

REVIEW ARTICLE

Glucagon-like peptide-1 receptor agonists as potential preventive and therapeutic agents in ischemic stroke

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Abstract

Stroke remains a significant contributor to mortality and morbidity worldwide, imposing a significant socioeconomic burden and underscoring the urgent need for both preventative and therapeutic strategies. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), initially developed for the treatment of metabolic disorders, have demonstrated promising neuroprotective properties through multiple mechanisms, including anti-inflammatory and antioxidation effects, as well as preservation of the blood–brain barrier. GLP-1RAs reduce the occurrence and severity of ischemic stroke by alleviating metabolic disorders that contribute to cerebrovascular disease. This review discusses the role of GLP-1RAs in ischemic stroke, focusing on their direct neuroprotective properties and indirect benefits through the modulation of metabolic risk factors, including metabolic syndrome and its components. By highlighting the therapeutic potential of GLP-1RAs, we demonstrate their value as both a preventative and therapeutic strategy against ischemic stroke.

Keywords: Glucagon-like peptide-1; Ischemic stroke; Neuroprotection; Neuroinflammation; Blood–brain barrier; Oxidative stress; Obesity; Metabolic disorders

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1. Introduction

According to the World Health Organization in 2021, stroke is the third leading cause of mortality, with ischemic stroke accounting for 80% of all stroke cases.^{1,2} Ischemic stroke occurs due to arterial occlusion, leading to insufficient cerebral blood flow (CBF).² The initial phase of injury is characterized by neuronal cell death resulting from the immediate deprivation of oxygen and nutrients, triggering glutamate excitotoxicity and the onset of an acute inflammatory response.² The secondary phase of injury can exacerbate neurological damage and result in persistent inflammation

and deterioration.² Mechanisms involved in the primary and secondary phases of ischemic stroke typically include neuronal inflammation, oxidative stress, and disruption of the blood–brain barrier (BBB), ultimately contributing to more severe cognitive and motor impairments.²

Modifiable metabolic risk factors play a crucial role in both the incidence and severity of ischemic stroke.³ Conditions such as type 2 diabetes mellitus (T2DM), obesity, hyperglycemia, hypertension, and a combination of these conditions—known as metabolic syndrome—significantly contribute to the pathophysiology of ischemic stroke.³ Current projections indicate a substantial increase in the incidence of ischemic stroke from 2020 to 2030, attributed partially to the rising prevalence of these metabolic disorders.⁴ Moreover, emerging evidence suggests that existing primary prevention strategies, including lifestyle modifications and pharmacological interventions, remain insufficient to curb the global burden of ischemic stroke. Therefore, alternative therapeutic approaches are urgently needed to mitigate ischemic stroke risk and improve long-term outcomes.⁴

Current clinical therapies for the treatment of ischemic stroke primarily focus on addressing the initial insult by restoring CBF through pharmacological and/or surgical interventions.⁵ Standard treatments include tissue plasminogen activator and mechanical thrombectomy, both of which effectively target arterial occlusion.⁵ Although these interventions are used in clinical settings, they demonstrate limited efficacy in preventing secondary injury following reperfusion and are associated with either inadequate effectiveness or severe side effects.^{5,6}

Given the limitations of current treatments, a multifaceted approach to the prevention and mitigation of ischemic stroke and its associated metabolic risk factors is urgently needed to ensure more effective care. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), initially developed for metabolic disorders such as obesity and T2DM, have shown potential for neuroprotection against ischemic stroke and its associated secondary injuries.⁷ Experimental models of ischemic stroke have demonstrated that GLP-1RAs reduce the severity of ischemic injury through both direct and indirect neuroprotective mechanisms.⁸

In addition, clinical studies have shown that GLP-1RAs effectively mitigate metabolic risk factors in patients, leading to a decreased risk of both cardiovascular and cerebrovascular events.⁹ GLP-1RAs confer neuroprotection through the modulation of anti-inflammatory pathways, preservation of the BBB, and reduction of oxidative stress. This review discusses the physiological basis for the clinical application of GLP-1RAs as a promising strategy for both

stroke prevention and therapeutic intervention, and highlights the current gaps in the literature.

2. The physiological role of glucagon-like peptide-1 and the development of GLP-1RAs

Glucagon-like peptide-1 is a 31-amino-acid incretin hormone produced via tissue-specific post-translational processing of the proglucagon gene.¹⁰ The biologically active forms, GLP-1 (7–37) and GLP-1 (7–36), were independently discovered by Holst and Habener in 1987, demonstrating insulinotropic effects.¹⁰ Endogenous GLP-1 is secreted by enteroendocrine cells in the gut and specific neuronal populations in the brain in response to food intake, primarily in response to carbohydrate and fat digestion, resulting in enhanced insulin release and suppression of glucagon secretion.¹¹

In addition, GLP-1 exerts its physiological effects through activation of the GLP-1 receptor (GLP-1R), a member of the G-protein-coupled receptor family. GLP-1 binds to GLP-1R in a two-step binding mechanism: The C-terminal region of GLP-1 binds to the N-terminal domain of GLP-1R, inducing a conformational change that facilitates the subsequent binding of the GLP-1 N-terminal region to the transmembrane domains of GLP-1R.¹² This binding triggers intracellular signaling cascades, primarily through cyclic AMP (cAMP)-dependent protein kinase A (PKA) activation.¹³

Beyond its role in glucose homeostasis, GLP-1R plays a critical role in energy balance and feeding behavior in the central nervous system (CNS).^{14,15} Activation of GLP-1R in the arcuate and paraventricular nuclei promotes satiety and suppresses food intake through anorexigenic signaling.¹⁶ Although a detailed discussion of GLP-1's metabolic functions is beyond the scope of this review, extensive literature highlights its regulatory role in metabolic disorders.^{17,18} Given its pivotal function in metabolic homeostasis, GLP-1R has emerged as a significant therapeutic target for T2DM and obesity. However, the therapeutic window of endogenous GLP-1 in clinical settings is limited by its short half-life (approximately 2 min), due to rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4), making it ineffective and unsuitable as a therapeutic agent.¹⁹

Due to the short half-life of endogenous GLP-1, pharmaceutical companies have focused on designing GLP-1RAs with extended half-lives, enhanced potency, and resistance to DPP-4 degradation.⁷ Several GLP-1RAs have been developed and approved for clinical use in metabolic disorders, including exenatide, liraglutide, semaglutide, and the recently developed dual GLP-1RA and glucose-dependent insulinotropic polypeptide (GIP) receptor

agonist, tirzepatide.⁹ Exendin-4, the first GLP-1RA, is a naturally occurring peptide isolated from the salivary gland of the Gila monster lizard.²⁰ Unlike endogenous GLP-1, exendin-4 resists DPP-4 degradation due to differences in its N-terminal sequence, resulting in a significantly prolonged half-life.²⁰ In addition, modification of exendin-4's C-terminal sequence enhances its binding affinity and potency relative to endogenous GLP-1.²⁰

The development of the GLP-1RA exenatide demonstrates significant antihyperglycemic effects and resistance to DPP-4 degradation, resulting in a prolonged half-life and increased potency.²¹⁻²³ Building on exenatide, further modifications led to the development of liraglutide, a GLP-1 analog conjugated to albumin, significantly extending its half-life to approximately 13–14 h and enabling once-daily dosing.^{21,22} Continued advancements in GLP-1RA development culminated in the development of semaglutide, a widely used agonist with an extended half-life of approximately 160 h, allowing for once-weekly administration and sustained efficacy.²² Key structural modifications in semaglutide include the substitution of alanine with α -aminoisobutyric acid and the attachment of a C18 fatty diacid via a polyethylene glycol spacer at lysine-26 to enhance half-life and albumin binding.²²

Tirzepatide, a dual agonist of GLP-1R and the GIP receptor, simultaneously activates both receptors, thereby enhancing insulinotropic responses and exerting superior efficacy in managing metabolic disorders.^{24,25} Recent clinical trials have demonstrated a greater dose-dependent response of tirzepatide compared to semaglutide, particularly in reducing obesity and improving metabolic parameters.²⁴ Tripeptide shows greater efficacy relative to semaglutide in various clinical trials involving patients with T2DM and obesity.^{26,27}

Tirzepatide exhibits biased agonism at GLP-1R, preferentially activating cAMP/PKA-dependent signaling pathways over the β -arrestin recruitment pathway.²⁸ This selective activation attenuates receptor internalization and degradation, thereby sustaining GLP-1R surface expression and enhancing downstream signaling intensity. As a result, tirzepatide promotes more prolonged and potent cAMP-mediated responses compared to earlier GLP-1RAs, ultimately optimizing insulin secretion and metabolic regulation.²⁸ Similarly, GIP receptor activation stimulates adenylate cyclase via Gs-coupled mechanisms, leading to elevated intracellular cAMP levels, insulin secretion, and enhanced cell survival and proliferation.²⁹ Notably, GLP-1R and GIP receptor signaling exhibit synergistic interactions, where the maintenance of functional receptor expression amplifies the combined effects of dual agonism.²⁸

RNA sequencing data from the human brain and proteomic analyses show significant expression of GLP-1R in various brain cells, including neurons, astrocytes, endothelial cells, and smooth muscle cells.³⁰ In neurons, GLP-1RAs promote signaling pathways related to cell survival and synaptic plasticity in the context of ischemic stroke in animal models. GLP-1RAs induce the release of B-cell lymphoma 2 protein and downregulate pro-apoptotic factors such as Bcl-2-associated X protein and caspase-3.^{31,32} Moreover, activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathways reduces neuronal cell death following ischemic stroke or neurodegeneration.^{31,32} GLP-1RAs also modulate astrocytes, endothelial cells, microglia, and smooth muscle cells to promote an anti-inflammatory environment, reduce oxidative stress through suppression of reactive oxygen species (ROS), and preserve the integrity of the BBB by upregulating tight junction proteins and increasing pericyte volume.³³⁻³⁸

The Italian Association of Hospital Cardiologists released a statement endorsing the use of the GLP-1RA semaglutide due to its strong cardiovascular, renal, and metabolic protective effects, as well as improved functional capacity in patients with heart failure with preserved ejection fraction. It also slows the progression of chronic kidney disease and significantly reduces major adverse cardiovascular events (MACE) in overweight and obese patients.³⁹ The SUMMIT clinical trial investigating the use of tirzepatide in patients with heart failure reported a lower risk of cardiovascular mortality, reduced severity of heart failure, and a preservation of ejection fraction.⁴⁰ These findings underscore the potential of GLP-1RAs, such as semaglutide and tirzepatide, as holistic treatment strategies for mitigating major adverse cardiovascular outcomes and providing significant renal, cardiovascular, and neuroprotective benefits.

