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Mini Review

GLP-1 Receptor Agonists beyond Glycemic Control: Physiology and Pharmacological Evidence

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Abstract

Glucagon-like peptide-1 receptor agonists were initially developed for the treatment of type 2 diabetes mellitus because they enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, and reduce appetite. In recent years, their use has expanded beyond glycemic control. Clinical studies have reported effects on body weight, cardiovascular outcomes, chronic kidney disease, and metabolic liver disease. Semaglutide reduced major adverse cardiovascular events in patients with overweight or obesity and established cardiovascular disease without diabetes in the SELECT trial. In the FLOW trial, semaglutide reduced clinically important kidney outcomes in patients with type 2 diabetes and chronic kidney disease. Tirzepatide, a dual GIP and GLP-1 receptor agonist, produced substantial body-weight reduction in adults with obesity or overweight without diabetes. GLP-1-based therapies have also been evaluated in metabolic dysfunction-associated steatohepatitis and inflammatory conditions. However, many observed benefits may be related to weight reduction, improved insulin sensitivity, lower blood pressure, and reduced metabolic stress. Therefore, direct receptor-mediated effects should be interpreted carefully. This mini review summarizes the physiological basis and current pharmacological evidence for GLP-1 receptor agonists beyond glucose lowering.

Introduction

Glucagon-like peptide-1 (GLP-1) is an incretin peptide secreted mainly from intestinal L-cells after nutrient intake. It regulates postprandial glucose levels by increasing insulin secretion in a glucose-dependent manner and reducing glucagon secretion. Native GLP-1 has a short biological half-life because it is rapidly degraded by dipeptidyl peptidase-4. To overcome this limitation, long-acting GLP-1 receptor agonists were developed for clinical use [1-3]. GLP-1 receptor agonists were first used mainly for type 2 diabetes mellitus. Over time, studies showed that their effects are not limited to glucose control. They also influence appetite, body weight, cardiovascular risk, kidney-related outcomes, and liver metabolism. Because of this, drugs such as liraglutide, semaglutide, dulaglutide, and tirzepatide are now often viewed as broader metabolic therapies rather than only antidiabetic agents. Drucker has also discussed this shift, describing GLP-1-based therapies as an expanding treatment class for diabetes, obesity, and related cardiometabolic disorders [4].

Clinical outcome studies also support this broader use. In patients with type 2 diabetes, liraglutide reduced cardiovascular events in the LEADER trial, semaglutide showed cardiovascular benefit in SUSTAIN-6, and dulaglutide showed similar benefit in REWIND [5,6]. More recently, the SELECT trial studied semaglutide in patients with overweight or obesity who already had cardiovascular disease but did not have diabetes. In that study, major adverse cardiovascular events were lower with semaglutide than with placebo [7].

Physiological basis of GLP-1 Action

The GLP-1 receptor is a class B G-protein-coupled receptor. After activation, it increases intracellular cyclic AMP and affects several processes, including insulin secretion, gastric

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emptying, appetite regulation, and cellular stress responses. In pancreatic β-cells, GLP-1 receptor activation increases insulin release mainly when blood glucose levels are high. Because of this glucose-dependent action, the risk of hypoglycemia is lower than with older insulin secretagogues. GLP-1 also works through gastrointestinal and central pathways. It delays gastric emptying and reduces appetite through gut-brain signalling. GLP-1 released from the intestine can act through vagal afferent pathways and brainstem regions involved in feeding behaviour. GLP-1-producing neurons in the nucleus tractus solitarius are also involved in satiety, nausea, autonomic control, and stress responses [1,3,8,9].

These actions help explain why GLP-1 receptor agonists reduce both glucose levels and body weight. At the same time, they make the clinical effects harder to interpret. When body weight decreases, insulin sensitivity, blood pressure, liver fat, inflammation, and cardiovascular workload may also improve. Because of this, the benefits of GLP-1 receptor agonists may come from both direct receptor-mediated actions and indirect metabolic improvement [4,10,11].

Molecular and cellular mechanisms

At the molecular level, GLP-1 receptor activation is mainly linked with cyclic AMP-dependent signalling, but its downstream effects are not limited to insulin secretion. Several studies suggest that GLP-1 receptor agonists may improve cellular energy handling by influencing mitochondrial function, oxidative stress, and substrate metabolism. Improvement in mitochondrial respiration and redox balance has been reported after GLP-1 receptor agonist treatment, along with reduction in inflammatory and vascular stress markers. These effects are relevant because mitochondrial dysfunction and oxidative stress are common features of obesity, type 2 diabetes, atherosclerosis, chronic kidney disease, and metabolic liver disease [12,13].

