Semaglutide and Neuroprotection: Exploring Mechanisms Against Ischemia-Reperfusion Injury Beyond Glycemic Control

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Abstract

Background: Ischemic stroke remains a leading cause of mortality and long-term disability worldwide, with ischemia-reperfusion (I/R) injury representing a major therapeutic challenge. Restoration of blood flow, though essential, paradoxically exacerbates neuronal damage through oxidative stress, excitotoxicity, inflammation, and mitochondrial dysfunction. Despite progress in reperfusion therapies such as thrombolysis and mechanical thrombectomy, effective pharmacological neuroprotection remains elusive. Thus, exploration of novel agents that target multiple injury cascades is of critical importance. Semaglutide, a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist originally developed for type 2 diabetes mellitus and obesity, has recently gained attention for its extra-glycemic effects, particularly in the cardiovascular and nervous systems. Unlike earlier incretin-based therapies, semaglutide demonstrates improved pharmacokinetics, enhanced receptor binding affinity, and the ability to penetrate the central nervous system. Preclinical studies suggest that semaglutide exerts anti-inflammatory, antioxidant, and anti-apoptotic effects in neuronal tissue, positioning it as a potential candidate for stroke-related neuroprotection even in non-diabetic settings. This review aims to evaluate the possible neuroprotective role of semaglutide against ischemia-reperfusion injury, with a particular emphasis on its underlying molecular mechanisms. We synthesize experimental evidence from animal models demonstrating improvements in infarct volume, neurological function, and survival following semaglutide administration. Mechanistic insights highlight attenuation of oxidative stress via modulation of Nrf2 and mitochondrial pathways, suppression of pro-inflammatory cytokines and microglial activation, reduction of neuronal apoptosis through PI3K/Akt signaling, and promotion of synaptic plasticity and neurotrophic support. Comparative analysis with other GLP-1 receptor agonists, such as liraglutide and exenatide, further suggests that semaglutide's longer half-life and CNS penetration may confer superior neuroprotective efficacy. In conclusion, semaglutide holds promise as a novel pharmacological strategy for ischemia-reperfusion injury beyond its established metabolic benefits. While preclinical evidence is compelling, translational gaps remain, including optimal dosing, timing of administration, and validation in human trials. Future research should prioritize well-designed studies to clarify its therapeutic potential in acute ischemic stroke, possibly positioning semaglutide as a dual-purpose agent bridging metabolic and neurovascular protection.

Keywords: *Semaglutide, Neuroprotection, Ischemia-Reperfusion Injury , Glycemic Control*

Introduction

Ischemic stroke continues to rank among the leading causes of mortality and long-term disability worldwide, accounting for nearly 80% of all cerebrovascular accidents. Despite advances in reperfusion strategies such as intravenous thrombolysis and mechanical thrombectomy, the outcome remains unsatisfactory for a substantial proportion of patients. The process of ischemia-reperfusion (I/R) paradoxically exacerbates neuronal injury, triggering cascades of oxidative stress, neuroinflammation, mitochondrial dysfunction, excitotoxicity, and apoptosis [1]. These complex mechanisms highlight the unmet need for pharmacological agents that provide robust neuroprotection in addition to reperfusion therapy.

Current neuroprotective strategies, including antioxidants, anti-inflammatory agents, and NMDA receptor antagonists, have largely failed to demonstrate consistent clinical benefit, underscoring the necessity for novel interventions capable of targeting multiple pathways simultaneously [2]. In this context, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), initially developed for glycemic control in type 2 diabetes, have emerged as promising candidates. Beyond their metabolic effects, GLP-1 RAs exhibit cardiovascular and neuroprotective actions through modulation of oxidative stress, inflammation, and neuronal survival [3].

Semaglutide, a next-generation long-acting GLP-1 RA, possesses unique pharmacological advantages, including extended half-life, high receptor affinity, and demonstrable central nervous system penetration [4]. While primarily used in diabetes and obesity, growing experimental evidence suggests its potential neuroprotective role in non-diabetic models of cerebral ischemia. Studies indicate semaglutide reduces infarct volume, improves neurological outcomes, and modulates cellular signaling cascades implicated in I/R injury [5]. These properties make semaglutide a compelling subject of investigation in the search for neuroprotective agents.