3. The intersection of metabolic disorders and ischemic stroke: Targeting both with GLP-1RAs

Metabolic risk factors, including T2DM and obesity, significantly increase both the risk and severity of ischemic stroke, while further exacerbating associated conditions such as hypertension or hyperglycemia³ (Figure 1). Current estimates of the prevalence of metabolic syndrome range between 20% and 30%, with its components—including T2DM, obesity, hyperglycemia, hypertension, and dyslipidemia—contributing to cardiovascular and cerebrovascular complications.^{3,41} GLP-1RAs provide protection against metabolic disorders by promoting weight loss, reducing body mass index (BMI), improving

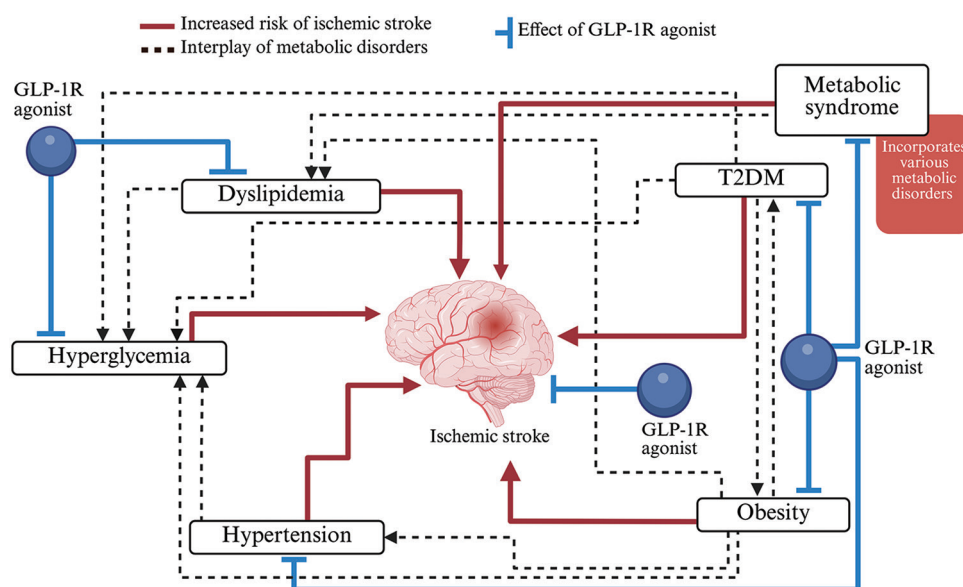


Figure 1. Role of GLP-1R agonist in mitigating ischemic stroke and associated metabolic risk factors. This diagram highlights the direct and indirect protective effects of GLP-1R agonists in ischemic stroke. Red arrows represent risk factors that contribute directly to the likelihood and severity of ischemic stroke. Blue lines indicate the effects of GLP-1R agonists on metabolic disorders and their protective actions in ischemic stroke. Dashed black lines represent the complex interplay between ischemic stroke and associated metabolic disorders, as well as the compounding risk these conditions pose to one another. Created in BioRender. Ali, M. (2025) <https://BioRender.com/vr8xqc5>.

Abbreviations: GLP-1R: Glucagon-like peptide-1 receptor; T2DM: Type 2 diabetes mellitus.

glucose homeostasis, enhancing insulin sensitivity, normalizing lipid profiles, and attenuating hypertension.⁴² GLP-1RA treatment in patients has been associated with the attenuation of atherosclerotic development, resulting in a significant reduction in all-cause mortality.⁴²⁻⁴⁴

In 2022, approximately 890 million adults were affected by obesity, with projections indicating a continued increase.⁴⁵ There is a strong positive correlation between stroke incidence and BMI, underscoring the proportional relationship between stroke and obesity.⁴⁵ Obese patients treated with GLP-1RAs have shown significant weight loss and improvements in metabolic parameters, thereby enhancing quality of life and lowering the risk of ischemic stroke.⁴⁶⁻⁴⁸ A meta-analysis investigating the effects of GLP-1RAs in non-diabetic obese patients reported substantial weight loss and improved glycemic control, resulting in better cardiovascular outcomes and reduced mortality.⁴⁹ GLP-1RA treatment has also been shown to improve lipid profiles, normalize glycemic regulation, and reduce atherosclerotic progression.⁵⁰

T2DM is another major independent risk factor of ischemic stroke, nearly doubling its likelihood.^{3,51} Notably, 20% of ischemic stroke-related deaths are associated with a previous history of T2DM.^{51,52} GLP-1RAs have demonstrated efficacy in improving multiple metabolic parameters, including reductions in body weight, blood pressure, and

insulin resistance, along with improved glycemic regulation in T2DM patients.^{13,53} When used in combination with metformin, GLP-1RAs have shown superior efficacy in managing T2DM compared to metformin alone.⁵⁴ Moreover, GLP-1RA treatment normalized glycemic indices in 84.1% of overweight patients by reducing blood glucose levels to prediabetic ranges.⁴⁶ In addition, GLP-1RAs enhance glucose uptake in peripheral tissues and increase insulin sensitivity,^{53,55} contributing to a reduction in both the incidence and severity of ischemic stroke in patients with T2DM.⁵⁶ Although some clinical trials report only modest improvements in T2DM severity, the associated reductions in mortality and cardiovascular risk are substantial.^{53,55}

Studies investigating long-term exposure to GLP-1RAs have reported lower rates of ischemic stroke in both incidence and severity.⁵⁷ Meta-analyses of T2DM patients receiving GLP-1RA treatment consistently demonstrate reduced incidence of ischemic stroke compared to control groups.⁵⁷⁻⁵⁹ A *post hoc* analysis comparing tirzepatide and semaglutide in the management of metabolic disorders further demonstrated a significant reduction in the severity of metabolic syndrome, suggesting a potential role for GLP-1RAs in mitigating stroke-related outcomes and cardiovascular risks.²⁵ Pre-clinical evidence for tirzepatide use in the CNS indicates neuroprotective effects through multiple molecular mechanisms, including increased production of cAMP response element-binding protein

and brain-derived neurotrophic factor, as well as the activation of PI3K/AKT pathways, resulting in neuronal differentiation, survival, and glycemic normalization.⁶⁰

Prolonged GLP-1RA exposure has also been associated with improved recovery and a reduced incidence of ischemic stroke-related complications.⁶¹ Studies have shown a duration- and dose-dependent relationship between GLP-1RA treatment and stroke outcomes, with longer treatment durations correlating with decreased hospitalization rates and enhanced therapeutic effectiveness.⁶¹ Some studies report up to a 39% reduction in stroke incidence among T2DM patients receiving GLP-1RAs.⁶² In addition, GLP-1RA treatment confers neurovascular protection against ischemic stroke in patients with metabolic disorders and a history of cardiovascular complications.⁶³ GLP-1RA treatment was associated with a 17.3% reduction in the incidence of ischemic stroke among patients with prior cardiovascular events and a 20.4% reduction among those without a history of cardiovascular disease.⁶³ **Figure 2** summarizes the recommended clinical approach for GLP-1RA administration.

4. Safety profile, risk management, and usage criterion of GLP-1RAs

GLP-1RAs exhibit an acceptable safety profile with manageable side effects and demonstrated greater

efficacy compared to common antihyperglycemic medications such as sulfonylureas, DPP-4, and sodium-glucose cotransporter-2 inhibitors in the treatment of T2DM and obesity.⁶⁴ A comparative study involving over 1.9 million United States veterans, monitored over a median duration of 3.68 years, evaluated 175 distinct health outcomes associated with GLP-1RA use relative to common antihyperglycemic medications.⁶⁴ The study concluded that GLP-1RAs significantly reduced the risk of cerebrovascular disease, neurodegenerative disease, infections, substance use disorders, antipsychotic-related disorders, pneumonia, and pulmonary disorders, compared to sulfonylureas, DPP-4 inhibitors, and sodium-glucose cotransporter-2 inhibitors. In contrast, GLP-1RA use was associated with an increased occurrence of nausea, vomiting, gastroesophageal reflux disease, and abdominal pain. Additional adverse events included notable sleep disturbances. In some patients, GLP-1RAs also resulted in severe hemodynamic instability, presenting an elevated risk of hypotension in comparison to DPP-4 inhibitors.⁶⁴

Despite the promising therapeutic efficacy of GLP-1RAs in metabolic and neurological disorders, several safety considerations have emerged regarding their clinical application. Gastrointestinal (GI) adverse events, including nausea, vomiting, and diarrhea, remain the most commonly reported side effects among patients treated

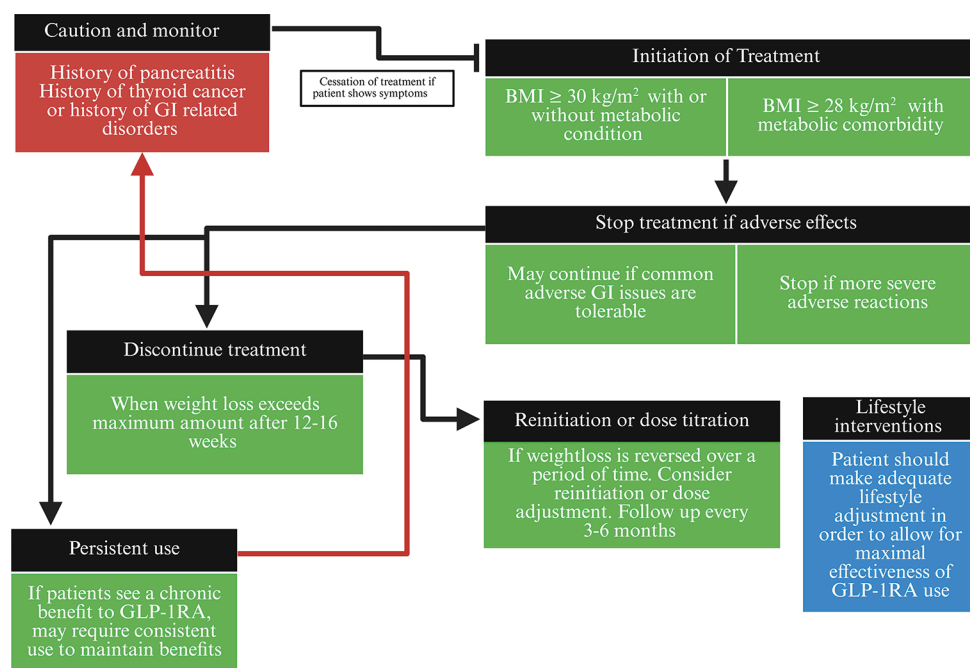


Figure 2. Summary of the recommended clinical approach for starting, continuing, or discontinuing GLP-1RA treatment in overweight or obese patients. Key clinical considerations include a history of pancreatitis, thyroid cancer, and GI disease. Created in BioRender. Ali, M. (2025) <https://BioRender.com/mw9woq2>.

Abbreviations: BMI: Body mass index; GI: Gastrointestinal; GLP-1RA: Glucagon-like peptide-1 receptor agonist.

with GLP-1RAs (20–40%).^{9,65,66} These effects are typically mild-to-moderate in severity, dose-dependent, and do not usually warrant discontinuation. Nonetheless, they represent a consistent class-related phenomenon that may influence treatment adherence.

