



MOLECULAR AND CELLULAR MECHANISMS OF GLP-1 RECEPTOR AGONISTS AND THEIR EMERGING CLINICAL APPLICATIONS

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Abstract

In the 21st century, obesity and type 2 diabetes mellitus represent some of the greatest challenges in modern medicine, affecting hundreds of millions of people worldwide and leading to systemic multiorgan dysfunction caused by cellular stress, glucotoxicity, and lipotoxicity. Glucagon-like peptide-1 (GLP-1) receptor agonists represent a promising incretin-based therapies, replacing the purely glucocentric model with an adipocentric approach that modulates the cellular mechanisms of metabolic diseases. By activating intracellular pathways dependent on cAMP, PKA, and Epac2, GLP-1RAs not only enhance glucose-dependent insulin secretion and suppress appetite but also actively reduce endoplasmic reticulum stress and protect pancreatic beta cells from apoptosis. Their pleiotropic effects extend significantly beyond glycemic control, demonstrating proven benefits in preventing pathological cardiac remodeling, improving vascular endothelial function, reducing oxidative stress in the kidneys, and modulating neuroinflammatory pathways. Despite substantial cardiometabolic and nephroprotective advantages, GLP-1 receptor agonist therapy is associated with safety concerns, such as gastrointestinal symptoms caused by delayed gastric emptying and an increased risk of biliary disorders. Given the complexity of these multiorgan effects, further studies with extended follow-up periods are essential to determine which benefits are direct receptor-mediated effects and which result secondarily from weight loss.

Running title: Mechanisms of action of GLP-1 receptor agonists

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Introduction

In the 21st century, obesity and type 2 diabetes mellitus (T2DM) pose major challenges in modern medicine. It is estimated that approximately 462 million people worldwide (6.28% of the global population) are affected by type 2 diabetes. Projections indicate that pathologies associated with high BMI-induced T2DM will continue to increase by 2045 [1,2]. To comprehensively understand this problem, it is necessary to examine it not only from a clinical perspective but also at the cellular level. Chronic caloric excess overloads cells and organs with an excess of energy substrates, leading to intracellular gluco- and lipotoxicity. Lipid and glucose overload induces endoplasmic reticulum (ER) stress, resulting in dysregulated adipokine secretion and generalized multiorgan dysfunction [3]. These cellular processes expose the limitations of the long-standing glucocentric approach, as focusing solely on lowering blood glucose levels neither reduced cellular stress nor decreased mortality associated with cardiovascular events. Consequently, this approach is increasingly being replaced by the adipocentric model [4], which focuses on reducing adipose tissue accumulation. Glucagon-like peptide-1 (GLP-1) receptor agonists fit within this concept, as they directly target the cellular mechanisms of the disease [5]. The development of this class of drugs was based on understanding the concept of the incretin effect.

The “incretin effect” refers to the phenomenon in which oral glucose administration elicits a greater insulin response than intravenous glucose administration despite an identical glycemic stimulus [6]. This process is driven by the incretin hormones glucose-dependent insulintropic polypeptide (GIP) and GLP-1, which are secreted by intestinal enteroendocrine cells (EECs) and whose secretion increases following nutrient intake [6,7]. GLP-1 plays a particularly important role in the gut–pancreas axis, where it enhances insulin secretion and suppresses glucagon release. In addition, it delays gastric emptying and suppresses appetite, consequently maximizing nutrient absorption while limiting weight gain. These properties have made the incretin system – and particularly GLP-1-mediated signaling – a major target in the modern treatment of type 2 diabetes and obesity, ultimately leading to the development of GLP-1 receptor agonists [7].

Initially, the primary clinical limitation of native GLP-1 was its very short plasma half-life (1.5–2 minutes) [8]. A breakthrough in the development of the first effective incretin-based therapies came with the discovery of exendin-4 in the venom of *Heloderma suspectum*, which

acts as a full GLP-1 receptor agonist and displays a longer half-life than native GLP-1 [9]. This discovery led to the development of the first drug in this class, exenatide, followed by later generations of long-acting agents such as semaglutide and liraglutide, including oral formulations of semaglutide [8,10]. The clinical benefits of GLP-1 receptor agonists resulted in the expansion of their clinical use from the treatment of type 2 diabetes to the management of obesity and related metabolic disorders [8].

The wide-ranging clinical advantages of GLP-1 receptor agonists were established in clinical practice sooner than the intracellular mechanisms underlying these effects could be fully understood [11–13]. Although it is now recognized that the effects of GLP-1 receptor agonist therapy extend beyond glucose lowering alone [11], understanding the full spectrum of their cellular actions remains an active area of research [12].

The aim of this article is to systematize current knowledge relating to the consequences of activating GLP-1-related signaling pathways that mediate the reduction of cellular stress and apoptosis. An analysis of these cellular mechanisms will allow for a more comprehensive understanding of the emerging clinical applications of GLP-1 receptor agonists, including their cardioprotective, nephroprotective, and neuroprotective effects.

