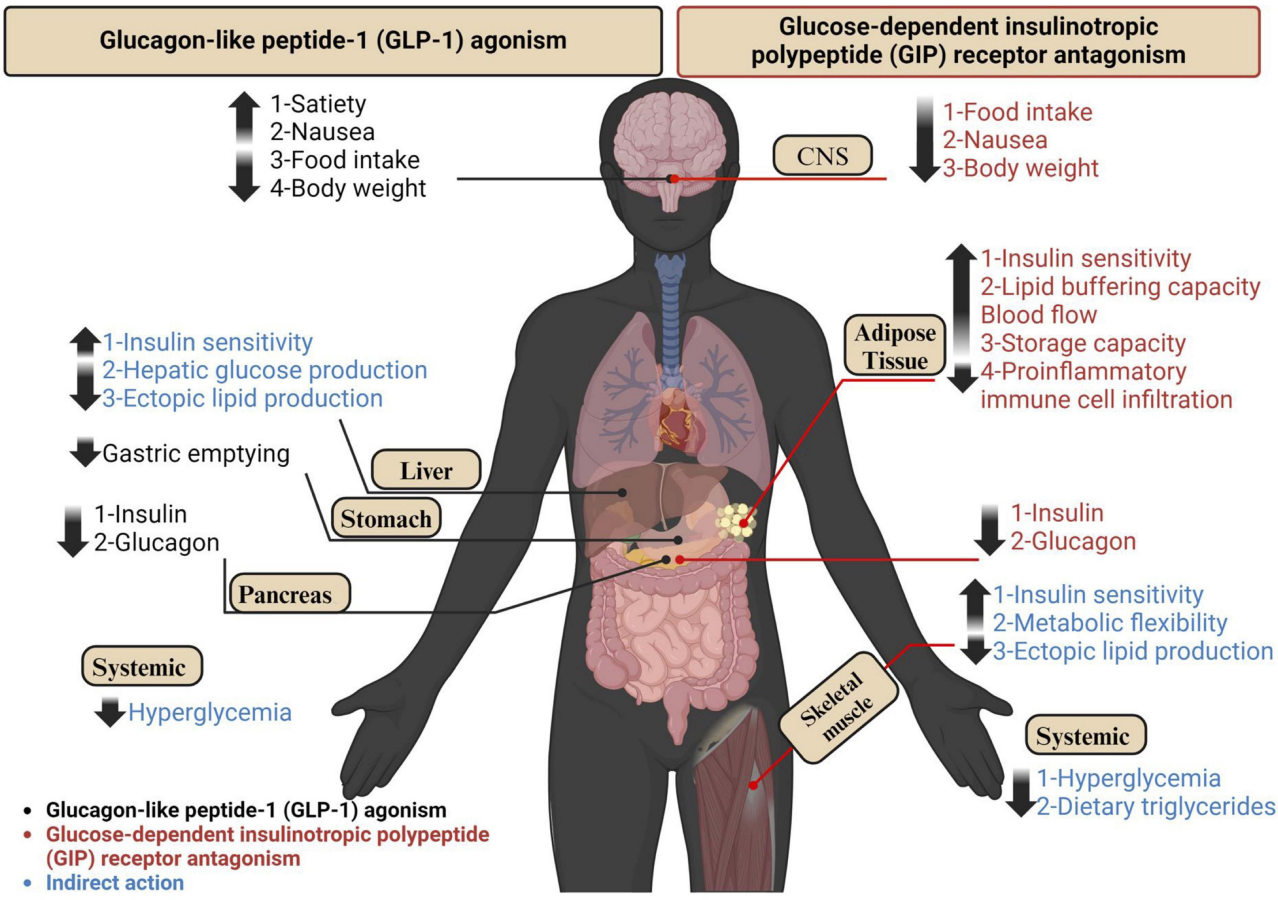

Figure 2 Therapeutic Benefits of Combined GIP/GLP-1 Receptor Agonists in Type 2 Diabetes: Enhanced Insulin Secretion, Reduced Caloric Intake, and Improved White Adipose Tissue Function. Adapted from Samms RJ, Coghlan MP, Sloop KW. How may GIP enhance the therapeutic efficacy of GLP-1? *Trends Endocrinol Metab*. 2020;31(6):410–421. Creative Commons.[32]

