GLP-1 Receptor Agonists in Metabolic Medicine: Mechanisms, Clinical Applications, Current Challenges, and Future Directions

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Abstract

Glucagon-like peptide-1 receptor agonists, often referred to as GLP-1RAs, may have ushered in a new era for treating type-2 diabetes, obesity, and adjacent metabolic ailments. These drugs bolster the natural effects of GLP-1, a gut hormone that assists the body in insulin release following meals, by reducing glucagon secretion, stagnating gastric emptying, and increasing the sensation of satiation. Due to natural GLP-1 being quickly broken down by dipeptidyl petidase-4 (DPP-4), researchers have developed longer-lasting synthetic alternatives that remain active for extended periods of time.

The following evaluation serves to examine how GLP-1 operates within the body, how alternatives have developed over time, and how they are being utilized in treating diabetes, obesity, heart disease reduction, and liver disease research. Although the benefits are nontrivial, there are legitimate practical and clinical concerns including gastrointestinal side effects, lean muscle loss, high cost, limited accessibility, and long term efficacy. In the future, research is likely to hone in on better-tolerated drugs, oral and small-molecule options, and therapies that simultaneously target multiple receptors.

1 Introduction

Metabolic disorders like type-2 diabetes (T2D) and obesity remain two of the most prevalent health issues across the globe (Nauck & Meier, 2018). For years, treating T2D has revolved around lowering blood glucose via insulin, sulfonylureas, metformin, and other glucose-reducing drugs. While these methods have shown to be beneficial, some traditional treatments have shown to cause hypoglycemia, leading to unwanted weight gain and others fail to address the decline in pancreatic β-cell function.

The discovery of incretin hormones has altered how clinicians and researchers view glucose regulation. Two of the most prominent incretin hormones are glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) (Holst, 2007). Among healthy people, oral food consumption produces a vastly stronger insulin response than intravenously receiving identical amounts of glucose. For those with T2D, the response is lower, partially due to β-cells being less responsive to incretin signaling (Nauck & Meier, 2018).

GLP-1 has risen in significance due to improved insulin secretion in a glucose-dependent manner; this leads to the pancreas releasing insulin while glucose is elevated and a lower risk of hypoglycemia than traditional diabetes medication. Nevertheless, naturally occurring GLP-1 only lasts for a few minutes in the body due to the aforementioned effects of DPP-4. GLP-1RAs have been designed to overcome this limitation and can last for hours or even days (Holst, 2007).

As a result, therapies based on GLP-1s are no longer viewed as exclusively glucose-lowering drugs, and they are now used and studied for weight loss, cardiovascular protection, kidney health, and liver disease. Simultaneously, many problems like reduced tolerability due to gastrointestinal symptoms, lean mass loss, retaining benefits following the end of treatment, and limited accessibility remain unresolved (Drucker, 2018).

2 Literature Review

2.1 Physiological Mechanisms and Incretin Action

GLP-1 is composed of thirty amino acids which derive from the proglucagon precursor, and Enteroendocrine L-cells in the distal ileum and colon are the main sources of secretion in the body. Additionally, GLP-1 is also produced by certain neurons in the brainstem's nucleus tractus solitarius. Following nutrients entering the intestines, L-cells release GLP-1, which then assists in the coordination of numerous metabolic processes.

One of the primary actions of GLP-1 occurs in the pancreas when GLP-1 binds to GLP-1 receptors on pancreatic β-cell, activating a signaling pathway involving adenylate cyclase, cyclic

AMP (cAMP), protein kinase A (PKA), and cAMP-regulated guanine nucleotide exchange factor II (Epac2) (Holst, 2007). This pathway consolidates the glucose-stimulated secretion of insulin. This effect critically depends on the presence of elevated glucose, offering a possible explanation of why GLP-1RAs have a relatively low risk of causing hypoglycemia when used independent of insulin or sulfonylureas.

Additionally, GLP-1 limits glucagon secretion from pancreatic α-cells, appearing to occur partially due to somatostatin release from adjacent δ -cells (Drucker, 2018). Lower glucagon levels lessen hepatic glucose production thereby improving fasting and postprandial blood glucose levels.

Outside of the pancrease, GLP-1 slows gastric emptying; this delays the movement of food from the stomach into the intestines and assists in limiting sharp increases in blood glucose following meals. Signals from circulating GLP-1 and locally produced neuronal GLP-1 impact areas of the brain involved with hunger and satiety such as the arcuate nucleus, paraventricular nucleus, and hindbrain. Through these pathways, GLP-1 reduces appetite and overall caloric intake (Drucker, 2018).