Characteristics and pharmacokinetics of GLP-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) constitute a structurally diverse class of peptide therapeutics that activate the GLP-1 receptor, a Class B G protein-coupled receptor. They reproduce the physiological actions of endogenous GLP-1, primarily glucose-dependent insulin stimulation, glucagon suppression, and delayed gastric emptying. However, native GLP-1 secreted by intestinal L-cells has a plasma half-life of only 1–2 minutes due to rapid inactivation by dipeptidyl peptidase-4 (DPP-4), which cleaves the peptide bond at the N-terminus between alanine at position 8 (Ala8) and glutamate at position 9 (Glu9). Consequently, the therapeutic utility of GLP-1RAs relies entirely on targeted structural modifications that confer resistance to enzymatic proteolysis and prolong systemic exposure [14,15].

Clinically utilized agents are categorized into short-acting (exenatide, lixisenatide) and long-acting formulations (liraglutide, dulaglutide, semaglutide), alongside the structurally related dual GIP/GLP-1 receptor agonist, tirzepatide [16]. Most GLP-1RAs require subcutaneous administration due to the poor gastrointes-

tinal stability and limited passive permeability inherent to peptide drugs.

Short-acting agents are based on the exenadin-4 structure and exhibit natural DPP-4 resistance due to an amino acid substitution at position 8 (e.g., Ala8→Gly in exenatide). Lixisenatide features an additional C-terminal modification of six lysine residues. With half-lives of approximately 2–4 hours, these agents are administered once or twice daily. Because their intermittent pharmacokinetic profile prevents the development of receptor tachyphylaxis, short-acting agents persistently slow gastric emptying, making them highly effective at blunting postprandial glucose excursions [17,18].

Conversely, long-acting human GLP-1 analogues provide continuous receptor stimulation to achieve deeper reductions in fasting glucose. Because continuous exposure induces rapid tachyphylaxis to delayed gastric emptying, their profound glycemic efficacy relies predominantly on sustained fasting insulin secretion and glucagon suppression [17]. Their prolonged pharmacokinetics are engineered through several distinct mechanisms. Liraglutide incorporates a C16 fatty acid side chain covalently attached to Lys26, which enables reversible, non-covalent binding to plasma albumin. This creates an endogenous depot that shields the peptide from renal clearance, extending its half-life to approximately 13 hours and permitting once-daily dosing [19,20].

Semaglutide represents a robust pharmacokinetic refinement of this strategy. It introduces an Ala8→Aib (α -aminoisobutyric acid) substitution to strictly prevent DPP-4 cleavage, alongside the acylation of Lys26 with a C18 fatty diacid attached via a hydrophilic mini-PEG spacer. These modifications drastically increase albumin affinity and limit renal clearance, extending the half-life to approximately 7 days to enable once-weekly subcutaneous dosing [21,22]. Tirzepatide utilizes a similar engineering strategy by employing a C20 fatty diacid moiety that supports robust albumin binding and yields an approximate 5-day half-life [23–25]. Rather than fatty acid acylation, dulaglutide achieves a 5-day half-life via fusion of modified GLP-1 analogues to an immunoglobulin IgG4 Fc fragment, which increases molecular bulk to prevent glomerular filtration [26].

Uniquely, semaglutide is also available as an oral tablet. This is achieved through co-formulation with the absorption enhancer sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC), which promotes localized transcellular gastric absorption and buffers against proteolytic degradation. Although absolute oral bioavailability remains low (approximately

1%) and requires administration under strict fasting conditions, semaglutide's long intrinsic half-life sustains clinically useful systemic distribution with once-daily dosing [27,28].

Regarding elimination, GLP-1RAs avoid major hepatic cytochrome P450 metabolism, thereby minimizing pharmacokinetic drug-drug interactions. While short-acting exenatide undergoes primary clearance via glomerular filtration and subsequent tubular proteolysis, large fusion proteins (dulaglutide) and strongly albumin-bound agents (liraglutide, semaglutide, tirzepatide) effectively evade renal excretion. Instead, they are slowly cleared via generalized, ubiquitous protein catabolism pathways that degrade them into constituent amino acids [16].