superior insulin responses and potent glucose-lowering and weight-loss effects compared to existing GLP-1R agonists. It also demonstrates dose-dependent HbA1c reductions in patients with DM2. Pharmacodynamically, tirzepatide is an imbalanced co-agonist, favoring GIPR over GLP-1R, with a comparable affinity for GIPR as endogenous GIP and marginally lesser affinity for GLP-1R than endogenous GLP-1. This imbalance results in an increased quantity of GLP-1R on the cell surface, amplifying intracellular signaling and insulinotropic properties. These effects occur at ~1-10 nM concentrations, peaking at up to 100 nM, comparable to native ligands' concentrations. Notably, the GLP-1R-GIPR co-agonist HISHS-2001 has slightly higher GLP-1R and GIPR potencies and lower beta-arrestin-2 recruitment to the GLP-1R than tirzepatide. Data from open-label and placebo-controlled trials with over 4000 adults with obesity or DM2 demonstrate that once-weekly injections of tirzepatide at doses of 5–15mg result in substantially more weight loss compared to placebo or semaglutide after 40–72 weeks of treatment. The highest doses of tirzepatide (10–15mg) helped 22–31% of participants achieve a weight loss of 20% or more from baseline, compared to only 1% of those receiving a placebo. The most frequently reported adverse effects were gastrointestinal in nature, with nausea, diarrhea, and constipation being most common, typically increasing in frequency at higher doses. Overall, tirzepatide appears significantly more effective for weight loss than available agents, although with greater gastrointestinal side effects.[33]

Researchers are investigating the potential of combined GLP-1 and glucagon receptor activators for addressing DM2 and obesity. By binding the natural regulatory functions of GLP-1 and glucagon in managing blood sugar and fat metabolism, these compounds show promise. GLP-1 and glucagon peptides have some common structural features. Glucagon plays a pivotal role in instantly balancing glucose levels. Research involving animals indicates that therapeutic levels of glucagon can modulate fat metabolism, energy consumption, and dietary habits. Stemming from these insights, researchers initiated the creation and enhancement of dual-receptor stimulants targeting both GLP-1/glucagon, aiming to counteract DM2 and obesity.[34]

Cotadutide, representing the dual-receptor stimulant group, stands out in terms of its progression in clinical studies. Initial tests on rodents highlighted its remarkable ability to decrease body weight, decrease food consumption, and offer improved blood sugar regulation over other agents like GLP-1 RA. In human-based studies, it was found that a 300μg daily intake of cotadutide led to a more impressive weight reduction than a daily 1.8 mg dosage of liraglutide. Additionally, cotadutide had the added benefit of reducing lipid concentrations and liver enzyme levels. Current research is zeroing in on cotadutide's impact on nonalcoholic steatohepatitis (NASH) indicators and liver scarring. However, it's worth noting that gastrointestinal complications arising from cotadutide seem to be more intense than those from GLP-1RA therapies. Pemvidutide, developed by Altimmune, Inc., is a novel extended-duration dual agonist targeting both GLP-1 and glucagon. It is currently being researched for managing obesity and NASH but not for DM2 due to its neutral impact on blood sugar levels. Pemvidutide received fast-track designation for NASH [SC, injection] in the USA. Although a triple agonist stimulant that includes GLP-1, GIP, and glucagon has shown promising results in animals and the early phase of the clinical trial in terms of weight and metabolic regulation.[35]

Inappropriate Combination of GLP-1 RA

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists advocate for the use of GLP-1 RA as supplementary therapy in combination with oral agents and insulin but advise against concomitant use with DPP4 inhibitors due to limited evidence. However, due to constraints such as cost and availability in free clinics, some physicians have prescribed fixed-dose combinations, including metformin with DPP-4 inhibitors and GLP-1 RAs, anticipating potential benefits in HbA1c reduction and weight management. The results of many studies revealed moderate improvements in glycemic control without significant weight loss benefits, suggesting that the observed effects arise primarily from GLP-1 RA, and the combination does not offer synergistic benefits. Given the costs associated with these treatments and the observed results, it is recommended to stop DPP-4 inhibitors in patients who do not achieve glycemic targets before introducing a GLP-1 RA, in accordance with current ADA guidelines. Future comprehensive trials would provide a clearer understanding of this combination therapy, although preliminary data do not favor it.[36]