More severe GI-related adverse outcomes—including pancreatitis, gastroparesis, and intestinal obstruction—have been reported, particularly with long-acting GLP-1RAs such as liraglutide and semaglutide.^{67,68} However, the association between GLP-1RA use and acute pancreatitis remains controversial. Several meta-analyses have reported conflicting outcomes, with no conclusive evidence establishing a significant correlation.^{67,68} Pooled studies demonstrated that the absolute risk of pancreatitis associated with GLP-1RA use is approximately 0.1%, similar to that of diabetes control patients.⁶⁹

There is also a concern regarding the use of GLP-1RAs before surgery due to their effect on delaying gastric emptying, which may increase the risk of pulmonary aspiration during anesthesia.⁷⁰ At present, no studies have directly investigated perioperative aspiration events associated with GLP-1RA use; thus, concerns remain largely anecdotal.⁷⁰ Despite the limited evidence of aspiration, the American Society of Anesthesiologists recommends cessation of GLP-1RAs on the day of the procedure for daily-dose medications, or 1 week prior for weekly-dose formulations.⁷¹

Concerns regarding the cardiovascular safety profile of GLP-1RAs have been addressed through multiple large-scale randomized controlled clinical trials and meta-analyses. These studies have demonstrated a significant reduction in MACE, as well as cardiovascular-related mortality, in both diabetic and non-diabetic populations receiving GLP-1RA therapy.^{72,73} The SUSTAIN-6 clinical trial, which investigated the cardiovascular outcomes of semaglutide, reported a significant reduction in cardiovascular complications compared to placebo.^{62,74} A significant reduction in major cardiovascular events has also been observed with GLP-1RA use in patients with and without a history of cardiovascular complications.⁶³

Although some debate persists regarding the cardiovascular protective effects of GLP-1RAs, the overall consensus supports their benefit.⁷⁵ These long-term studies demonstrated a significant reduction in MACE over several years of therapy. Nevertheless, the safety profile of GLP-1RAs requires ongoing vigilance. While the overall incidence of adverse events remains low, these findings reinforce the cardioprotective potential of GLP-1RAs and challenge earlier concerns regarding their association with MACE.

While hypoglycemia is not a typical side effect of GLP-1RAs when used as monotherapy, cases have been reported, primarily in patients concurrently receiving insulin or sulfonylureas.⁶⁶ This underscores the importance of individualized dosing and careful monitoring in combination regimens. Furthermore, an increased incidence of upper respiratory and urinary tract infections has been observed in select clinical studies, though these events were generally mild and not associated with systemic complications.⁶⁶

The current evidence on GLP-1RA therapy indicates that chronic treatment may be necessary to sustain its benefits on weight loss and metabolism, even when combined with lifestyle improvements in diet and exercise.⁷⁶ The discontinuation of GLP-1RAs has been associated with significant weight regain despite ongoing lifestyle modifications, highlighting the potential need for continued therapy to maintain both weight loss and cardioprotective effects.⁷⁶ Treatment with semaglutide elicits more than a 5% reduction in body weight in 80% of patients, and two-thirds of patients experience a reduction of $\geq 10\%$. However, discontinuation of the drug results in regaining approximately two-thirds of the weight initially lost through GLP-1RA therapy.⁷⁶ The STEP-Withdrawal trial and the STEP Treatment Effect study, which investigated the effects of semaglutide withdrawal, reported significant weight regain within 1 year of treatment discontinuation.⁷⁷ These findings suggest that continued treatment of GLP-1RAs, such as semaglutide, may be necessary to sustain the weight loss and cardiometabolic benefits associated with their use.⁷⁷

Some clinical studies have raised concerns regarding a potential increased risk of thyroid-related cancers in humans, prompting the United States Food and Drug Administration (FDA) to issue a black box warning.^{9,78} However, the association between GLP-1RA use and thyroid cancer in humans remains unclear, as findings from clinical trials are conflicting—although animal studies have demonstrated a significant risk, including the proliferation of cancerous C cells.^{1,2} Given these concerns, screening patients for a history of GI disorders is advisable. Although most clinical trials do not report the discontinuation of GLP-1RA therapy due to common GI symptoms, early identification of adverse events and implementation of clearly defined discontinuation criteria are recommended.⁷⁶ Current FDA guidelines provide standardized dosing recommendations and contraindications for GLP-1RAs, including tirzepatide.⁷⁹

At present, patients are prescribed GLP-1RAs for obesity if their BMI is >27 kg/m² with a known metabolic

comorbidity, or ≥ 30 kg/m² regardless of comorbidities. Criteria for discontinuation by the FDA and other regulatory bodies include GI-related adverse effects or a personal or family history of contraindicating conditions, as previously mentioned. Clinicians should exercise caution when prescribing GLP-1RAs to patients with a history of pancreatitis, severe GI disorders, or hypersensitivity reactions (Figure 1). Additional contraindications include a personal or family history of multiple endocrine neoplasia syndrome type 2, as well as pregnancy and lactation, due to insufficient safety data in these populations. Furthermore, GLP-1RA use is not recommended in individuals with moderate-to-severe renal impairment due to limited pharmacokinetic data and an increased risk of adverse outcomes. For a more comprehensive overview of GLP-1RA safety, including individual case reports and trial-level meta-analyses, readers are referred to the systematic review conducted by Badve *et al.*, 2025,⁸⁰ which consolidates safety data across diverse patient populations and evaluates the effectiveness of GLP-1RA therapy following discontinuation.

The association between metabolic disorders and ischemic stroke highlights the urgent need for therapeutic strategies that address both conditions simultaneously. GLP-1RAs offer a promising dual approach by mitigating metabolic risk factors while providing direct cardiovascular and neurovascular protection. Collectively, these findings suggest that GLP-1RA treatment may significantly reduce ischemic stroke occurrence and recurrence, highlighting the potential indirect preventative effects of GLP-1R activation. The growing body of clinical and pre-clinical evidence supports the potential of GLP-1RAs in reducing stroke incidence, severity, and associated mortality, positioning them as a valuable therapeutic avenue for patients at high risk of cerebrovascular disease.

5. Molecular mechanisms underlying ischemic stroke prevention through metabolic regulation by GLP-1RAs

Glucagon-like peptide-1 receptor activation results in adenylyl cyclase stimulation, increasing intracellular cAMP levels and activating PKA, which leads to diverse downstream effects across multiple cell types.¹³ Clinical and pre-clinical data indicate that GLP-1RAs improve metabolic parameters, including lipid profiles, serum glucose levels, insulin resistance, weight, and hypertension, which are key risk factors for ischemic stroke.^{3,81}

In β -cells, GLP-1R activation enhances insulin secretion and β -cell survival through the cAMP response-binding protein (CREB), PKA, and exchange protein directly activated by cAMP.¹³ Liraglutide has been shown to activate

the PI3K/AKT pathway, promoting β -cell proliferation while preserving β -cell mass by inhibiting apoptosis via AMP-activated protein kinase (AMPK).^{82,83} In addition, liraglutide suppresses oxidative stress by inhibiting c-Jun N-terminal kinases (JNK1/2) and nicotinamide adenine dinucleotide phosphate oxidase 2, while simultaneously enhancing the antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (NRF2).⁸⁴ These protective mechanisms collectively mitigate the progression of T2DM, indirectly reducing ischemic stroke risk by alleviating metabolic dysfunction.⁸²

Glucagon-like peptide-1 receptor signaling in pancreatic δ -cells activates the cAMP/PKA pathways, stimulating somatostatin release, which in turn suppresses glucagon secretion from α -cells.¹³ In addition, GLP-1RAs promote direct α -cell modulation via cAMP/PKA-dependent pathways, reducing glucagon exocytosis.¹³ It is important to note that the effect of GLP-1 is relatively limited on α -cells compared to other pancreatic cells, although indirect GLP-1 regulation plays a significant role.¹³ Moreover, in diabetic mouse models, GLP-1RAs have also been shown to induce the transdifferentiation of α -cells into insulin-producing β -cells.^{85,86}

Beyond pancreatic regulation, GLP-1RAs improve lipid metabolism by upregulating the mitogen-activated PKA/extracellular signal-regulated kinase (ERK1/2) pathway and increasing the expression of ATP-binding cassette transporter A1, thereby enhancing cholesterol transport and reducing hepatic lipid accumulation.⁸⁷ Independent of cAMP, GLP-1R activation also modulates antioxidant signaling via the PKA-AMPK-peroxisome proliferator-activated receptor γ coactivator 1- α axis, alleviating vascular dysfunction and promoting adipose tissue remodeling through pathways such as the AMPK-endothelial nitric oxide synthase (eNOS) pathway, signal transducer and activator of transcription 3 (STAT3)/JNK1/2, and sirtuin.⁸⁸⁻⁹¹ Moreover, GLP-1 signaling enhances leptin receptor expression and activates NRF2, increasing antioxidant enzyme activity and mitigating oxidative stress, ultimately resulting in improvements in metabolic disorders.⁹²

GLP-1RAs also exert strong anti-inflammatory effects, reducing endoplasmic reticulum (ER) stress and promoting protective autophagy.^{31,82,83,87-90,92,93} Activation of the cAMP/PKA pathway further enhances insulin sensitivity and restores glucose homeostasis in mouse models of T2DM and obesity.⁹⁴ While a detailed review of the molecular signaling mechanisms of GLP-1R activation is beyond the scope of this paper, comprehensive analyses are available in prior reviews.¹³ Figure 3 illustrates the generalized primary signaling pathways and their direct and indirect roles in GLP-1R activation.