Molecular and cellular mechanisms in pancreatic β -cells

The cellular actions of GLP-1 receptor agonists are initiated through activation of the glucagon-like peptide-1 receptor (GLP-1R), a class B1 G protein-coupled receptor highly expressed in pancreatic β -cells [29]. Upon agonist binding, the receptor undergoes structural transitions enabling its interaction with heterotrimeric Gs proteins, resulting in activation of adenylyl cyclase and a rapid increase in intracellular cyclic adenosine monophosphate (cAMP) levels [14,30]. This signaling cascade constitutes the molecular basis of the incretin effect, whereby oral glucose administration elicits a substantially greater insulin secretory response than an equivalent intravenous glucose load [31]. Recent structural and signaling studies have further demonstrated that GLP-1R activity is spatially organized within specialized signaling nanodomains that concentrate cAMP and its downstream effectors, thereby enhancing signaling efficiency [29]. In addition, GLP-1R signaling is not restricted to the plasma membrane. Following activation, the receptor undergoes dynamic trafficking between the cell surface and endosomal compartments, allowing the persistence of intracellular cAMP signaling after internalization [32]. This compartmentalized signaling architecture contributes to the regulation of downstream signaling pathways involved in β -cell function and insulin secretion [29,32].

The increase in intracellular cAMP initiates two complementary signaling pathways that amplify glucose-stimulated insulin secretion. The first is mediated by protein kinase A (PKA), which promotes membrane depolarization through modulation of ATP-sensitive potassium (KATP) channels and facilitates the opening of voltage-dependent calcium channels. The re-

sulting influx of extracellular calcium serves as a critical trigger for insulin granule exocytosis. In addition to calcium entry through the plasma membrane, cAMP signaling further enhances intracellular calcium dynamics by promoting calcium release from endoplasmic reticulum stores through ryanodine receptors, thereby strengthening the secretory response [33].

Alongside PKA activation, cAMP directly engages a second effector pathway through exchange protein directly activated by cAMP 2 (Epac2), originally identified as a cAMP-regulated guanine nucleotide exchange factor involved in regulated exocytosis [34]. Activation of Epac2 stimulates the small GTPase Rap1, which plays a central role in insulin granule trafficking and recruitment of secretory vesicles to the plasma membrane [35]. Consequently, the coordinated actions of PKA-dependent calcium signaling and Epac2/Rap1-mediated vesicle mobilization enhance the efficiency of glucose-stimulated insulin secretion following GLP-1 receptor activation.

The elevation of intracellular calcium generated through PKA- and Epac2-dependent signaling ultimately converges on the exocytotic machinery responsible for insulin release. Synaptotagmins act as calcium sensors that couple intracellular calcium signals to vesicle fusion events [36]. Following calcium binding, these proteins interact with membrane phospholipids and components of the SNARE complex, thereby facilitating fusion of insulin-containing granules with the plasma membrane [37]. In addition to predocked granules, β -cells recruit newly arriving secretory vesicles that contribute to sustained insulin secretion during prolonged stimulation, a process enhanced by cAMP signaling [37].

Importantly, insulin secretion is coordinated at the level of the entire pancreatic islet. Gap junction-mediated coupling synchronizes membrane potential oscillations, intracellular calcium dynamics, and secretory activity between neighboring β -cells [38]. As a result, local cAMP-dependent signals are integrated across the islet, generating coordinated pulses of insulin release that contribute to the maintenance of glucose homeostasis [38].

Beyond its acute effects on insulin secretion, cAMP signaling also regulates transcriptional programs that support long-term β -cell function and growth. In pancreatic β -cells, activation of the cAMP/PKA pathway promotes phosphorylation of the transcription factor CREB and facilitates recruitment of its coactivator CRTC2 [39,40]. Following nuclear translocation, the CREB/CRTC2 complex binds to cAMP-responsive regulatory elements and stimulates tran-

scription of genes involved in maintaining β -cell identity and insulin production [39,41]. In addition to sustaining functional capacity, this transcriptional program contributes to adaptive β -cell growth through regulation of cell-cycle genes. Notably, CREB-dependent signaling increases cyclin D1 expression, thereby promoting G1-to-S phase progression and supporting β -cell proliferation [40].

The cytoprotective effects of GLP-1 receptor signaling become particularly important under conditions of glucolipotoxic stress. Akt activation attenuates endoplasmic reticulum stress by increasing BiP expression and suppressing CHOP signaling [42]. In parallel, this pathway promotes cell survival by inhibiting pro-apoptotic proteins such as Bax and Bad while enhancing the activity of anti-apoptotic factors including Bcl-2 and Bcl-xL [43]. Furthermore, Akt-mediated inhibition of GSK-3 β contributes to the stabilization of PDX-1, which is essential for maintaining β -cell identity and insulin-secretory function [44]. Collectively, these mechanisms contribute to the preservation of functional β -cell mass and provide a molecular basis for the protective effects of GLP-1 receptor agonists on pancreatic islets.