The rationale for focusing on semaglutide extends beyond its direct neuronal effects. Its favorable cardiovascular safety profile, demonstrated in large outcome trials, and its capacity to influence endothelial function and systemic inflammation suggest additional protective benefits in ischemic stroke patients [6]. Importantly, semaglutide's actions appear to transcend glycemic regulation, opening therapeutic opportunities for non-diabetic individuals at risk of or affected by ischemic stroke.

This review aims to synthesize current knowledge on the potential neuroprotective effects of semaglutide in ischemia-reperfusion injury. We highlight experimental evidence from animal models, explore underlying molecular mechanisms, compare semaglutide with other GLP-1 receptor agonists, and discuss its translational relevance. By doing so, we provide a pharmacological perspective on semaglutide as a novel therapeutic avenue for ischemic stroke beyond glucose lowering.

Pharmacological Profile of Semaglutide

Semaglutide is a synthetic glucagon-like peptide-1 receptor agonist (GLP-1 RA) structurally modified to resist enzymatic degradation by dipeptidyl peptidase-4 (DPP-4) and to bind with high affinity to albumin, thereby extending its half-life to approximately one week [7]. These structural modifications, which include substitution of alanine at position 8 with α-aminoisobutyric acid and the addition of a C18 fatty diacid side chain, enhance both stability and pharmacokinetics, allowing for once-weekly subcutaneous administration [8].

The principal pharmacological action of semaglutide involves activation of GLP-1 receptors, which are widely expressed not only in pancreatic β-cells but also in cardiovascular tissues, kidneys, and the central nervous system. In the pancreas, GLP-1 receptor stimulation augments glucose-dependent insulin secretion, suppresses glucagon release, and delays gastric emptying, underpinning its antidiabetic efficacy [9]. However, the discovery of GLP-1 receptor expression in neurons and glial cells has shifted interest toward its extra-glycemic actions. Within the brain, receptor activation enhances cell survival pathways, modulates neurotransmitter release, and improves synaptic plasticity [10].

Pharmacokinetic studies indicate that semaglutide crosses the blood–brain barrier, albeit at low concentrations compared to peripheral tissues, likely via receptor-mediated mechanisms at circumventricular organs and endothelial transport systems [11]. Even at low CNS concentrations,

semaglutide initiates signaling cascades, including PI3K/Akt and cAMP/PKA, which contribute to anti-apoptotic and neurotrophic responses [12]. Its long half-life and stable plasma levels further ensure sustained CNS receptor engagement, a distinct advantage over short-acting GLP-1 analogs.

Beyond glycemic control, semaglutide has demonstrated cardiovascular and anti-inflammatory benefits in large-scale outcome trials, such as SUSTAIN-6, where it reduced major adverse cardiovascular events [13]. These systemic effects are highly relevant to ischemic stroke, where vascular dysfunction and systemic inflammation amplify neuronal injury. The pleiotropic pharmacology of semaglutide thus positions it as a candidate drug capable of acting at multiple levels: endothelial protection, anti-inflammatory modulation, and direct neuronal survival.

Taken together, the pharmacological profile of semaglutide extends far beyond its role as an antidiabetic drug. Its ability to reach the CNS, modulate neuroprotective signaling, and exert systemic vascular benefits provides a strong foundation for exploring its potential role in ameliorating ischemia-reperfusion injury.

Pathophysiology of Ischemia-Reperfusion Injury

Ischemia-reperfusion (I/R) injury is a biphasic process characterized by initial deprivation of oxygen and glucose during ischemia, followed paradoxically by cellular and molecular damage upon reperfusion. Neurons are especially vulnerable due to their high metabolic demands and limited regenerative capacity. The complex interplay of oxidative stress, excitotoxicity, inflammation, and apoptosis defines the neuropathology of I/R and presents multiple targets for pharmacological intervention [14].

Oxidative Stress:

Reperfusion generates a burst of reactive oxygen species (ROS) through mitochondrial dysfunction, activation of NADPH oxidase, and xanthine oxidase pathways. Excessive ROS overwhelms endogenous antioxidant defenses, resulting in lipid peroxidation, protein denaturation, and DNA damage. This oxidative imbalance is a major driver of neuronal injury in stroke [15].

Neuroinflammation:

I/R activates resident microglia and recruits peripheral immune cells across a compromised blood–brain barrier. Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 amplify neuronal damage, while adhesion molecules facilitate leukocyte infiltration. Chronic activation of glial cells further contributes to delayed neurodegeneration [16].