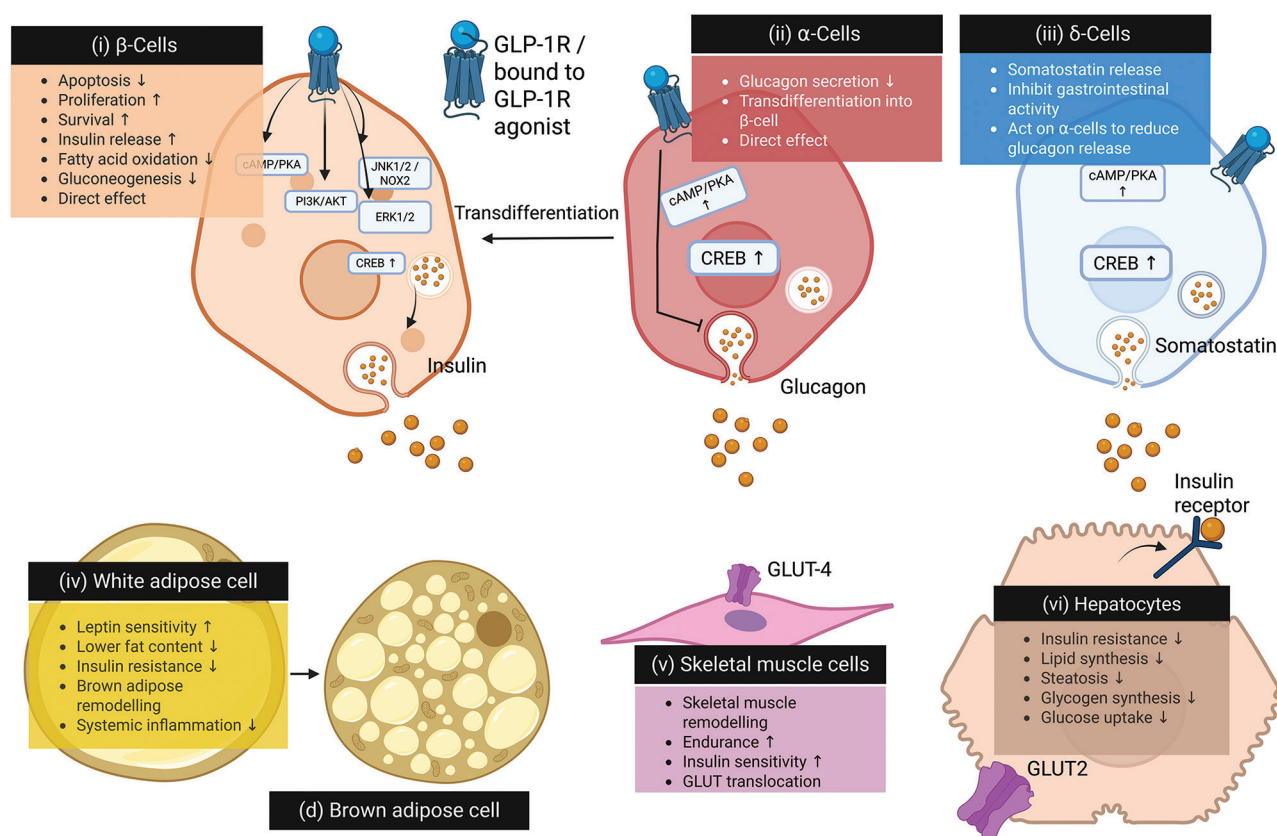


Figure 3. Overview of the metabolic regulation involved in GLP-1R activation across various cell types implicated in energy homeostasis. Direct activation of GLP-1R enhances insulin secretion, reduces apoptosis, and promotes cell survival and proliferation, while simultaneously reducing the activity of δ -cells. These signaling pathways underscore the multifaceted roles of GLP-1R activation in improving metabolic health and mitigating risk factors associated with ischemic stroke. Created in BioRender. Ali, M. (2025) <https://BioRender.com/v23r783>.

Abbreviations: AKT: Protein kinase B; cAMP: Cyclic adenosine monophosphate; CREB: cAMP response element-binding protein; ERK 1/2: Extracellular signal-regulated kinase 1/2; GLP-1R: Glucagon-like peptide-1 receptor; GLUT: Glucose transporter; GLUT2: Glucose transporter type 2; JNK 1/2: c-Jun N-terminal kinase 1/2; NOX2: NADPH oxidase 2; PI3K: Phosphoinositide 3-kinase; PKA: Protein kinase A.

6. The therapeutic potential of GLP-1RAs in ischemic stroke

Ischemic stroke primarily affects the cerebral cortex of the brain, a region highly susceptible to hypoxic and ischemic insults due to its high metabolic demand and limited collateral blood supply.⁵ Studies investigating GLP-1R expression in the human brain reveal that its levels are highest in cortical regions,⁹⁵ in contrast to animal models, where GLP-1R is predominantly expressed in the hypothalamus.⁹⁵ While the precise physiological role of cortical GLP-1R remains unclear, its distribution suggests a potential role in neuroprotection, which warrants further investigation.⁹⁵

The high cortical expression of GLP-1R positions it as a key mediator of neuroprotection in ischemic stroke. GLP-1R activation has been shown to facilitate anti-apoptotic signaling and promote neuronal survival, as evidenced by the

preservation of primary cortical and dopaminergic neurons in murine models of ischemic stroke.⁹⁶ These findings suggest a role for GLP-1R in mitigating neuronal apoptosis following secondary injury, particularly in cortical regions where affected neuronal populations express GLP-1R. The neuroprotective effects of GLP-1RAs in ischemic stroke are mediated through several mechanisms, including anti-inflammatory signaling, reduction of oxidative stress, and preservation of the BBB (Figure 4). These findings underscore the potential therapeutic utility of GLP-1RAs in stroke treatment and recovery.

7. The mechanism of action underlying GLP-1RA

7.1. Anti-inflammatory effect of GLP-1RAs

Several studies suggest that GLP-1R is expressed in primary human microglia and astrocytes, highlighting its potential role

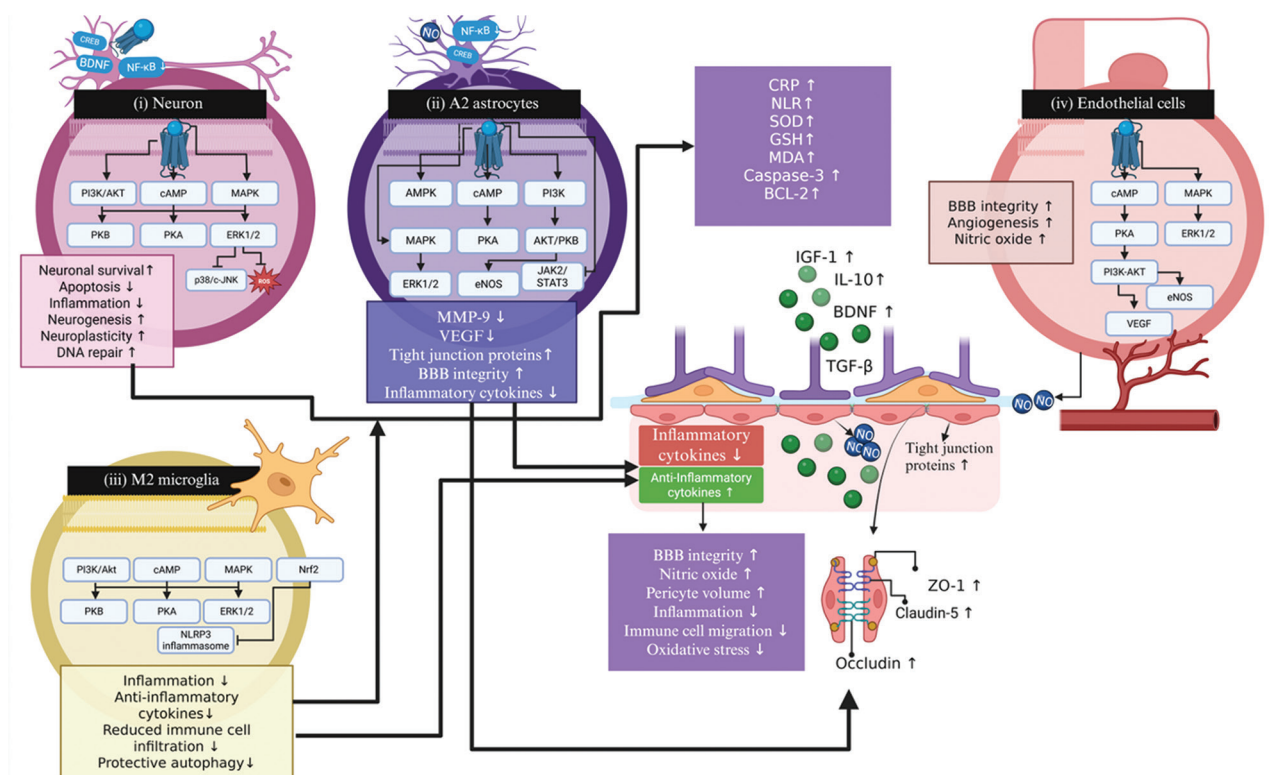


Figure 4. Schematic representation of GLP-1R activation and its signaling transduction pathways in the context of stroke. This figure illustrates the potential GLP-1R-mediated signaling and its neuroprotective effects at the molecular level in (i) neurons, (ii) A2 astrocytes, (iii) M2 microglia, and (iv) endothelial cells in the context of ischemic stroke. GLP-1R is shown to improve a dysregulated BBB by modulating glial cells, endothelial cells, and pericytes, demonstrating a wide array of pleiotropic neuroprotective effects. These include the attenuation of neuroinflammation, enhanced neuronal survival, and inhibition of apoptosis. However, it remains unclear whether these cells express GLP-1R. Created in BioRender. Ali, M. (2025) <https://BioRender.com/x15f015>.

Abbreviations: AKT: Protein kinase B; AMPK: AMP-activated protein kinase; BBB: Blood-brain barrier; BCL-2: B-cell lymphoma 2; BDNF: Brain-derived neurotrophic factor; cAMP: Cyclic adenosine monophosphate; c-JNK: c-Jun N-terminal kinase; CREB: cAMP response element-binding protein; CRP: C-reactive protein; eNOS: Endothelial nitric oxide synthase; ERK1/2: Extracellular signal-regulated kinase 1/2; GLP-1R: Glucagon-like peptide-1 receptor; GSH: Glutathione; IGF: Insulin-like growth factor; IL: Interleukin; JAK2: Janus kinase 2; MAPK: Mitogen-activated protein kinase; MDA: Malondialdehyde; MMP-9: Matrix metalloproteinase 9; NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; NLR: Neutrophil-to-lymphocyte ratio; NLRP3: NOD-like receptor protein 3; NO: Nitric oxide; Nrf2: Nuclear factor erythroid 2-related factor 2; PI3K: Phosphoinositide 3-kinase; PKA: Protein kinase A; PKB: Protein kinase B; ROS: Reactive oxygen species; SOD: Superoxide dismutase; STAT3: Signal transducer and activator of transcription 3; TGF: Transforming growth factor; VEGF: Vascular endothelial growth factor; ZO-1: Zonula occludens-1.

in both immunological and energy regulatory processes within the brain (Table 1).^{97,118} Moreover, infiltrating macrophages and other monocytic cells show upregulated GLP-1R expression following acute traumatic spinal cord injury, with receptor activation correlating with reduced inflammation and improved neurofunctional outcomes.⁹⁹ In persistent brain injury-associated inflammation, GLP-1R expression increased in both neuronal and glial cells, including microglia and astrocytes. Its activation exerts anti-apoptotic and anti-inflammatory effects, particularly in ischemic injury.^{97,118} Post-stroke inflammatory responses are mediated by microglia, astrocytes, endothelial cells, and other immune populations, with GLP-1R expression significantly upregulated in these cells following ischemic injury (Figure 5).^{97,119}

Despite evidence supporting GLP-1R expression in glial cells under pathological conditions, findings remain inconsistent regarding its basal expression in non-pathological states. Single-cell RNA sequencing data from human brains revealed that GLP-1R is expressed in excitatory neurons, inhibitory neurons, and astrocytes, but not detected in microglia.^{30,120} However, GLP-1R expression in microglia has been reported in conditions such as sepsis, nerve injury, spinal cord injury, and migraines, suggesting an inducible role in neuroinflammation or regionally specific expression.⁹⁸⁻¹⁰⁰ In contrast, single-cell RNA sequencing in ischemic murine models has not shown significant changes in GLP-1R expression in the brain, implying that GLP-1R may exert neuroprotection