GLP-1-based therapies may also affect cellular energy metabolism by improving glucose utilization, fatty acid oxidation, and lipid handling. In metabolic tissues, these changes may reduce lipotoxicity and improve insulin sensitivity. In the liver, GLP-1 receptor agonists have been reported to reduce hepatic fat accumulation, improve liver enzymes, and influence pathways related to de novo lipogenesis and fatty acid oxidation. However, the hepatic effects should be interpreted carefully because weight loss and improved insulin resistance also contribute strongly to the reduction in liver fat and inflammation [12,14,15].

In metabolic liver disease, the possible mechanisms include reduced hepatic lipid accumulation, lower oxidative stress, improved insulin sensitivity, and reduced inflammatory signalling. Some experimental studies suggest direct hepatic or indirect neuro-metabolic effects, but hepatic GLP-1 receptor expression and its functional relevance remain debated. Therefore, the liver benefits of GLP-1 receptor agonists are better explained as a combination of systemic metabolic improvement and possible tissue-level mechanisms, rather than a purely direct antifibrotic action [16,17].

Effects on obesity and cardiovascular outcomes

Most obesity-related data for this class come from studies with semaglutide and tirzepatide. Semaglutide reduces body weight mainly by suppressing appetite, lowering energy intake, and delaying gastric emptying [18]. Tirzepatide has a broader incretin profile because it acts on both glucose-dependent insulinotropic polypeptide and GLP-1 receptors. In the SURMOUNT-1 trial, tirzepatide was studied in adults with obesity or overweight without diabetes and showed sustained body-weight reduction over 72 weeks [19]. Cardiovascular outcomes have also been assessed in large clinical trials. In the SELECT trial, patients with overweight or obesity and established cardiovascular disease, but without diabetes, were treated with semaglutide or placebo. The primary cardiovascular endpoint occurred in 569 of 8803 patients in the semaglutide group and 701 of 8801 patients in the placebo group, corresponding to event rates of 6.5% and 8.0%, respectivel. This finding is important because the patients in SELECT did not have diabetes. Therefore, the cardiovascular benefit cannot be linked only to glucose lowering. Other factors such as weight reduction, lower blood pressure, improved lipid profile, reduced vascular inflammation, and better endothelial function may also contribute. Overall, the evidence supports GLP-1 receptor agonists as cardiometabolic therapies, although the exact role of each mechanism is still not fully clear [20].

The cardiovascular benefits of GLP-1 receptor agonists are unlikely to be explained only by glucose lowering. This is supported by the SELECT trial, where semaglutide reduced major adverse cardiovascular events in patients with overweight or obesity and established cardiovascular disease without diabetes. Other mechanisms may therefore contribute to the observed cardiovascular protection. Several mechanisms have been proposed. Weight reduction can lower cardiovascular workload and improve blood pressure, lipid profile, insulin resistance, and systemic inflammation. GLP-1 receptor agonists may also improve endothelial function and reduce vascular oxidative stress. Endothelial protection is important because endothelial dysfunction is closely involved in atherosclerosis, vascular inflammation, and impaired nitric oxide signalling. Reviews on GLP-1 receptor agonists and cardiovascular biology suggest that these drugs may influence vascular inflammation, oxidative stress, endothelial repair, and atherosclerotic processes [21-23].

Anti-inflammatory effects may also contribute to cardiovascular benefit. GLP-1-based therapies have been reported to reduce inflammatory signalling in metabolic and vascular tissues. Proposed mechanisms include reduced NF-κB activation, lower oxidative stress, altered macrophage activity, and improved endothelial homeostasis. Still, these mechanisms should be described cautiously because clinical cardiovascular outcomes may result from combined effects of weight loss, improved metabolic control, blood pressure reduction, vascular protection, and possible direct cardiovascular actions [24,25].

Kidney protection

Kidney-related benefits were initially noted as secondary findings in earlier cardiovascular outcome trials. The

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FLOW trial gave more direct evidence for this area because it specifically studied semaglutide in patients with type 2 diabetes and chronic kidney disease. Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes. The renal effect may be due to multiple factors. Improved glycemic control can reduce metabolic stress on the kidney. Weight loss and lower blood pressure may reduce glomerular injury. Reduction in albuminuria, vascular stress, oxidative stress, and inflammation may also be involved. However, it is difficult to assign the renal benefit to direct GLP-1 receptor activation alone. Human kidney outcomes are likely influenced by both systemic metabolic changes and tissue-level effects [26-29].