Metabolic and neuroendocrine effects

The metabolic and neuroendocrine pathways linking central and peripheral control of appetite and nutrient sensing are influenced by GLP-1 [5,7]. Following food consumption, GLP-1 is released by endocrine L-cells in the gut, activating vagal afferent neurons. Via the nucleus tractus solitarius (NTS) and the area postrema (AP), this pathway carries visceral signals to higher regulatory centers [7,45,46]. These structures, in conjunction with the vagal nuclei, constitute the dorsal vagal complex, which combines circulating chemical signals, afferent input, and the gastrointestinal system's autonomic outputs [45,47]. Because of their greater stability, pharmacological GLP-1 agonists can influence specific brain regions, such as the AP, brainstem, and hypothalamus, as well as periventricular and circumventricular areas. While AP and NTS circuit activation aids in satiety and the cessation of food intake, overstimulating these circuits can also result in nausea, vomiting, aversion, and overfullness [47,48].

Apart from peripheral signaling, the brain has its own system for generating GLP-1. GLP-1 is synthesized in the CNS by preproglucagon neurons, which are found in the caudal NTS. These neurons produce GLP-1 from preproglucagon and express the *Gcg* gene. Stress reactions and feeding behavior are influenced

by locally released GLP-1 [49]. Visceral afferent input, gastrointestinal distension, stress, and endocrine signals like cholecystokinin and leptin all affect its activity [49,50].

The G-protein-coupled receptor GLP-1R controls the cAMP signaling in neurons. PKA- and EPAC-dependent pathways are triggered, changing transcription, synaptic transmission, neuronal excitability, and ion channel activity [29]. Following activation, the receptor may degrade, internalize into endosomal compartments, become phosphorylated, or return to the cell membrane. GLP-1R signaling intensity and duration are controlled by these mechanisms [32]. In addition to altering cellular responsiveness, prolonged receptor stimulation may also cause desensitization or tachyphylaxis [32,51].

GLP-1R stimulation activates anorexigenic POMC/CART neurons in the hypothalamic arcuate nucleus via cAMP and PKA signaling. By raising L-type calcium currents, these cascades have anorexigenic effects. In the process, satiety signaling is improved and food intake is decreased [52]. On the other hand, orexigenic NPY/AgRP neurons are suppressed by GLP-1R-related inhibitory pathways via GABAergic mechanisms. This reduces appetite and causes the hypothalamic balance to change in favor of satiety-promoting activity [53,54].

Synaptic transmission is altered in reward-related brain regions by GLP-1R activation. NTS GLP-1 neurons connect mesolimbic food reward with brainstem satiation signals by projecting to the ventral tegmental area (VTA) and nucleus accumbens (NAc) [55]. GLP-1R activation in the NAc core increases glutamatergic transmission mediated by AMPA/kainate receptors, which prevents feeding [56]. By decreasing excitatory synaptic drive onto mesolimbic dopamine neurons in the VTA, GLP-1 can also decrease consumption of high-fat foods [57]. The motivational value of appetizing food and reward-based intake are diminished by these glutamatergic and dopaminergic processes [55–57].

GLP-1R agonists affect vagal reflexes, brainstem autonomic regulation, and stomach motility. All of these mechanisms work together to prevent stomach emptying. Proximal stomach compliance, antral food fragmentation, pyloric opening, and duodenal feedback are all necessary for the mechanism to function [58–60]. In a physiological sense, eating causes intestinal GLP-1 to be released from L-cells, delaying the transit of stomach contents to the duodenum. The biological half-life of native GLP-1 is brief due to its degradation by DPP-4. Consequently, vagal afferent fiber localization has significant physiological significance. Information is sent

to the NTS via this pathway, and the dorsal motor nucleus of the vagus transforms the signal into autonomic output by the dorsal vagal complex [7,45,61].

The motor pattern necessary for gastric emptying is altered by the vagal-brainstem reflex. Because GLP-1 decreases antral and duodenal contractility, the antral pump's ability to grind solid food and move chyme in the direction of the pylorus is diminished. GLP-1 simultaneously creates functional resistance at the gastric outlet by increasing tonic and phasic pyloric activity [59].

GLP-1 uses enteric pathways to affect the gastric antrum as well. Nitric oxide plays a role in one mechanism by relaxing the smooth muscle of the stomach and decreasing the antral motility [62]. Nutrition enters the small intestine more slowly as a result. As demonstrated specifically with semaglutide in obesity, this aids in lowering postprandial glucose peaks [58,63]. Retained stomach contents, nausea, vomiting, and post-meal fullness can all be symptoms of delayed gastric emptying [47,64,65].

The length of time and pattern of GLP-1R stimulation determine how strong this effect is. Rapid tachyphylaxis may result from prolonged exposure to GLP-1, most likely due to vagal nervous system activation [17]. This explains the tendency for short-acting GLP-1R agonists to more significantly postpone gastric emptying than long-acting agonists. Because retained gastric contents can increase the risk of aspiration and regurgitation, clinicians should consider delayed gastric emptying before anesthesia or endoscopy [47].