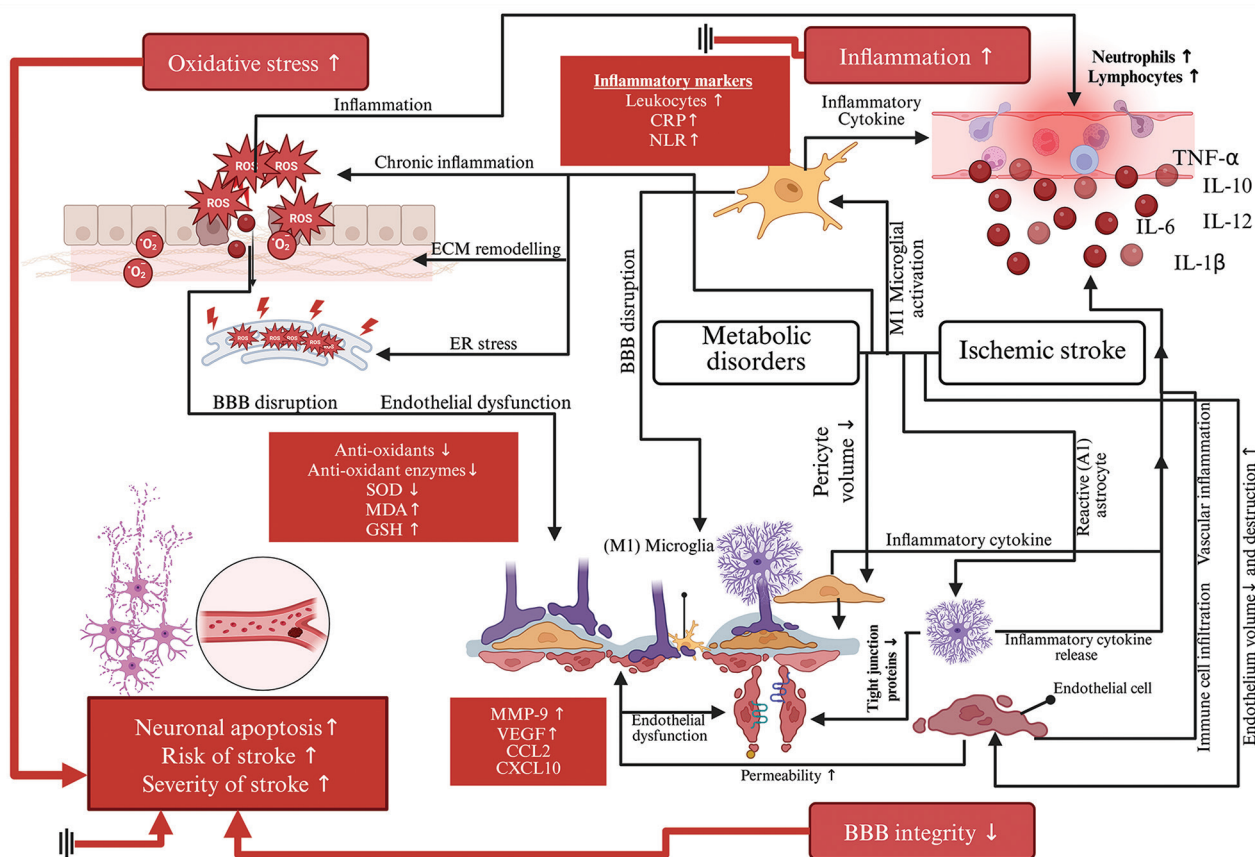


Figure 5. Graphical abstract illustrating the complex interplay between metabolic disorders and ischemic stroke. Metabolic disorders and ischemic stroke share overlapping pathologies, both of which contribute to increased neuronal death and elevate the risk and worsen the severity of ischemic stroke. Metabolic syndrome exacerbates ischemic stroke risk and outcomes through mechanisms such as BBB disruption, persistent inflammation, and heightened oxidative stress. Furthermore, these processes interact in a feed-forward manner, where BBB disruption promotes cytokine release, leading to increased inflammation and immune cell infiltration, which in turn amplifies neurovascular damage. Image created by the author using Created in BioRender. Ali, M. (2025) <https://BioRender.com>.

Abbreviations: BBB: Blood-brain barrier; CCL2: C-C motif chemokine ligand 2; CRP: C-reactive protein; CXCL10: Chemokine (C-X-C motif) ligand 10; ECM: Extracellular matrix; ER: Endoplasmic reticulum; GSH: Glutathione; IL: Interleukin; MDA: Malondialdehyde; MMP-9: Matrix metalloproteinase-9; NLR: Neutrophil-to-lymphocyte ratio; O₂: Molecular oxygen; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TNF-α: Tumor necrosis factor-α; VEGF: Vascular endothelial growth factor.

through indirect mechanisms. Regardless of the ongoing debate surrounding its expression in glial cells, GLP-1R likely plays an indirect yet critical role in modulating neuroinflammation. Given its pronounced expression across different brain cell types under both pathological and physiological conditions, GLP-1RA treatment may elicit cell-type-specific effects.

GLP-1RAs exert direct neuroprotective actions in ischemic stroke mouse models by activating multiple signaling pathways in neurons.¹⁰¹ The cAMP/PKA pathway activates CREB and neurotrophic factors such as brain-derived neurotrophic factor, which together promote neuronal survival, reduce neuroinflammation, and inhibit apoptosis.¹⁰²⁻¹⁰⁴

Systemic inflammation is a hallmark of metabolic disorders and a major risk factor for ischemic stroke (Table 2).¹²¹ An elevated leukocyte count serves as both a marker and a predictor of ischemic events, with higher levels correlating with increased stroke severity.¹²¹ GLP-1RAs may confer protection by reducing systemic inflammation, thereby reducing the risk of ischemic stroke.¹¹⁴ In a mouse model of arterial hypertension, GLP-1R activation led to a significant reduction in vascular inflammation and improved endothelial function.¹²² Moreover, GLP-1RAs attenuate monocyte- and neutrophil-driven inflammation, thereby reducing neuroinflammatory responses.¹²² In patients with T2DM, GLP-1RAs significantly reduce systemic inflammation, lowering leukocyte counts and

Table 1. Summary of preclinical studies investigating glucagon-like peptide-1 receptor agonists in models of central nervous system injury and disease

Pre-clinical model	GLP-1RA and treatment	Neuroprotective outcome	Neurofunctional outcome	Age	References
<i>In vitro</i> (primary microglia from P1 mice)	Exendin-4	↓ iNOS, COX-2, TNF- α , and IL-1 β ; ↑ CD206; M1 \rightarrow M2 polarization; ↑ p-PI3K	N/A	P1	Qian <i>et al.</i> ⁹⁷
<i>In vitro</i> microglia and astrocyte coculture	Exendin-4	↓ TNF- α and IL-1 α secretion; ↓ GFAP/Nestin expression; ↓ astrocyte migration	N/A	P1	Qian <i>et al.</i> ⁹⁷
<i>In vivo</i> (C57BL/6J SCI adult mice model)	Exendin-4	↓ iNOS, GTP-RhoA, TNF- α , IL-1 β , and IL-6; ↑ CD206 and ARAP3; ↓ glial scar	Improved neurofunctional outcomes	8-week adult	Qian <i>et al.</i> ⁹⁷
<i>In vivo+ex vivo</i> (glial cells from P1 mice; spinal cords from SCI adult mice)	Exendin-4	↓ demyelination; ↑ MBP+axons; ↓ G-ratio; ↑ neuronal survival	Decreased lesion area, increased neuronal counts in Nissl staining	8-week adult and P1 for cell-specific analysis	Qian <i>et al.</i> ⁹⁷
Male C57BL/6 mice; chronic migraine model induced by repeated NTG injection	Liraglutide (agonist); Exendin (9-39) (antagonist, for controls)	↓ Iba-1; ↓ IL-1 β ; ↓ TNF- α ; ↓ c-fos; ↓ CGRP; ↓ PI3K/p-AKT	Improved neurofunctional outcome	Adult mice	Jing <i>et al.</i> ⁹⁸
Female Sprague-Dawley rat contusion SCI model	Exenatide	M2 microglial markers (↑ Arg1+, CD163+, and CD206+) M1 microglial marker (↓ iNOS+, CD16+, and CD86+) ↓ TNF- α , IL-1 β ↑ IL-4, and IL-10 (specific days only)	Improved neurofunctional outcome with significantly greater recovery after day 7	Adult mice (10-week-old)	Noguchi <i>et al.</i> ⁹⁹
Adult rat models of chronic pain	Exenatide GLP-1 (7–36) amide	β -endorphin ↑	(i) Suppression of pain sensitization and hypersensitivity (ii) Loss of spontaneous pain behaviors (iii) Improved neurofunctional recovery (iv) Improved neurofunctional recovery reversed by antagonist, opioid receptor antagonist, and β -endorphin knockdown	Adult (8–10 weeks)	Gong <i>et al.</i> ¹⁰⁰
Adult Swiss mice	Exenatide GLP-1 (7–36) amide	β -endorphin ↑	Reversal of mechanical allodynia	6–8 weeks old	Gong <i>et al.</i> ¹⁰⁰
Adult Wistar rats (occlusion of bilateral common carotid)	Lixisenatide	CA1 neuronal count ↑; SOD ↑; GSH ↓; ↓ MDA; Bax ↓; Caspase-3 ↓	(i) Preservation of hippocampal CA1 neurons (ii) No behavioral testing done	Adult Wistar rats	Gad <i>et al.</i> ¹⁰¹
APP/PS1 and WT mice	Tirzepatide	Amyloid- β ↓; GFAP ↓; BACE ↓; SCAF1 ↑; ATF4 ↑; GluN2A ↑; GluN2B ↑; GLUT1 ↑; HK ↑; PFK ↑	Apoptotic cells ↓; glucose metabolism ↑; no significant improvements in learning and memory tests	6 months	Yang <i>et al.</i> ¹⁰²
C57BL/6 transient focal cerebral ischemia mice model	Exendin-4+reperfusion	8-OHdG ↓; HHE ↓; Microglial activation: ↓ Iba-1+; iNOS ↓ ↑ cAMP; ↑ pCREB	(i) Improved neurological deficit score (ii) Reduced infarction (iii) Fewer apoptotic cells (TUNEL staining)	8 weeks	Teramoto <i>et al.</i> ¹⁰³
Male Sprague-Dawley rats+SOD2 knockout and SOD1 transgenic mice; tMCAO	Exendin-4	cAMP ↑; ↓ COX-2; ↓ PGE2; ↓ p-JNK; ↑ I β 1/JIB1; ↑ GLP-1R	(i) ↓ Infarct volume; ↓ neuroinflammation (ii) ↑ Neurofunctional outcome	8 weeks	Kim <i>et al.</i> ¹⁰⁴

(Cont'd...)