2.2 Clinical Applications: Glycemic Control, Weight Management, and Organ Protection

GLP-1RAs are utilized in several sectors of metabolic medicine.

For T2D, GLP-1RAs commonly lower HbA1c by about one to two percentage points, improve insulin secretion after meals, and reduce excess glucagon, restoring a more normal post-meal glucose pattern (Nauck & Meier, 2018). Because their insulin-stimulating effect is glucose-dependent, GLP-1RAs are less likely to cause hypoglycemia compared to most traditional diabetes therapies (Drucker, 2018).

In regards to obesity, higher-dose GLP-1RA treatment produces substantial weight loss. Examples include daily dosages of 3.0mg liraglutide and weekly dosages of 2.4mg semaglutide.

In large clinical trials, these medications have been associated with weight loss ranging from about 8% to more than 15% of total body weight. The main driver of this effect is reduced energy intake through increased satiety, rather than a large increase in daily energy expenditure (Drucker, 2018).

Moreover, GLP-1RAs appear to provide cardiovascular benefits in high-risk patients. Cardiovascular outcome trials such as LEADER for liraglutide and SUSTAIN-6 for semaglutide found reductions in major adverse cardiovascular events, including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death among patients with T2D at elevated cardiovascular risk. These benefits may not be explained by glucose lowering alone. Anti-inflammatory effects, improvements in endothelial function, weight loss, and changes in blood pressure or lipids may all contribute (Drucker, 2018).

Finally, there is growing interest in liver and kidney effects. In non-alcoholic steatohepatitis (NASH), GLP-1RAs may reduce liver fat, inflammation, and fibrosis progression. Secondary analyses from cardiovascular outcome trials have also suggested kidney benefits, including stagnated decline in estimated glomerular filtration rate and reduced macroalbuminuria (Drucker, 2018).

3 Research Gaps and Future Directions

Despite the progress made with GLP-1-based therapies, several questions remain important.

First, gastrointestinal tolerability continues to be a major limitation. Nausea, vomiting, diarrhea, and constipation are among the most common adverse effects (Drucker, 2018). Gradual dose escalation can help many patients, but some still stop treatment because the symptoms are difficult to manage. Newer drug designs, including biased agonists that favor certain intracellular signaling pathways, may eventually improve tolerability.

Second, additional research is needed on body composition. Weight loss with GLP-1RAs includes both fat mass and some lean mass. This is especially important for older adults and

people at risk for sarcopenia. Future strategies may combine GLP-1RAs with resistance training, adequate protein intake, or drugs that help preserve muscle.

Third, multi-receptor agonists are changing the field. Tirzepatide, a dual GIP and GLP-1 receptor agonist, has shown strong effects on glucose control and weight loss. Other agents, such as retatrutide, target GLP-1, GIP, and glucagon receptors (Finan et al., 2015) . These medicines suggest that future metabolic therapy may rely less on single receptor treatment and more on coordinated signaling across several hormonal pathways .

Fourth, long-term treatment durability remains a concern. Many patients regain weight and experience worsening glycemic control after stopping GLP-1RA therapy. This suggests that these drugs may need to be viewed as long-term treatments for chronic disease rather than short-term interventions. More studies are needed to determine maintenance doses, discontinuation strategies, and realistic long-term treatment plans.

Finally, access and cost are major barriers. GLP-1RAs are expensive, and supply shortages have made access considerably inequitable. Injectable peptide drugs can also be more difficult to manufacture and distribute than many traditional medicines. Oral small-molecule GLP-1 receptor agonists may eventually reduce cost and improve availability, but more evidence is needed before they can replace current therapies (Davies et al., 2017).

4 Conclusion

Glucagon-like peptide-1 receptor agonists represent a landmark advancement in metabolic medicine. By harnessing incretin biology, GLP-1RAs provide effective glycemic normalization, substantial weight loss, and broad cardiovascular and renal protection. The field continues to evolve beyond single-receptor mono-therapeutics toward oral formulations, biased signaling molecules, and multi-agonist combinations. As research clarifies the mechanisms of GLP-1 action across diverse organ systems, GLP-1-based therapies will play an increasingly prominent role in mitigating the global burden of metabolic disease.

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