Cardioprotective and vascular mechanisms

Cardiovascular protection observed during treatment with GLP-1 receptor agonists is not limited to glucose lowering or body weight reduction. These drugs also influence cellular processes in the myocardium, vascular endothelium, vascular smooth muscle cells and inflammatory cells. GLP-1R is a G-protein-coupled receptor, and its activation may stimulate cAMP-dependent signaling, including PKA, EPAC, AMPK and PI3K/Akt pathways. In cardiovascular tissues these cascades are associated with improved cell survival, better mitochondrial function and reduced inflammatory activation [66,67]. Although the exact distribution of GLP-1R in adult cardiomyocytes remains discussed, many cardioprotective effects can be explained by combined actions on endothelial cells, immune cells, autonomic regulation and cardiometabolic stress [68,69].

One of the most important aspects of GLP-1RA activity is their influence on cardiac re-

modeling. In heart failure and diabetic cardiomyopathy, chronic metabolic stress promotes cardiomyocyte hypertrophy, mitochondrial dysfunction, impaired calcium handling, apoptosis and interstitial fibrosis. GLP-1RAs may counteract these processes by activating AMPK-dependent signaling and regulating the mTOR pathway, which supports more balanced autophagy and limits pathological hypertrophic growth. They may also improve mitochondrial bioenergetics and reduce endoplasmic reticulum stress, thereby decreasing cardiomyocyte apoptosis and preserving contractile function [66,69]. In the fibrotic component of remodeling, these drugs are thought to reduce the activation of fibroblasts and the production of extracellular matrix indirectly through lowering oxidative stress, inflammatory cytokines and adipose tissue-related cardiometabolic burden [69].

The endothelium is another major target of GLP-1RA-mediated cardiovascular protection. Under hyperglycemic, lipotoxic and inflammatory conditions, endothelial cells produce excessive reactive oxygen species, mainly through NADPH oxidase activation and mitochondrial dysfunction. This decreases nitric oxide bioavailability and favors vasoconstriction, leukocyte adhesion and vascular stiffness. GLP-1RAs may restore endothelial function by increasing eNOS activity through PI3K/ Akt and AMPK pathways, which enhances nitric oxide production and improves vasodilation [68,70]. At the same time, they reduce the expression of adhesion molecules such as ICAM-1 and VCAM-1, as well as inflammatory mediators including TNF- α and IL-6. This weakens leukocyte-endothelium interactions and may slow the early stages of atherosclerotic plaque formation [67,71].

The relationship between GLP-1RAs, oxidative stress and inflammation is especially important in atherosclerosis. In endothelial cells and macrophages, excessive ROS activates NF- κ B signaling, which increases cytokine release and promotes the recruitment of immune cells into the vascular wall. GLP-1RAs can reduce ROS generation, support mitochondrial homeostasis and limit excessive mitophagy. These effects are connected with inhibition of inflammatory signaling and protection against endothelial dysfunction [67,68]. In macrophages, GLP-1RA activity is also associated with suppression of the NLRP3 inflammasome. This pathway normally promotes caspase-1 activation, IL-1 β and IL-18 release and pyroptosis. By reducing NLRP3 activation, GLP-1RAs may decrease macrophage-driven inflammation, limit foam cell formation and contribute to plaque stabilization [67]. In vascular smooth muscle cells, these drugs may additionally reduce abnormal pro-

liferation, migration and phenotype switching, partly through inhibition of NF- κ B, ERK1/2 and oxidative stress-related pathways [67].

These molecular and cellular mechanisms are reflected in emerging clinical applications. In the SELECT trial, semaglutide reduced major adverse cardiovascular events in patients with overweight or obesity and established cardiovascular disease without diabetes [72]. In patients with obesity-related heart failure with preserved ejection fraction, semaglutide improved symptoms, physical limitation and exercise capacity, and was also associated with lower inflammatory markers such as C-reactive protein [73,74]. These observations suggest that GLP-1RAs may act as cardiometabolic and anti-inflammatory agents. However, their vascular and myocardial benefits should be interpreted as the result of several overlapping mechanisms rather than a single receptor-dependent pathway. Further studies are needed to determine which cellular targets are most important in different cardiovascular phenotypes.

Emerging clinical applications in nephrology

The nephroprotective effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been well described, but it does not solely result from systemic effects such as improved glycaemic control, reduced blood pressure, or weight loss. Increasing evidence indicates that GLP-1RAs may also exert direct effects within the renal tissues by modulating renal haemodynamics, reducing production of reactive oxygen species (ROS), and attenuate glomerular inflammation [75–81].