Table 1. (Continued)

Pre-clinical model	GLP-1RA and treatment	Neuroprotective outcome	Neurofunctional outcome	Age	References
Primary cortical neurons from E16 ICR mice; OGD-treated	Exendin-4	↑ cAMP	N/A	Embryonic day 16	Kim <i>et al.</i> ¹⁰⁴
BV-2 microglia; OGD treated	Exendin-4	↑ GLP-1R	N/A	N/A	Kim <i>et al.</i> ¹⁰⁴
bEnd. 3 endothelial cells; OGD-treated	Exendin-4	↑ GLP-1R	N/A	N/A	Kim <i>et al.</i> ¹⁰⁴
db/db (diabetic) mouse model; MCAO	Exendin-4 and liraglutide	↓ ICAM-1; ↓ NF-κB; ↓ caspase 3; ↓ TUNEL; ↓ Bax/Bcl-2 ratio; ↑ p-AKT; ↑ p-eNOS; ↑ MnSOD	(i) ↑ Cognition; ↑ motor; ↑ bladder function; (ii) ↑ Cerebral microcirculation; ↓ brain edema;	10–12 weeks	Li <i>et al.</i> ³²
MCAO model of Sprague-Dawley rat	Liraglutide	↓ TUNEL; ↓ caspase-3/8/9; ↓ ROS; ↑ Bcl-xL/Bad; ↑ Bcl-2/Bad; ↑ p-AKT/AKT; ↓ p-JNK/JNK; ↑ p-ERK/ERK; ↓ p-P38/P38	↓ Infarct volume; ↓ neuronal apoptosis; ↑ motor and sensory function; ↓ ROS; ↑ mitochondrial function	Male Sprague-Dawley rats	Zhu <i>et al.</i> ³¹
Primary cortical neurons; OGD (<i>in vitro</i>)	Liraglutide	↓ TUNEL; ↓ caspase-3/8/9; ↓ ROS; ↑ Bcl-xL/Bad; ↑ Bcl-2/Bad; ↑ p-AKT/AKT; ↓ p-JNK/JNK; ↑ p-ERK/ERK; ↓ p-P38/P38	N/A	Primary neurons from neonatal Sprague-Dawley rats	Zhu <i>et al.</i> ³¹
MCAO mouse model+Warfarin	Exendin-4	↑ p-AKT; ↓ p-GSK-3β/GSK-3β; ↓ p-β-catenin/β-catenin; ↑ Claudin-3/5; ↓ ICAM-1; ↓ VCAM-1; ↓ HHE; ↓ 8-OHdG	(i) ↓ Hemorrhagic transformation; ↑ BBB integrity; ↑ neurological function; ↓ microglial activation; ↓ neutrophil (ii) No effect on infarction volume	Male C57BL/6	Chen <i>et al.</i> ⁵⁰
EAE-induced MS mouse	Semaglutide	↑ p-PI3K; ↑ p-AKT; ↑ p-GSK-3β (Ser9); ↑ p-CREB; ↑ BDNF; ↑ MBP; ↑ Nrf2; ↑ SOD; ↓ p65-NF-κB; ↓ TNF-α	↓ EAE clinical score; ↑ cognitive function; ↑ locomotion; ↑ muscle strength; ↓ demyelination	Adult male Swiss albino mice	Sadek <i>et al.</i> ¹⁰⁵
Primary cortical neurons	GLP-1; Exendin-4	↑ p-AKT; ↑ p-CREB; ↑ APE1	↑ Neuronal survival after oxidative stress	E17 Sprague-Dawley rat	Yang <i>et al.</i> ¹⁰⁶
MCAO rat model	Exendin-4	↑ APE1	↓ Infarct size; ↓ DNA damage; ↓ apoptosis	7–8 weeks old male Sprague-Dawley rats	Yang <i>et al.</i> ¹⁰⁶
MCAO rat model	Exendin-4	↑ ZO-1; ↓ VEGF-A; ↓ MMP-9; ↓ CXCL-1; ↓ MCP-1; ↓ p-JAK2; ↓ p-STAT3	↑ Neurological deficit scores; ↓ infarct size; ↓ BBB permeability;	Adult male Sprague-Dawley rats	Shan <i>et al.</i> ¹⁰⁷
Mouse primary cortical astrocytes	Exendin-4	↓ VEGF-A; ↓ MMP-9; ↓ MCP-1; ↓ MCP-1; ↑ claudin-5; ↑ occludin; ↑ ZO-1; ↓ p-JAK2; ↓ p-STAT3; ↓ eNOS; ↓ p-PLCγ; ↓ p-PKCα; ↓ IL-1β; ↓ IL-6	N/A	P1 neonatal C57BL/6 mice	Shan <i>et al.</i> ¹⁰⁷
MCAO Rat model with Nrf2 knockout	Liraglutide	↓ Iba1+; ↑ Nrf2; ↓ NLRP3; ↓ IL-1β; ↓ caspase 1; ↓ CD16; ↑ CD206	↑ Neuronal survival; ↓ apoptosis; ↓ reduced infarct; ↓ edema	Male Sprague-Dawley rats	Tu <i>et al.</i> ¹⁰⁸
Primary rat microglia/ LPS stimulation	Liraglutide	↓ TNF-α; ↓ CD16; ↓ iNOS; ↓ Iba-1; ↑ CD206; ↑ Arg-1; ↑ Nrf2; ARE-luciferase; ↓ NLRP3; ↓ IL-1β; ↓ caspase 1	↓ M1; ↑ M2 polarization; ↓ inflammasome activation; ↑ Nrf2 activity	P1–P2 Sprague-Dawley rat pups	Tu <i>et al.</i> ¹⁰⁸

(Cont'd...)

Table 1. (Continued)

Pre-clinical model	GLP-1RA and treatment	Neuroprotective outcome	Neurofunctional outcome	Age	References
Diabetic adult male Wistar rats	Lixisenatide	↓ MDA; ↓ TNF- α ; ↓ Caspase-3; ↓ iNOS; ↓ NOX2; ↑ eNOS; ↑ GSH	↑ Catalase; ↓ infarct volume; ↑ neurobehavioral outcome; ↓ neurodegeneration	8 weeks	Abdel-Latif <i>et al.</i> ¹⁰⁹
Transient ischemic stroke mouse model	Exendin-4	↑ Neural Progenitor cells; ↑ GFAP (penumbra); ↓ GFAP (infarct area)	Inflammation	N/A	Lu <i>et al.</i> ¹¹⁰
Primary mouse astrocyte cultures (OGD-treated)	Exendin-4	N/A	↓ Neuroinflammation	N/A	Lu <i>et al.</i> ¹¹⁰
Adult male tMCAO models	Semaglutide	↓ C3d+/GFAP+astrocytes; ↓ CD16/32 microglia; ↓ EB/IgG leakage; ↑ TJ proteins; ↓ Iba-1+/CD16/32+; ↓ IL-1 α ; ↓ TNF α ; ↓ C1q; ↓ ZO-1; ↓ claudin-5; ↓ occludin	↓ Infarction; ↓ neuroinflammation; ↓ BBB permeability	Adult mice	Zhang <i>et al.</i> ¹¹⁰
Primary astrocytes	Exendin-4	↓ C3d+/GFAP+astrocytes; ↓ IL-1 α ; ↓ TNF- α ; ↓ C1q	N/A	P1–P3 ICR mice	Zhang <i>et al.</i> ¹¹¹
tMCAO mouse model	Exendin-4	↓ MMP-9; ↓ Iba-1; ↓ TNF- α ; ↓ IgG leakage; ↓ dinitrophenol	↑ Improved neurobehavioral tests; ↓ apoptosis; ↑ survival rate following surgery	10 weeks; C57BL/6	Kuroki <i>et al.</i> ¹¹²
dMCAO adult mice	Liraglutide	↓ CD31; ↑ BrdU+/CD31+cells; ↑ VEGF;	↑ Motor function; ↑ microvessel density; ↑ infarct volume;	Adult CD-1 mouse	Chen <i>et al.</i> ¹¹³
T2DM induced in STZ mice	Exendin-4	↑ Occludin; ↑ GLP-1R; ↑ Nrf2; ↓ TNF- α ; ↓ IL-1 β ; ↓ Cleaved caspase-3; ↓ VEGF; ↓ ROS; ↑ GSH;	↑ Neurobehavioral outcomes	8–12 weeks; C57BL/6J mice, Pdgfr- β -CreERT2	Bailey <i>et al.</i> ³⁸
Human pericyte cell culture	Exendin-4	↓ Nitrotyrosine; ↓ ROS; ↑ GSH; ↓ VEGF; ↑ pAKT/AKT; ↓ TNF- α ; ↓ IL-1 β ; ↑ Occludin;	N/A	N/A	Bailey <i>et al.</i> ³⁸

Abbreviations: 8-OHdG: 8-Hydroxy-2'-deoxyguanosine; AKT: Protein kinase B; APP: Amyloid precursor protein; APE1: Apurinic/apyrimidinic endonuclease 1; Arg-1: Arginase-1; ARAP3: Arf-GAP with Rho-GAP domain; ankyrin repeat and PH domain-containing protein 3; ARE: Antioxidant response element; ATF4: Activating transcription factor 4; Bad: Bcl-2-associated death promoter; BACE: Beta-site amyloid precursor protein cleaving enzyme; Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma-extra large; BDNF: Brain-derived neurotrophic factor; BrdU: Bromodeoxyuridine; C1q: Complement component 1q; cAMP: Cyclic adenosine monophosphate; CD: Cluster of differentiation; CGRP: Calcitonin gene-related peptide; c-fos: Cellular proto-oncogene Fos; COX-2: Cyclooxygenase-2; CXCL-1: Chemokine (C-X-C motif) ligand 1; dMCAO: Distal middle cerebral artery occlusion; EAE: Experimental autoimmune encephalomyelitis; EB: Evans blue; eNOS: Endothelial nitric oxide synthase; ERK: Extracellular signal-regulated kinase; GFAP: Glial fibrillary acidic protein; GLP-1R: Glucagon-like peptide-1 receptor; GLUT1: Glucose transporter 1; GluN2A: Glutamate ionotropic receptor NMDA type subunit 2A; GluN2B: Glutamate ionotropic receptor NMDA type subunit 2B; GSH: Glutathione; GSK-3 β : Glycogen synthase kinase-3 beta; HK: Hexokinase; HHE: 4-Hydroxy-2-hexenal; Iba-1: Ionized calcium-binding adaptor molecule 1; ICAM-1: Intercellular adhesion molecule-1; ICR: Institute of Cancer Research; IgG: Immunoglobulin G; IL: Interleukin; iNOS: Inducible nitric oxide synthase; IB1: Islet brain 1; JIB1: JNK-interacting protein 1; JNK: c-Jun N-terminal kinase; MDA: Malondialdehyde; MBP: Myelin basic protein; MBP: Myelin basic protein; MCAO: Middle cerebral artery occlusion; MCP-1: Monocyte chemoattractant protein-1; MnSOD: Manganese superoxide dismutase; MMP-9: Matrix metalloproteinase-9; MS: Multiple sclerosis; N/A: Not applicable; NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3; NOX2: NADPH oxidase 2; Nrf2: Nuclear factor erythroid 2-related factor 2; NTG: Non-transgenic; OGD: Oxygen-glucose deprivation; p-CREB: Phosphorylated cAMP response element-binding protein; Pdgfr- β -CreERT2: Platelet-derived growth factor receptor beta-Cre recombinase estrogen receptor T2; PFK: Phosphofructokinase; p-AKT: Phosphorylated AKT; p-ERK: Phosphorylated extracellular signal-regulated kinase; PI3K: Phosphoinositide 3-kinase; p-PI3K: Phosphorylated phosphoinositide 3-kinase; p-GSK-3 β : Phosphorylated glycogen synthase kinase-3 beta; p-JAK2: Phosphorylated Janus kinase 2; p-JNK: Phosphorylated c-Jun N-terminal kinase; p-PKC α : Phosphorylated protein kinase C- α ; p-PLC γ : Phosphorylated phospholipase C- γ ; p-STAT3: Phosphorylated signal transducer and activator of transcription 3; PS1: Presenilin-1; RhoA: Ras homolog family member A; ROS: Reactive oxygen species; SCAF1: Supercomplex assembly factor 1; SCI: Spinal cord injury; SOD: Superoxide dismutase; STZ: Streptozotocin; tMCAO: Transient middle cerebral artery occlusion; T2DM: Type 2 diabetes mellitus; TNF: Tumor necrosis factor; TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling; VCAM-1: Vascular cell adhesion molecule-1; VEGF-A: Vascular endothelial growth factor A; WT: Wild type; ZO-1: Zonula occludens-1.