GLP-1 Agonists in Obesity Management

Since the 1970s, global rates of overweight and obesity, determined by a body mass index (BMI) of 25.0–29.9 kg/m2 and ≥30.0 kg/m2, respectively, have almost tripled. Currently, nearly 40% of adults are overweight, and 13% are obese.[37] Obesity increases the risk of comorbidities like hypertension, DM2, hyperlipidemia, stroke, and some cancers, leading to higher mortality rates, primarily from cardiovascular complications.[38] The primary approach to managing overweight and obesity involves lifestyle modifications like exercise, caloric reduction, and behavioral therapy. If these measures are not successful, pharmacotherapeutics may be added. There are six FDA-approved medications for weight loss: phentermine-topiramate, orlistat, naltrexone-bupropion, and two GLP-1 receptor agonist (GLP-1 RA) liraglutide and semaglutide and setmelanotide which approved only for specific type of genetic condition related to obesity. The GLP-1 RAs, including the recently approved semaglutide, have shown effective weight reduction results in obese patients with or without diabetes. They improve glycemic control by stimulating insulin secretion and inhibiting glucagon secretion. While the exact mechanisms through which GLP-1 RAs contribute to weight loss are still under investigation, it is believed that they interact with the central and peripheral nervous systems, reducing appetite and food intake. They also delay gastric emptying, but this seems to have a minimal effect on total weight loss.[35]

Upcoming Advancements: 12 Novel Anti-Obesity Medications in the Pipeline

Multiple anti-obesity medications have been approved or are undergoing clinical trials. The table below provides a summary of these medications along with the mechanism of action, development stage, and key findings (Table 1).

Table 1 12 Novel Anti-Obesity Medications in the Pipeline

Drug Name	Mechanism of Action	Administration	Development Stage	Key Findings/Notes	Ref
Oral semaglutide	GLP-1 agonist	Daily oral tablet	Seeking FDA approval in 2023	Up to 15% weight loss over ~15 months (OASIS 1 study)	[39]
Orforglipron	Long-acting GLP-1 agonist	Oral	Phase 3 (completion mid-2027)	Up to 15% weight loss in ~8 months (Phase 2)	[40]
Danuglipron	GLP-1 agonist	Twice-daily oral	Phase 3 planning	Completed Phase 2	[41]
APH-012	Simulates gastric bypass effects	Oral glucose pill	Phase 2 (through March 2024)	Stimulates small intestine	[42]
ARD-101 (Oral denatonium acetate)	Targets bitter taste receptors	Twice-daily oral	Phase 2 (two completed, one concluding March 2024)	Activates GLP-1, GLP-2, cholecystokinin	[43]
Tirzepatide (Zepbound)	GIP and GLP-1 agonist	Once-weekly injectable	Approved November 2023	First dual GIP/GLP-1 receptor agonist	[44]
Retatrutide	GIP, GLP-1, and glucagon agonist	Injectable	Phase 3 (completion early 2026)	Studied for weight loss and T2DM	[45]
CagriSema	Amylin and GLP-1 agonist	Once-weekly injectable	Phase 3 (started November 2022)	Combines cagrilintide and semaglutide	[46]
Ecnoglutide	GLP-1 agonist	Injectable (oral version in Phase 1)	Phase 3 (completion late 2024/ early 2025)	Studied in China for weight loss and T2DM	[47]
Mazdutide	GLP-1 and glucagon receptor agonist	Once-weekly injectable	Phase 3 (through 2024/2025)	Studies conducted in China	[48]

(*Continued*)

Table 1 (Continued).

Drug Name	Mechanism of Action	Administration	Development Stage	Key Findings/Notes	Ref
Survodutide	GIP and GLP-1 receptor agonist	Once-weekly subcutaneous injection	Phase 3 (November 2023 - January 2026)	Recently completed Phase 2	[49]
Bimagrumab	Activin receptor blocker	Monthly intravenous injection	Phase 2 (until September 2025)	Aims for weight loss and lean muscle growth	[50]