Apoptosis and Necrosis:

Ischemia triggers both necrotic and apoptotic pathways. Energy depletion leads to necrotic cell death in the ischemic core, whereas reperfusion promotes apoptosis in the penumbra through mitochondrial cytochrome c release and caspase activation. PI3K/Akt and MAPK pathways are critical checkpoints that determine neuronal survival versus apoptosis [17].

Excitotoxicity:

Glutamate accumulation during ischemia overstimulates NMDA and AMPA receptors, leading to excessive calcium influx and subsequent activation of proteases, lipases, and endonucleases. This excitotoxic cascade exacerbates oxidative stress and apoptosis, compounding neuronal loss [18].

Mitochondrial Dysfunction:

Mitochondria are central to I/R injury. During reperfusion, opening of the mitochondrial permeability transition pore (mPTP) disrupts membrane potential, impairs ATP synthesis, and accelerates ROS production. Mitochondrial damage also triggers pro-apoptotic signaling, further propagating neuronal death [19].

Thus, ischemia-reperfusion injury represents a multifactorial process with overlapping and self-perpetuating pathways. Conventional neuroprotective agents targeting a single mechanism have largely failed, underscoring the importance of therapies like semaglutide that may modulate multiple injury cascades simultaneously.

Experimental Evidence of Semaglutide in Neuroprotection

Preclinical studies have increasingly highlighted the neuroprotective potential of semaglutide in models

of cerebral ischemia-reperfusion (I/R) injury. While initially designed for metabolic control, semaglutide's pleiotropic actions have been evaluated in non-diabetic rodent models, providing valuable insights into its direct effects on the central nervous system [20].

Reduction of Infarct Volume and Neurological Deficits:

In rodent models of middle cerebral artery occlusion (MCAO), semaglutide administration significantly reduced infarct size and improved neurological function scores compared with untreated controls. These benefits were observed even in normoglycemic animals, supporting the hypothesis that neuroprotection is independent of glycemic modulation [21]. Behavioral assessments demonstrated improved motor coordination, grip strength, and exploratory activity, further underscoring functional recovery.

Timing and Route of Administration:

Studies suggest semaglutide retains efficacy when administered both before ischemia (preconditioning model) and shortly after reperfusion, though earlier administration produces greater benefits. Subcutaneous injection, the clinically approved route, has shown effectiveness in animal models, suggesting translational feasibility. Intracerebroventricular administration, used experimentally, demonstrated enhanced CNS effects but is unlikely to be clinically relevant [22].

Histological and Cellular Outcomes:

Histopathological analysis of ischemic brain tissue revealed reduced neuronal degeneration, decreased apoptotic cell counts, and preservation of hippocampal architecture in semaglutide-treated groups. Immunohistochemical staining demonstrated suppression of microglial activation and decreased expression of inflammatory markers such as IL-1β and TNF-α [23].

Systemic and Vascular Effects:

Beyond direct neuronal protection, semaglutide improved endothelial function and reduced systemic markers of oxidative stress in experimental stroke models. Enhanced cerebral perfusion and stabilization of the blood–brain barrier were observed, indicating that vascular modulation may complement neuronal survival mechanisms [24].

Comparative Efficacy with Other GLP-1 RAs:

When compared with liraglutide and exenatide, semaglutide exhibited longer-lasting neuroprotection due to its extended half-life and stable plasma concentrations. This pharmacokinetic advantage suggests fewer fluctuations in CNS exposure and may underpin superior efficacy in sustained neuroprotection [25].

Taken together, experimental evidence supports semaglutide as a promising agent for mitigating ischemia-reperfusion injury, with benefits spanning infarct reduction, functional recovery, and modulation of cellular injury pathways. These findings provide a preclinical foundation for mechanistic exploration and potential translational application in non-diabetic stroke patients.

Possible Mechanisms of Neuroprotection by Semaglutide

The neuroprotective potential of semaglutide in ischemia-reperfusion (I/R) injury is underpinned by its ability to act on multiple overlapping injury pathways. Unlike conventional neuroprotective agents that target a single mechanism, semaglutide engages pleiotropic signaling cascades that include antioxidant, anti-inflammatory, anti-apoptotic, mitochondrial, and neurotrophic processes [26].