Table 2. Summary of clinical studies on the anti-inflammatory and cardiovascular effects of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes and/or obesity

Clinical	GLP-1R agonist	Parameters	Outcomes	References
Type 2 diabetes patients	Varies	↓ ROS; ↓ mtROS ↓; SOD; ↑ O ₂ consumption; ↓ MPO; ↓ adhesion; ↓ ICAM-1; ↓ VCAM; ↓ IL-6; ↓ TNF-α; ↓ IL-12; ↑ IL-10	Carotid intima media thickness was decreased, suggesting a reduced risk of atherosclerosis	Luna-Marco <i>et al.</i> ¹¹⁴
Type 2 diabetes patients	Semaglutide	N/A	↓ MACE; ↓ Cardiovascular-related death; ↓ all-cause death in low/medium NLR; No reduction in high NLR tertile. High NLR tertile = ↑ risk for all events	Verma <i>et al.</i> ¹¹⁵
Overweight/obese adults without type 2 diabetes	Semaglutide	↓ CRP; ↓ bodyweight; ↓ waist circumference;	Increased shift from lower CVD events	Verma <i>et al.</i> ¹¹⁵
Overweight/obese adults with type 2 diabetes	Semaglutide	↓ CRP; ↓ bodyweight; ↓ waist circumference; ↓ glucose	Increased shift from lower CVD events	Verma <i>et al.</i> ¹¹⁵
7 randomized control studies for type 2 diabetes patients (meta-analysis)	Varies	↓ CRP significantly down; ↑ adiponectin	↓ Inflammation; greater GLP-1R agonist exposure leads to lower inflammation	Mazidi <i>et al.</i> ¹¹⁶
Type 2 diabetes patients with/without chronic kidney disease	Semaglutide and exenatide	↓ CRP in all clinical trials	(i) Cardiovascular outcomes are mentioned in the studies utilized (ii) ↑ High risk→low risk categories independent of weight change	Mosenzon <i>et al.</i> ¹¹⁷

Abbreviations: CRP: C-reactive protein; CVD: Cardiovascular disease; GLP-1R: Glucagon-like peptide-1 receptor; ICAM-1: Intercellular adhesion molecule 1; IL: interleukin; MACE: Major adverse cardiovascular event; MPO: Myeloperoxidase; mtROS: Mitochondrial reactive oxygen species; N/A: Not applicable; NLR: Neutrophil-to-lymphocyte ratio; O₂: Molecular oxygen; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TNF: Tumor necrosis factor; VCAM: Vascular cell adhesion molecule.

suppressing pro-inflammatory cytokines, including interleukin (IL)-6, tumor necrosis factor- α (TNF- α), and IL-12, while simultaneously increasing anti-inflammatory cytokines such as IL-10.¹¹⁴

A quantifiable marker of systemic inflammation is the neutrophil-to-lymphocyte ratio (NLR), which reflects the balance between innate and adaptive immune activation.¹²³ Increased NLR correlates with greater stroke severity and poor clinical outcomes, as observed in patients with atherosclerotic disease, intracranial artery stenosis, and metabolic disorders.^{124,125} Higher NLR levels in diabetic and prediabetic patients are also associated with an increased risk of cardiovascular mortality.¹²⁶ GLP-1RA treatment in metabolic syndrome patients reduces all-cause mortality and cardiovascular-related outcomes in individuals with low and medium NLR levels, but not in those with the highest NLR ratios.¹¹⁵ This finding suggests a potential threshold effect of GLP-1RAs, beyond which severe inflammatory states may exceed their therapeutic window.

The inflammatory marker C-reactive protein (CRP) is highly elevated in patients following ischemic stroke and correlates with increasing stroke severity.¹²⁷ Moreover, CRP levels proportionally reflect the severity of metabolic syndrome and its components, reinforcing its role as a predictive marker for both metabolic disorders

and stroke.^{127,128} A study in 2001 demonstrated that metabolic disorder-induced elevations in CRP levels increase susceptibility to ischemic stroke and transient ischemic attacks.¹²⁹ Clinical studies have demonstrated that GLP-1RAs significantly reduce serum CRP levels in individuals with metabolic disorders.^{116,117,130} Notably, semaglutide treatment in overweight and obese patients resulted in CRP reduction independent of weight loss or glycemic control.¹³⁰ Reduced CRP levels in GLP-1R-treated patients also correlate with improved cardiovascular outcomes, suggesting an indirect protective effect against ischemic stroke via metabolic modulation.^{116,117,130}

Collectively, these findings suggest that GLP-1R activation exerts both direct and indirect anti-inflammatory effects in ischemic stroke, ultimately reducing its incidence and severity.¹⁰⁸ While pre-clinical studies provide strong evidence for the neuroprotective and immunomodulatory roles of GLP-1RAs, further clinical trials are necessary to fully elucidate their therapeutic potential in human stroke patients. The mechanisms by which GLP-1RAs preserve neuronal integrity, suppress inflammation, and inhibit apoptosis have direct implications for both stroke prevention and mitigation. In pre-clinical models, GLP-1RAs have been shown to reduce infarct size and improve post-stroke functional outcomes.¹⁰⁸ These findings, combined with their favorable safety and tolerability profile, suggest

that GLP-1RAs may serve as a viable adjunct therapy for individuals with pre-existing risk factors for ischemic stroke or be used alongside current treatment regimens. Moreover, GLP-1R activation has been associated with reduced systemic inflammation, as evidenced by decreases in circulating inflammatory markers, further supporting its clinical relevance in ischemic stroke.

7.2. Oxidative stress reduction by GLP-1RAs

Oxidative stress is a major pathological hallmark of metabolic disorders and ischemic stroke, driven by the accumulation of ROS.¹³¹ These free radicals contribute to neuronal and tissue damage through inflammation, extracellular matrix (ECM) remodeling, ER stress, or dysregulated autophagic flux.¹³¹ In ischemic stroke, the abrupt loss of CBF, followed by reperfusion injury, leads to a substantial surge in ROS, thereby overwhelming endogenous antioxidants and exacerbating necrosis and apoptosis.¹³² The oxidative imbalance in ischemic stroke is further aggravated by T2DM, as evidenced by elevated levels of malondialdehyde (MDA) and decreased levels of key antioxidants, such as glutathione (GSH) and catalase.^{109,133} Serum levels of MDA and ROS increase significantly following ischemic stroke, with higher levels associated with greater stroke severity and clinical impact.¹³⁴ Aging also increases oxidative stress levels, which are associated with lower recovery and reduced neuroplasticity following stroke, further exacerbating its severity.¹³⁴ Given the central role of oxidative stress in ischemic injury, therapeutic strategies targeting ROS through GLP-1R activation-mediated inflammatory regulation have shown promise in mitigating stroke progression and alleviating neuronal injury.¹³⁵

GLP-1RAs exhibit potent antioxidative effects in chronic metabolic disorders, such as T2DM and obesity, by reducing ROS production and enhancing antioxidant enzyme activity, such as superoxide dismutase and GSH reductase.¹³³ These protective effects are mediated through multiple signaling pathways, including cAMP-PKA-ERK1/2-CREB, PI3K-AKT-eNOS, and protein kinase C- δ pathways, enhancing antioxidant capability and activating Nrf2, a key regulator of oxidative stress response.¹³³ By mitigating oxidative damage and restoring redox balance, GLP-1RAs help attenuate the progression and severity of chronic metabolic disorders.¹³³

In a rat model of ischemic stroke with T2DM, GLP-1RAs significantly reduced oxidative stress by upregulating the AKT-eNOS pathway, leading to decreased MDA levels and increased GSH and catalase activity.¹⁰⁹ Western blot analysis further confirmed a significant reduction in oxidative stress and apoptosis, with lower expression of TNF- α and caspase 3, suggesting both direct and indirect

neuroprotective effects of GLP-1RA.¹⁰⁹ Moreover, the GLP-1RA lixisenatide demonstrated superior efficacy in reducing oxidative stress compared to glimepiride, a conventional antidiabetic agent, in TD2M rodent models of ischemic stroke.¹⁰⁹

The antioxidant properties of GLP-1RAs in ischemic stroke also reduce ER stress and oxidative injury, further contributing to neuroprotection.¹³³ Notably, activation of the AKT-eNOS pathway has been implicated in these effects, as demonstrated in rat models of cerebral ischemia.¹³³ In addition, pre-treatment with GLP-1RA has been shown to reduce infarct volume and improve neurobehavioral outcomes in experimental stroke models.¹³³ In primary neurons subjected to oxygen-glucose deprivation (OGD), GLP-1RAs attenuate ROS production by activating the PI3K-AKT-ERK pathway while simultaneously downregulating stress-activated apoptotic signaling molecules, such as phosphorylated p38 and c-JNK, thereby exerting significant neuroprotective effects.³¹ These studies highlight the potential of GLP-1RAs to combat oxidative stress by reducing ROS, making them strong candidates for therapeutic use in ischemic stroke.