Metabolic liver disease

GLP-1 receptor agonists have also been studied in metabolic liver disease. This is relevant because obesity, insulin resistance, hepatic fat accumulation, and inflammation are major drivers of metabolic dysfunction-associated steatohepatitis. Liraglutide was evaluated in the LEAN trial and was reported to improve histological resolution of non-alcoholic steatohepatitis compared with placebo. Semaglutide has been evaluated further in metabolic dysfunction-associated steatohepatitis. In the phase 3 ESSENCE trial, semaglutide improved liver histology in patients with biopsy-defined MASH and fibrosis. A reduction in liver fibrosis without worsening of steatohepatitis was reported in 36.8% of patients in the semaglutide group and 22.4% in the placebo group [30-32].

Tirzepatide has also been evaluated in MASH with liver fibrosis. In the SYNERGY-NASH trial, tirzepatide was superior to placebo for resolution of MASH without worsening of fibrosis over 52 weeks. These findings indicate that incretin-based therapy may be useful in metabolic liver disease. However, liver benefits should be interpreted along with weight reduction and improved insulin resistance. At present, GLP-1-based therapy appears more clearly linked with metabolic improvement than with a purely direct antifibrotic mechanism [33-35].

Inflammation and immune-related effects

Inflammation is involved in obesity, type 2 diabetes, atherosclerosis, chronic kidney disease, and metabolic liver disease. GLP-1 receptor agonists may reduce inflammatory burden through weight loss-dependent and weight loss-independent mechanisms. A recent review in the *Journal of Clinical Investigation* described anti-inflammatory effects of GLP-1-based therapies in mice and humans and discussed both direct and indirect mechanisms. Proposed mechanisms include reduced NF-κB activation, lower oxidative stress, decreased cytokine release, altered macrophage activity, and improved endothelial function. However, receptor expression in some immune and peripheral tissues remains difficult to define. Therefore, it is more appropriate to state that GLP-1 receptor agonists reduce inflammatory burden in metabolic disease, rather than describing them as direct anti-inflammatory drugs in all tissues [24,36-38].

Neuroprotective evidence

GLP-1 receptor agonists have been investigated in neurodegenerative disorders because GLP-1 signaling may affect brain metabolism, mitochondrial function, neuronal stress, and neuroinflammation. Parkinson's disease has received particular attention. Earlier clinical studies with exenatide suggested possible benefit, but a later phase 3 randomized trial did not confirm disease-modifying efficacy.

In the 2025 phase 3 trial, once-weekly exenatide was compared with placebo in people with Parkinson's disease. The study reported no evidence to support exenatide as a disease-modifying treatment. Thus, neuroprotection should be discussed cautiously. The biological rationale is present, but clinical confirmation is limited. Further studies may need improved patient selection, longer follow-up, better central nervous system exposure, and validated biomarkers before GLP-1 receptor agonists can be considered useful in neurodegenerative disease [39-41].

Safety and current limitations

Gastrointestinal adverse effects such as nausea, vomiting, diarrhea, and constipation are common with GLP-1 receptor agonists. These effects are usually related to dose escalation and delayed gastric emptying. Gallbladder and biliary events are also clinically relevant. A systematic review and meta-analysis of randomized clinical trials reported that GLP-1 receptor agonist use was associated with increased risk of gallbladder or biliary diseases, especially at higher doses, longer treatment duration, and use for weight loss.Another limitation is long-term dependence on therapy. Weight regain and worsening of metabolic risk factors may occur after treatment discontinuation. Long-term use may also be limited by cost, availability, need for injections, and tolerability in some patients. A major limitation is that direct GLP-1 receptor-mediated effects are difficult to separate from the secondary effects of weight loss. After weight reduction, several changes occur at the same time. Blood pressure may decrease, insulin sensitivity may improve, hepatic fat may reduce, and inflammatory markers may also fall. Because of this overlap, mechanistic conclusions need to be made carefully [4,42-45].

Conclusion

GLP-1 receptor agonists were first developed as glucose-lowering drugs, but current evidence supports a wider pharmacological role. Their strongest established uses are in type 2 diabetes mellitus, obesity, cardiovascular risk reduction, and chronic kidney disease. Evidence in metabolic liver disease is also increasing, especially with semaglutide and tirzepatide. However, some indications are still evolving, and direct organ-specific mechanisms should not be overinterpreted. The concept of GLP-1 receptor agonists as multi-system metabolic therapies is promising, but it remains an area of ongoing investigation. Their benefits appear to involve combined effects on appetite, body weight, insulin sensitivity, vascular function, renal stress, hepatic lipid metabolism, oxidative stress, and inflammatory burden. Further studies are required to separate direct GLP-1 receptor-mediated effects from secondary benefits related to weight loss and improved metabolic health.

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