The GLP-1 receptor is a transmembrane receptor coupled to the G α s protein which, upon ligand binding, it activates the canonical signalling cascade associated with increased intracellular cyclic adenosine monophosphate (cAMP) levels and activation of protein kinase A (PKA) [29]. Preclinical studies in animal models have suggested that activation of GLP-1R in afferent glomerular arterioles induces phosphorylation of multiple transmembrane potassium channels, including ATP-sensitive potassium channels (K_{ATP}), voltage-sensitive potassium channels (K_v), large-conductance calcium-activated potassium channels (BK_{Ca}), and inward rectifier potassium channels (K_{IR}), leading to rapid hyperpolarisation of the cell membrane. As a consequence, voltage-operated calcium channels (VOCCs) close, intracellular Ca^{2+} concentrations decrease, and vascular smooth muscle relaxation occurs, leading to vasodilation [29,77,81,82]. In parallel, increased intracellular cAMP activates exchange protein

directly activated by cAMP (EPAC), which stimulates ryanodine receptors (RyR) in the sarcoplasmic reticulum, resulting in Ca^{2+} release. This, in turn, opens BK_{Ca} channels in the plasma membrane, further enhancing membrane hyperpolarisation and promoting vascular relaxation [29,81,82]. A second mechanism by which GLP-1R agonists induce vasodilation involves endothelial cells of the afferent arterioles, where PKA directly phosphorylates endothelial nitric oxide synthase (eNOS), increasing nitric oxide (NO) production [78,83,84]. The aforementioned effects leading to afferent arteriole vasodilation may increase local glomerular perfusion and reduce ischemia.

GLP-1RAs also directly inhibit the sodium-hydrogen exchanger 3 (NHE3) located in the brush border of proximal tubular cells, thereby increasing sodium excretion [78,80,81,85]. The increased sodium load reaching the macula densa is transported into these cells via the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter (NKCC2), inducing increased sodium-potassium ATPase activity. The enhanced ATP consumption leads to elevated intracellular adenosine generation, which is subsequently released into the extracellular space. Adenosine then binds to A1 adenosine receptors on the afferent arteriole, inducing vasoconstriction [77,81]. It is important to note that although the direct effects of GLP-1RAs on afferent arterioles mediated through vascular smooth muscle cells and increased NO availability promote vasodilation in diabetic nephropathy, where glomerular hyperfiltration is typically present, the tubuloglomerular feedback mechanism may predominate. This results in constriction of the afferent arteriole, reduction of intraglomerular pressure, and protection of the filtration barrier [77,81,86].

Experimental data from both in vitro and in vivo studies indicate that GLP-1RAs protect the glomerular filtration barrier, including through direct effects on podocytes, where activation of the GLP-1R/cAMP/PKA pathway leads to phosphorylation of 5' AMP-activated protein kinase (AMPK) [78–80,87]. Phosphorylated AMPK activates nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 dissociates from Kelch-like ECH-associated protein 1 (Keap1) and translocates to the cell nucleus, where it induces the expression of genes encoding antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), glutathione synthetase (GSS), and haem oxygenase-1 (HO-1). These enzymes neutralise harmful reactive oxygen species, thereby reducing oxidative stress and contributing to preservation of the filtration barrier [80,84,87,88].

Experimental data also suggest that phosphorylated AMPK activates the transcription factors Forkhead box protein O1 (FOXO1) and O3 (FOXO3), which are involved in mitochondrial homeostasis, including among other processes, autophagic clearance of damaged organelles and indirect support of mitochondrial regeneration, ultimately helping to restore normal cellular respiration [80,88,89]. It has also been proposed that FOXO activation in immune cells infiltrating the glomeruli may promote differentiation of T lymphocytes into regulatory T cells (Tregs), thereby suppressing the inflammatory response [75,88]. In addition, activation of GLP-1R signalling through PKA may lead to phosphorylation and inhibition of I κ B kinase (IKK). Inhibition of IKK prevents degradation of the nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (I κ B α). As a result, I κ B α remains in the cytoplasm and prevents the nuclear translocation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B). Inhibition of this canonical pro-inflammatory pathway limits the production of inflammatory mediators, including TNF- α , IL-1 β , IL-6, MCP-1, TGF- β 1, a key mediator of glomerular fibrosis [78,79,90].

The nephroprotective effects of GLP-1RAs in humans have been demonstrated in large randomised clinical trials. In the FLOW trial, published in 2024, the effect of semaglutide on the progression of chronic kidney disease in patients with type 2 diabetes was evaluated. The study demonstrated a 24% reduction in the risk of the primary composite endpoint, which included kidney-related death, end-stage kidney disease, or a sustained decline in estimated glomerular filtration rate [75,91]. Furthermore, an observational target trial emulation analysis showed a significant 27% reduction in the risk of nephropathy progression when a GLP-1RA was added to ongoing therapy with SGLT2 inhibitors, compared with the addition of a DPP-4 inhibitor or a sulfonylurea. The analysis also showed no significant increase in the risk of adverse events such as acute pancreatitis or diabetic retinopathy [92].