7.3. BBB preservation by GLP-1RAs

The BBB is a highly selective and restrictive structure that maintains an immune-privileged environment, regulating the entry of specific substrates into the CNS.¹³⁶ This barrier plays a crucial role in preserving neuronal function by isolating CNS circulation from systemic circulation.¹³⁷ However, metabolic syndrome often results in increased BBB permeability and loss of integrity due to systemic inflammation associated with metabolic disorders, which in turn promotes immune cell infiltration and neuroinflammation.¹³⁷ Disruption of the BBB is a hallmark of ischemic stroke and contributes to secondary injury, leading to significant neurological impairments and the loss of vital substrates required for neuronal functioning.¹³⁶ Studies have shown that patients suffering from ischemic stroke commonly exhibit elevated levels of matrix metalloproteinase-9 (MMP-9), which is frequently used as a biomarker for BBB disruption and is inversely correlated with stroke severity and outcome.¹³⁸

GLP-1RAs help preserve BBB integrity, in part by mitigating metabolic disorders and reducing levels of MMP-9, a key mediator of BBB disruption.¹³⁶ In diabetic mice with ischemic stroke, GLP-1RAs have been shown to protect and preserve BBB integrity, resulting in improved neurocognitive recovery and repair to the BBB.¹⁰⁷ MMP-9 is a crucial enzyme involved in BBB disruption and ECM degradation, facilitating the release of pro-inflammatory cytokines such as TNF- α and IL-1 β . Its levels are directly

proportional to the severity of ischemic stroke, serving as a biomarker of neuronal damage, inflammation, and immune dysregulation.^{102,139,140} While some studies have reported conflicting findings regarding MMP-9 levels in metabolic disorders, the consensus is that serum MMP-9 levels are elevated in patients with metabolic syndrome and correlate with disease severity.^{141,142}

Astrocytes play a pivotal role in maintaining BBB integrity and regulating its permeability.¹⁴³ Following ischemic stroke, reactive astrocytes promote a pro-inflammatory environment by releasing cytokines such as IL-6, IL-1 β , and TNF- α , leading to the breakdown of tight junction proteins and increased BBB permeability.¹⁴³ The GLP-1RA exendin-4 has been shown to modulate astrocyte activity and preserve BBB integrity in an experimental OGD stroke model.¹⁰⁷ GLP-1R signaling in OGD-treated astrocytes and ischemic stroke rat models inhibits the JAK2/STAT3 pathway, reducing the expression of key BBB-disruptive biomarkers such as MMP-9, vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1, and chemokine C-X-C motif ligand 1.¹⁰⁷ This astrocytic modulation by GLP-1RAs results in increased tight junction protein expression and decreased immune cell infiltration, ultimately preserving BBB integrity.¹⁰⁷

Astrocyte polarization plays a critical role in BBB stability. The transition from the resting A0 phase to the pro-inflammatory A1 phase is associated with BBB disruption, inflammation, and ECM degradation following ischemic stroke.¹¹¹ GLP-1RA treatment promotes the polarization toward the A2 anti-inflammatory astrocyte phenotype, thereby maintaining BBB integrity and recovery.¹¹¹ A2 astrocyte activation in the context of ischemic injury results in reduced MMP-9 and VEGF expression, as well as decreased activation of the nuclear factor kappa-light-chain-enhancer of activated B cells inflammatory pathway.¹¹¹ Thus, GLP-1RA regulates astrocyte function and preserves BBB integrity in both ischemic stroke and metabolic syndrome.¹⁰⁷ This regulation, in turn, may reduce the severity of cardiovascular events and outcomes, including ischemic stroke, thereby underscoring the potential of GLP-1RA for the prevention and mitigation of ischemic stroke.

Post-stroke endothelial dysfunction exacerbates ischemic stroke by increasing BBB permeability, facilitating immune cell infiltration, and triggering neuroinflammation and neuronal death.¹⁴⁴ GLP-1RAs modulate astrocytic signaling pathways, including cAMP/PKA, PI3K/AKT, and AMPK, thereby reducing inflammation and maintaining BBB integrity.^{107,110,111} In addition, GLP-1R activation in endothelial cells supports BBB preservation through

the PKA-PI3K-AKT-eNOS pathway, which promotes angiogenesis.¹⁰⁷ An increase in VEGF signaling via the AKT-VEGF pathway further enhances endothelial cell-mediated angiogenesis.¹⁰⁷ Furthermore, GLP-1RAs reduce systemic MMP-9 levels, thereby restoring BBB integrity and attenuating inflammation-induced brain damage.¹¹² The GLP-1RA exendin-4 has been shown to reduce infarct volume, lower MMP-9 levels, and improve glucose regulation in hyperglycemic mice with focal cerebral ischemia.¹¹²

In addition to endothelial protection, GLP-1RAs enhance nitric oxide bioavailability, which exerts anti-inflammatory effects in endothelial cells and contributes to BBB stabilization.¹¹³ These agents have also been shown to reduce infarct volume, enhance functional recovery, and promote angiogenesis in ischemic models.¹¹³ In addition, GLP-1R signaling upregulates ERK1/2 in cerebral ischemic rats, leading to reduced apoptosis, increased neuroplasticity, and decreased ER stress.¹⁰¹

Pericytes play a vital role in maintaining BBB integrity and exhibit significant volume loss in metabolic disorders and ischemic stroke, leading to BBB dysfunction and impaired CBF.^{38,145} One study demonstrated that GLP-1RAs protect pericytes from oxidative stress and promote BBB integrity³⁸ through survival signaling via the AKT pathway, thereby reducing pericyte inflammation and apoptosis while promoting cell survival.³⁸ In stroke-induced T2DM mouse models, GLP-1RAs have been shown to restore pericyte volume, enhance vascular remodeling and angiogenesis, and ultimately support functional recovery and neuronal stability.¹⁴⁵ These findings suggest that GLP-1RAs may confer clinical benefits by reducing post-stroke BBB dysfunction and facilitating recovery, with significant improvements in pericyte volume and endothelial function, thereby contributing to the restoration of hemodynamic stability and BBB integrity.

8. Therapeutic perspective of GLP-1RA

As the global prevalence of metabolic syndrome and its associated conditions continues to rise, the incidence of cardiovascular and cerebrovascular complications, including ischemic stroke, will also increase (Figure 4).⁴ These metabolic disorders significantly impact long-term quality of life, increase the health-care burden on both individuals and their families, and exacerbate neurological outcomes following stroke.⁴ Moreover, metabolic disorders not only elevate the risk of ischemic stroke but also contribute to its severity, often leading to neurocognitive deficits and long-term disability.³ Current treatment strategies for ischemic stroke remain largely ineffective in preventing stroke onset, particularly in individuals with metabolic comorbidities.⁵

It may be valuable to evaluate the pharmacoeconomic potential of GLP-1RAs in ischemic stroke to determine their cost-effectiveness relative to current standard therapies.¹⁴⁶ Combination therapies involving GLP-1RAs may offer improved cost-effectiveness due to their pleiotropic effects on multiple metabolic risk factors, including glycemic control, weight reduction, and cardiovascular protection.¹⁴⁶ Established regimens, such as angiotensin-converting enzyme inhibitors and beta-blockers, are considered cost-effective in vascular conditions due to their low cost and proven mortality benefit. If GLP-1RAs can provide both preventative and therapeutic benefits in the context of stroke through metabolic and vascular modulation, they may represent a superior cost-effective strategy despite their higher upfront costs.¹⁴⁶ However, current GLP-1RAs, such as tirzepatide and semaglutide, have shown limited cost-effectiveness in obese populations, primarily due to high drug prices—highlighting the need for pricing adjustments to improve accessibility.¹⁴⁷

Metabolic disorders exacerbate both the incidence and severity of ischemic stroke.³ Secondary injury following the initial vascular occlusion is driven by mechanisms such as inflammation, oxidative stress, and BBB disruption, leading to more severe neurological damage.² Despite advances in stroke management, no effective clinical interventions currently exist to specifically mitigate secondary injury, alleviate metabolic risk factors, and protect against ischemic stroke.^{2,5} Given the complex interplay between metabolic disorders, ischemic stroke, and secondary injury, a multifaceted therapeutic approach is necessary to address the underlying pathological mechanisms, including oxidative stress, inflammation, and vascular dysfunction.

GLP-1RAs offer a promising therapeutic avenue due to their dual metabolic and neuroprotective effects.¹³ These agents modulate inflammatory and oxidative pathways, providing indirect protection against ischemic stroke by reducing its incidence and severity.^{121,136} Clinical studies indicate that GLP-1RA treatment improves stroke outcomes and mitigates post-stroke severity in patients with metabolic disorders, including diabetes, obesity, hypertension, and hyperglycemia.^{42-44,57} Within the CNS, GLP-1R activation promotes neuronal survival, reduces neuronal apoptosis, attenuates inflammation and oxidative stress, and enhances BBB integrity. In addition, by mitigating metabolic risk factors and reducing atherosclerotic development, GLP-1RAs indirectly reduce the risk of ischemic stroke.^{59,148,149} While many studies highlight the indirect cerebrovascular benefits of GLP-1R activation, limited research has been conducted on its direct therapeutic potential following ischemic stroke.

The functional role of GLP-1R expression in the cerebral cortex remains incompletely understood. Some studies suggest that GLP-1R primarily exerts anti-inflammatory effects, while others describe its role in insulin regulation and energy homeostasis within the brain. It is plausible that GLP-1R expression in the cortex serves both insulinotropic and neuroprotective functions, with modulation of inflammation as either a primary or secondary effect. Moreover, GLP-1R expression declines with age, which may impact the therapeutic efficacy of GLP-1RAs in elderly patients.⁹⁵ While clinical data suggest that GLP-1RAs reduce cardiovascular events in older adults, their direct neuroprotective effects in aging populations remain unclear. Further investigation is needed to elucidate whether this reduction in GLP-1R expression leads to a diminished neuroprotective response or if compensatory mechanisms mitigate its impact.

Despite promising evidence supporting GLP-1RAs in stroke prevention, there remains a critical gap in understanding their role in post-stroke neuroprotection within clinical settings. At present, no studies have comprehensively examined GLP-1R expression in ischemic brain injury using single-cell RNA sequencing. The distribution and regulation of GLP-1R in CNS cells, including microglia, brain endothelial cells, and pericytes, under pathological conditions remain largely unknown. Future research employing transcriptomic approaches could provide deeper insights into the mechanistic distinctions between direct versus indirect neuroprotective mechanisms of GLP-1R activation in ischemic stroke. Moreover, it remains unclear whether GLP-1R-mediated neuroprotection results from systemic metabolic modulation or localized CNS effects. Resolving these uncertainties is essential for advancing GLP-1RAs as a targeted therapeutic strategy for ischemic stroke.

GLP-1RAs, widely prescribed for metabolic disorders, have demonstrated significant reductions in stroke-related morbidity.¹⁴⁸ As a result of their neuroprotective mechanisms, GLP-1RAs represent ideal candidates for ischemic stroke intervention and prevention via the modulation of metabolic risk factors. However, despite their safety and efficacy in metabolic disease, GLP-1RAs remain largely unexplored as a treatment for ischemic stroke in clinical practice.

Clinical trials investigating the therapeutic potential of GLP-1RAs in ischemic stroke are urgently needed. These agents may serve as adjunctive therapy alongside existing stroke interventions, such as tissue plasminogen activator or mechanical thrombectomy, offering neuroprotection against both primary ischemic injury and secondary inflammatory damage. Pre-clinical models consistently

support the neuroprotective effects of GLP-1R activation in ischemic stroke.¹⁵⁰ Given their widespread use in metabolic disorders such as obesity and diabetes, GLP-1RAs hold substantial promise for mitigating ischemic stroke severity and its associated inflammation.⁴⁶ A deeper understanding of their neuroprotective mechanisms, both direct and indirect, could pave the way for their integration into treatment against ischemic stroke.

9. Conclusion

Currently while therapeutic intervention continuously progresses, effective strategies for the prevention and long-term managements of cerebral ischemic stroke remain limited. This review reveals that pre-clinical studies show that GLP-1RAs reduce infarct size, improve neurofunctional recovery, and provide metabolic protection. Clinical studies also demonstrate GLP-1RA therapy in patients with metabolic syndrome and its individual components reduce mortality of cardio- and cerebro-vascular diseases. However, the molecular and cellular mechanisms by which GLP-1R signaling mitigates cerebral ischemic stroke in humans are still poorly characterized, and clinical evidence supporting effectiveness of GLP-1RA remains sparse. Moving forward, further clinical investigations are essential to clarify the therapeutic potential of GLP-1RAs in mitigating ischemic stroke severity and improving long-term neurological outcomes.

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Conflict of interest

Hong-Shuo Sun and Zhong-Ping Feng are Editorial Board Members of this journal, but were not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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