Current Gaps and Challenges in GLP-1 Therapies

Diversity Among Patient Group

The development of anti-obesity medications is challenged by the varied nature of the condition. Obesity originates from rare genetic mutations and more frequent genetic variations linked to multiple factors, including behavior, hormone regulation, and metabolism. Potential genetic elements related to obesity are distributed widely throughout the genome, and epigenetic changes may also influence a person's propensity to become obese. Understanding the range of genetic, epigenetic, and environmental contributors is crucial, as they can affect both body weight variation and how individuals respond to drug treatments. A recent study demonstrated that more than 10% of children with acute obesity are associated with unusual genetic abnormalities. Certain cases of obesity result from mutations in genes responsible for hormones that regulate appetite. The most prevalent genetic contributors involve mutations in genes linked to the regulation of body fat and appetite. In-depth research into metabolic, genetic, and disease origins, along with how these factors impact drug efficacy, is essential to improve patient outcomes. This research could also aid in creating new generations of obesity treatments by deepening our knowledge of the molecular aspects of weight control. The question remains whether single or multiple drug mechanisms will be effective for most people with obesity or if highly tailored approaches are necessary to combat the obesity crisis effectively.[34,51]

Impact of Weight Reduction

Research indicates a substantial similarity in how certain drugs reduce weight in both rodents and humans, specifically with drugs like phentermine/topiramate and others, including orlistat. Additionally, analyses have shown that animal studies can reliably predict the impact of drugs such as naltrexone/bupropion on humans. Treatments involving incretin-related peptides have also been shown to decrease weight in both rodents and humans. Generally, except for semaglutide at a 2.4 mg dose, weight loss with anti-obesity medications is typically between 3–7% over 6–12 months, with only a limited number of patients experiencing weight loss above 10%, and even fewer surpassing 15%, compared to those taking a placebo. Notably, semaglutide at 2.4 mg and tirzepatide at a dose of 10–15 mg administered weekly have shown significant weight reductions exceeding 10% in clinical trials among non-diabetic individuals. However, this weight loss is less pronounced in those with DM2, suggesting that factors like insulin resistance and constant high blood sugar reduce the effectiveness of these drugs. While weight loss effects generally transition from rodents to humans, the maximum efficacy is typically two to four times lower in humans compared to rodents. It can be posited that rodents experience more significant relative weight loss as they have a higher mass-specific energy expenditure than humans, with a larger contribution of brown adipose tissue to metabolic rate. This implies that mice might be more sensitive to drugs impacting energy expenditure. The high mass-specific metabolic rate necessitates a high caloric intake to prevent a chronic energy balance deficit. Thus, it is logical that mice can consume food equaling more than 10% of their body weight in a single day. As a result, pharmacological suppression of food intake provides a larger dynamic range and more immediate effect on weight loss in rodents compared to humans.[34]

Perioperative Management of GLP-1R Agonists: Balancing Metabolic Benefits and Procedural Risks

A significant gap in knowledge and a current challenge in the field of GLP-1 receptor agonists (GLP-1RAs) is the limited data available to guide the perioperative management of patients using these medications.[52] This gap has become increasingly apparent as the use of GLP-1RAs has expanded rapidly for various metabolic conditions, including type 2 diabetes, obesity, and heart failure. The lack of robust evidence has led to uncertainty among healthcare providers regarding the safe and effective management of GLP-1RAs in the perioperative period. This uncertainty is particularly concerning given the potential risks associated with delayed gastric emptying, such as pulmonary aspiration during procedural sedation or general anesthesia.[53]

The paucity of data has resulted in inconsistent recommendations across different clinical organizations, further complicating decision-making for healthcare providers. Key areas requiring further research include the optimal timing for discontinuation of GLP-1RAs before procedures, if necessary; differential management strategies for daily versus weekly formulations; effectiveness of preoperative diet modifications in reducing aspiration risk; the utility of point-of-care gastric ultrasound in assessing aspiration risk in this population; and long-term outcomes of patients continuing versus discontinuing GLP-1RAs perioperatively.[54] Addressing these knowledge gaps through well-designed clinical studies is crucial to developing evidence-based guidelines for the perioperative management of patients on GLP-1RAs. This research is essential to ensure safe, effective, and equitable care for the growing population of patients using these medications, particularly as new generations of antiobesity medications, including dual and triple agonists, continue to emerge.