Antioxidant Effects

Oxidative stress is a central driver of I/R injury. Semaglutide enhances endogenous antioxidant defenses by upregulating nuclear factor erythroid 2–related factor 2 (Nrf2) and downstream enzymes such as superoxide dismutase and heme oxygenase-1. Experimental models show decreased lipid peroxidation and reduced ROS accumulation following semaglutide treatment. By stabilizing redox balance, semaglutide helps preserve neuronal membrane integrity and DNA stability [27].

Anti-Inflammatory Pathways

Semaglutide suppresses neuroinflammation by inhibiting activation of NF-κB and reducing pro-inflammatory cytokine release, including IL-1β, TNF-α, and IL-6. It also attenuates microglial and astrocytic activation in peri-infarct regions. This immunomodulatory effect minimizes secondary

neuronal injury and prevents expansion of the ischemic penumbra [28].

Anti-Apoptotic and Pro-Survival Signaling

Activation of GLP-1 receptors triggers intracellular cascades such as PI3K/Akt and MAPK/ERK pathways, which promote neuronal survival. In I/R models, semaglutide reduced cytochrome c release from mitochondria and downregulated caspase-3 activity, thereby inhibiting apoptosis. This preservation of neuronal populations in vulnerable regions like the hippocampus is strongly linked to improved functional outcomes [29].

Mitochondrial Protection

Mitochondria are critical targets in reperfusion injury. Semaglutide stabilizes mitochondrial membrane potential, reduces opening of the mitochondrial permeability transition pore (mPTP), and maintains ATP production. These effects not only mitigate ROS generation but also support neuronal energy homeostasis, preventing cell death cascades [30].

Neurotrophic and Synaptic Plasticity Modulation

Semaglutide enhances expression of brain-derived neurotrophic factor (BDNF) and synaptic proteins, which support neuronal repair and plasticity. Experimental studies show improved dendritic spine density and synaptic integrity in semaglutide-treated animals, suggesting a role in long-term recovery and cognitive resilience after ischemic injury [31].

Collectively, these mechanisms highlight semaglutide as a multi-target neuroprotective agent. By modulating oxidative stress, inflammation, apoptosis, mitochondrial dysfunction, and synaptic plasticity, semaglutide offers a pharmacological profile uniquely suited to the multifactorial nature of ischemia-reperfusion injury.

Comparative Insights: Semaglutide vs Other GLP-1 Receptor Agonists

While the neuroprotective properties of GLP-1 receptor agonists (GLP-1RAs) are increasingly recognized, semaglutide appears to offer distinct advantages compared to its predecessors such as exenatide, liraglutide, and dulaglutide. The differences lie in pharmacokinetics, blood–brain barrier (BBB) penetration, receptor affinity, and downstream signaling dynamics [32].

Pharmacokinetics and CNS Penetration

Semaglutide has an extended half-life of approximately one week, enabling once-weekly administration. This prolonged exposure ensures stable receptor activation and reduces fluctuations in CNS drug concentrations compared to shorter-acting agents like exenatide. Animal studies suggest that semaglutide achieves higher CNS bioavailability, which is critical for sustained neuroprotection during ischemia-reperfusion events [33].

Receptor Affinity and Potency

Compared to liraglutide, semaglutide demonstrates higher affinity for GLP-1 receptors and stronger activation of intracellular cAMP pathways. This translates into more robust stimulation of neuroprotective signaling cascades such as PI3K/Akt and ERK, which govern neuronal survival, plasticity, and mitochondrial stability [34].

Comparative Anti-Inflammatory and Antioxidant Actions

Both liraglutide and semaglutide attenuate microglial activation and cytokine release; however, semaglutide shows superior efficacy in reducing oxidative stress markers and lipid peroxidation in preclinical ischemia models. This may be attributed to its stronger induction of Nrf2 signaling and downstream antioxidant enzymes [35].

Clinical Implications Beyond Diabetes

Although all GLP-1RAs were initially developed for glycemic control, semaglutide's superior cardiovascular and neuroprotective effects in large outcome trials (e.g., SUSTAIN-6) suggest that it may be the most promising candidate for repurposing in ischemia-reperfusion injury. Its prolonged duration of action reduces treatment burden, which is particularly advantageous in acute neurological conditions where adherence is a concern [36].

Taken together, semaglutide distinguishes itself from other GLP-1RAs by combining strong receptor potency, enhanced CNS penetration, and favorable pharmacokinetics. These properties position it as a leading agent in exploring GLP-1–based strategies for neuroprotection beyond diabetes.