Although the clinical reduction in renal risk is well established, the multifaceted effects of GLP-1RAs on the nephron described above require further investigation. Such studies are necessary to determine the relative importance of individual cellular mechanisms and to verify the extent to which findings from experimental models, both in vitro and animal studies, translate into direct nephroprotective effects in humans [75,77,78,81,92].

Emerging clinical applications in neurology and safety considerations

GLP-1 receptor agonists are increasingly regarded as therapeutic agents with biological effects extending beyond glycemic control and weight reduction. Their relevance to neurology is supported by the expression of GLP-1 receptors in brain regions involved in cognition, autonomic regulation, reward processing and neuroendocrine integration [7]. At the cellular level, GLP-1 receptor activation may influence neuroinflammation, oxidative stress, mitochondrial function, autophagy and neuronal insulin signaling. These mechanisms provide a rationale for investigating GLP-1 receptor agonists as potential neuroprotective agents, although most neurological indications remain experimental [93].

Neuroprotective potential in Alzheimer's disease

Alzheimer's disease is one of the main neurodegenerative conditions in which GLP-1 receptor agonists have been investigated. The rationale is based on the overlap between neurodegeneration, impaired cerebral glucose metabolism, brain insulin resistance, mitochondrial dysfunction and chronic neuroinflammation [94]. Experimental studies suggest that GLP-1 receptor agonists may reduce microglial activation, improve neuronal energy metabolism and modulate pathways associated with amyloid-beta and tau pathology. However, translation into clinically meaningful disease modification remains uncertain, and these agents should not currently be described as established treatment for Alzheimer's disease [95]. A randomized clinical study with liraglutide suggested preservation of cerebral glucose metabolism in patients with Alzheimer's disease, but it did not provide definitive evidence of cognitive improvement [96].

Potential role in Parkinson's disease

Parkinson's disease is another important field of GLP-1 receptor agonist research because its pathophysiology includes mitochondrial dysfunction, oxidative stress, neuroinflammation and progressive dopaminergic neuronal loss. GLP-1 receptor agonists may theoretically support dopaminergic neuron survival by reducing inflammatory signaling and improving cellular stress responses [93]. Exenatide was one of the first GLP-1 receptor agonists tested clinically in Parkinson's disease. An earlier randomized trial suggested possible motor benefit after treatment, but a later phase 3 study did not confirm a clear disease-modifying effect, showing that early signals require validation in larger trials [97,98]. Lixisenatide has also been investigated

in early Parkinson's disease. In a phase 2 trial, lixisenatide was associated with less progression of motor disability over 12 months, but gastrointestinal adverse effects were frequent and longer studies are required [99].

Reward pathways and addiction-related disorders

GLP-1 receptor signaling also interacts with reward-related neural circuits, particularly mesolimbic dopaminergic pathways. This creates a mechanistic rationale for investigating GLP-1 receptor agonists in alcohol use disorder, nicotine dependence and other substance use disorders [100]. Preclinical evidence suggests that GLP-1 receptor activation may reduce reward-seeking behavior, craving-like responses and substance intake. These effects appear to be mediated by modulation of dopamine and glutamatergic neurotransmission rather than only by appetite suppression [101]. In alcohol use disorder, exenatide reduced alcohol cue-reactivity in reward-related brain areas but did not clearly reduce heavy drinking days in the entire study population [102]. A small randomized trial of semaglutide showed reductions in selected alcohol consumption outcomes and craving, but larger studies are needed before clinical recommendations can be made [103].

Safety profile and molecular basis of adverse effects

The most common adverse effects of GLP-1 receptor agonists are gastrointestinal, including nausea, vomiting, diarrhea, constipation, abdominal discomfort and reduced appetite. These symptoms are usually dose-dependent and are most pronounced during treatment initiation or dose escalation [104]. The mechanism of gastrointestinal intolerance involves peripheral and central GLP-1 receptor pathways related to nausea, satiety and gut-brain communication. Brainstem structures such as the area postrema and nucleus tractus solitarius are particularly relevant to nausea and vomiting during treatment [105]. Pancreatitis has historically been considered a rare but clinically relevant concern, although a strong causal relationship has not been confirmed in long-term randomized trials. Symptoms suggestive of acute pancreatitis still require immediate clinical evaluation and temporary discontinuation until the diagnosis is clarified [104,106]. Gallbladder and biliary tract disorders are more consistently recognized safety concerns. GLP-1 receptor agonists have been associated with increased risk of gallbladder and biliary disease, especially with higher doses, longer treatment duration and use for weight reduc-

tion [107]. Hypoglycemia is uncommon during GLP-1 receptor agonist monotherapy because insulin secretion remains glucose-dependent. The risk increases when these drugs are combined with insulin or sulfonylureas, which may require adjustment of the accompanying glucose-lowering therapy [7]. Diabetic retinopathy worsening has been reported mainly in the context of rapid improvement in glycemic control rather than proven direct retinal toxicity. Thyroid C-cell tumors remain a theoretical concern based mostly on animal data, which explains contraindications in patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 [104,108].