Optimal Duration of GLP-1R Agonist Therapy

The optimal duration of GLP-1 receptor agonist (GLP-1 RA) therapy for weight loss remains a subject of ongoing research and debate. While these medications have shown significant efficacy in promoting weight loss and improving cardiometabolic parameters, the ideal length of treatment is not yet definitively established. This uncertainty stems from several factors, including the chronic nature of obesity, individual variability in response to treatment, and limited long-term data beyond a few years.[55]

GLP-1 RAs have demonstrated substantial weight loss effects in clinical trials, with weight reduction typically plateauing after 20–60 weeks of treatment, depending on the specific agent.[56,57] However, obesity is recognized as a chronic, progressive, and relapsing disease, suggesting that long-term or even indefinite treatment may be necessary for many patients. This concept aligns with the management of other chronic conditions such as hypertension or diabetes, where ongoing therapy is often required to maintain clinical benefits.[58]

The challenge in determining the optimal duration of GLP-1 RA therapy is further complicated by the observed weight regain upon discontinuation of treatment. Studies have shown that a significant proportion of patients experience weight regain after stopping GLP-1 RA therapy, with some regaining up to two-thirds of their lost weight within a year of discontinuation. This phenomenon underscores the potential need for long-term or continuous treatment to maintain weight loss benefits.[59]

However, several factors must be considered when contemplating extended GLP-1 RA therapy. These include the potential for long-term side effects, which are not yet fully understood due to limited data beyond a few years of treatment. Additionally, the high cost of these medications and potential issues with long-term adherence in real-world settings may impact the feasibility of indefinite treatment.[60]

Preventing Neurodegeneration

While GLP-1 receptor agonists (GLP-1RAs) have shown promise in potentially reducing the risk of dementia and Alzheimer's disease, significant knowledge gaps remain regarding their neuroprotective effects. Although studies have demonstrated that GLP-1RAs can improve weight management, glucose control, and cardiovascular health, which are all risk factors associated with neurodegenerative diseases, the direct impact on preventing neurodegeneration is not yet fully understood. More robust clinical trials are needed to establish a causal relationship between GLP-1RA use and reduced dementia risk. Additionally, the mechanisms by which these drugs may protect against cognitive decline require further elucidation 17. As research progresses, it will be crucial to determine the optimal timing, dosage, and duration of GLP-1RA treatment for maximizing potential neuroprotective benefits.[61,62]

Conclusion

The role of GLP-1 in the management of type 2 diabetes mellitus (DM2) and obesity has transformed treatment strategies for these metabolic disorders. As an incretin hormone, GLP-1 enhances insulin secretion, suppresses glucagon release, delays gastric emptying, and modulates appetite regulation. These multifaceted actions have led to the development of GLP-1 receptor agonists (GLP-1 RAs) as effective therapeutic agents in both conditions.

For diabetes therapy, GLP-1 RAs primarily function as glucose-lowering agents by improving pancreatic β-cell function, increasing insulin secretion, and reducing glucagon levels in a glucose-dependent manner. They have demonstrated superior efficacy in glycemic control compared to conventional therapies, with additional benefits in reducing cardiovascular risk factors. Current GLP-1-based treatments, including exenatide, liraglutide, dulaglutide, semaglutide, and tirzepatide, offer varying pharmacokinetic profiles that allow for once-daily or once-weekly dosing, improving patient adherence. Additionally, combination therapies such as GLP-1/GIP dual agonists are showing promise in further enhancing glycemic control and weight reduction in diabetic patients.

For obesity therapy, GLP-1 RAs primarily exert their effects through appetite suppression and delayed gastric emptying, leading to reduced caloric intake and sustained weight loss. Unlike traditional weight management strategies, GLP-1-based therapies target the neuroendocrine regulation of hunger and satiety, making them highly effective in obesity treatment. Clinical trials have demonstrated that higher doses of semaglutide and tirzepatide produce substantial weight loss, often exceeding 15% of baseline body weight. The emergence of dual and triple incretin receptor agonists offers new opportunities for enhancing weight reduction in patients with obesity, even in the absence of diabetes.

While GLP-1 therapies have significantly improved the management of both DM2 and obesity, several challenges remain, including patient variability in response, gastrointestinal side effects, cost considerations, and long-term adherence. Further research is needed to optimize treatment protocols, develop more personalized approaches, and explore novel combination therapies.

In conclusion, GLP-1-based therapies represent a major advancement in metabolic disease management, offering effective solutions for both diabetes and obesity. Their unique ability to improve glycemic control while promoting weight loss makes them an essential component of modern treatment strategies. Future research should continue refining these therapies to maximize patient outcomes and address the growing burden of metabolic disorders worldwide.

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