Translational and Preclinical Evidence in Ischemia-Reperfusion Models

Preclinical studies in rodent models have provided compelling insights into semaglutide's neuroprotective actions in cerebral ischemia-reperfusion (I/R) injury, particularly in non-diabetic contexts. Male albino rats subjected to middle cerebral artery occlusion (MCAO), a widely used model of stroke, have demonstrated consistent benefits with semaglutide treatment [37].

Infarct Size and Functional Recovery

Administration of semaglutide in rats undergoing MCAO significantly reduced infarct volume, as evidenced by TTC staining and MRI evaluation. Treated rats also exhibited improved neurological deficit scores and motor coordination compared with vehicle-treated controls, underscoring semaglutide's ability to preserve neuronal function [38].

Histological Protection

Histopathological assessments revealed reduced neuronal loss, diminished vacuolization, and preserved hippocampal pyramidal cell integrity in semaglutide-treated animals. Immunohistochemical analysis further demonstrated decreased expression of caspase-3 and Bax, alongside enhanced Bcl-2, indicating a marked anti-apoptotic effect [39].

Anti-Inflammatory Modulation

Semaglutide reduced pro-inflammatory cytokine levels (IL-1β, TNF-α, IL-6) in brain homogenates of I/R rats. Microglial activation, typically heightened in ischemic brains, was notably suppressed following semaglutide administration. These findings highlight its ability to shift neuroinflammation toward a more neuroprotective phenotype [40].

Oxidative Stress and Mitochondrial Stability

Markers of oxidative stress, including malondialdehyde (MDA) and reactive oxygen species (ROS), were significantly lower in semaglutide-treated groups. Meanwhile, antioxidant enzyme activity (SOD, catalase, glutathione peroxidase) was preserved. Electron microscopy confirmed maintenance of mitochondrial cristae integrity and reduced swelling, indicating direct mitochondrial protection [41].

Vascular and BBB Protection

In MCAO rats, semaglutide was shown to reduce Evans Blue dye extravasation, reflecting improved blood–brain barrier (BBB) integrity. Furthermore, treated animals had reduced vascular adhesion molecule expression, mitigating leukocyte infiltration into the ischemic brain parenchyma [42].

Timing of Administration

Preconditioning with semaglutide (administered before ischemia) produced robust neuroprotection, but post-reperfusion treatment also conferred significant benefits. This highlights its therapeutic potential in both preventive and acute clinical settings [43].

Collectively, preclinical evidence supports semaglutide as a potent neuroprotective agent in ischemia-reperfusion models, demonstrating anti-apoptotic, antioxidant, and anti-inflammatory effects, with preservation of neuronal and vascular integrity. These findings establish a translational rationale for investigating semaglutide in human stroke therapy, independent of its glycemic control properties.

Conclusion

Semaglutide, originally developed as a glucose-lowering therapy, has emerged as a promising candidate for neuroprotection in ischemia-reperfusion injury. Experimental data from non-diabetic animal models demonstrate its ability to reduce infarct volume, improve functional recovery, and modulate key injury pathways. Unlike conventional neuroprotective agents that target isolated mechanisms, semaglutide exerts pleiotropic effects spanning antioxidant defense, suppression of neuroinflammation, stabilization of mitochondrial function, inhibition of apoptosis, and support of synaptic plasticity.

Beyond its neuronal actions, semaglutide also protects vascular integrity and preserves blood–brain barrier function, two critical determinants of secondary injury following reperfusion. Its long half-life,

high receptor affinity, and established cardiovascular safety further strengthen its potential translational value in acute ischemic stroke. Importantly, the neuroprotective effects observed in non-diabetic models underscore that its benefits extend beyond glycemic regulation, opening therapeutic avenues for a wider patient population.

Despite these promising findings, significant challenges remain before clinical application can be realized. Optimal dosing, timing of administration, and long-term outcomes need careful evaluation in well-designed translational and clinical studies. Future research should also address sex differences, age-related responses, and combination strategies with reperfusion therapies. Incorporation of advanced imaging and biomarker endpoints will be essential in bridging experimental results to human stroke populations.

In summary, semaglutide represents a novel pharmacological strategy with the potential to transform the management of ischemia-reperfusion injury. By targeting multiple overlapping injury cascades, it offers a comprehensive neuroprotective approach that could complement existing reperfusion therapies and improve outcomes for patients with ischemic stroke.

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