Clinical implications and limitations

Current evidence indicates that GLP-1 receptor agonists should not be viewed only as glucose-lowering agents. Their effects on insulin secretion, glucagon suppression, gastric emptying, appetite regulation and body weight reduction explain why this drug class has gradually moved beyond diabetology, although individual agents still differ in pharmacokinetics, duration of action and tolerability [15]. An important turning point was the observation that cardiovascular benefit may also occur in patients without diabetes. In the SELECT trial, semaglutide reduced major adverse cardiovascular events in individuals with overweight or obesity and established cardiovascular disease, which suggests that GLP-1 receptor agonism may modify cardiovascular risk through mechanisms not restricted to glycemic control [72]. This interpretation is supported by pooled randomized evidence. A large meta-analysis showed that GLP-1 receptor agonists reduced clinically relevant kidney outcomes, kidney failure, major cardiovascular events and all-cause mortality, although treatment discontinuation due to adverse events was more frequent in the active treatment groups [109]. From a translational perspective, these findings suggest that GLP-1 receptor agonists act through several overlapping biological processes rather than through one dominant pathway. Weight reduction, improved cardiometabolic parameters, lower ectopic adiposity and modulation of systemic inflammation may all contribute to organ protection. Experimental and clinical data indicate that GLP-1-based therapies can reduce inflammatory signaling through both weight loss-dependent and weight loss-independent mechanisms, including effects on cytokine release, immune cell activity, NF- κ B-related pathways and neuroimmune communication [110].

At the same time, the quality of evidence is not equal across all proposed indications. Cardiovascular and kidney outcomes are supported by large randomized outcome trials, whereas some newer applications remain closer to mechanistic or early translational research. This is particularly relevant in neurology, where selected GLP-1 receptor agonists may engage central nervous system pathways, but blood-brain barrier penetration differs between agents, and human evidence is still often indirect or based on imaging and biomarker observations rather than definitive clinical endpoints [111]. Several limitations should therefore be taken into account. Many pivotal trials included selected high-risk populations, such as patients with established cardiovascular disease, obesity, type 2 diabetes or chronic kidney disease. As a result, the findings cannot be automatically transferred to younger patients, lower-risk groups or primary prevention settings. In addition, current follow-up periods may still be too short to fully assess very long-term outcomes and safety. Safety and tolerability remain important issues in chronic GLP-1 receptor agonist therapy. A systematic review and meta-analysis of randomized trials reported increased risks of cholelithiasis and gastroesophageal reflux disease, emphasizing the need for careful monitoring of adverse events during treatment [112]. Psychiatric safety also needs cautious interpretation. A meta-analysis of randomized controlled trials did not show an increased risk of psychiatric disorders, depression, anxiety or suicidal behavior during GLP-1 receptor agonist therapy. However, patients with moderate or severe mental illness are often excluded from clinical trials, and psychiatric adverse events are rarely predefined endpoints, which limits the applicability of these results to patients with pre-existing psychiatric disorders [113]. Overall, GLP-1 receptor agonists represent a promising therapeutic class with effects across metabolic, vascular, renal, inflammatory and possibly neurological pathways. Future research should include longer follow-up, more diverse populations, direct comparisons between incretin-based agents and mechanistic studies that can distinguish direct receptor-mediated effects from secondary consequences of weight loss and metabolic improvement.

Conclusions

Current evidence indicates that GLP-1 receptor agonists represent a therapeutic class whose clinical value extends beyond glucose lowering. Their effects on insulin secretion,

glucagon suppression, gastric emptying, appetite regulation and body weight reduction provide the mechanistic basis for their established role in type 2 diabetes and obesity [15]. At the same time, increasing experimental and clinical data suggest that these agents may also modulate cellular stress, inflammation, oxidative injury, mitochondrial function, apoptosis and tissue remodeling [110]. These mechanisms help explain their cardioprotective, nephroprotective and potentially neuroprotective effects [72,109,111].

The strongest evidence currently supports cardiovascular and renal benefits, especially in patients with obesity, type 2 diabetes, chronic kidney disease or established cardiovascular disease [72,109]. Neurological and addiction-related applications remain promising, but they require further validation in larger randomized trials with clinically meaningful endpoints [111]. Future studies should determine which effects are directly mediated by GLP-1 receptor signaling and which result from secondary improvements in weight, glycemia and cardiometabolic status. Long-term safety, tolerability and treatment persistence also remain important areas of investigation, particularly in broader and more diverse patient populations [112,113]. Overall, GLP-1 receptor agonists should be viewed as multifunctional cardiometabolic agents with expanding clinical relevance and substantial potential for future therapeutic development.

Ethical approval

The conducted research is not related to either human or animal use.

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Conflict of interest

The authors declare they have no conflict of interest.

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