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GLP-1 AND DUAL GLP-1/GIP RECEPTOR AGONISTS AS NEUROPROTECTIVE AGENTS: MECHANISMS, CLINICAL EVIDENCE, AND TRANSLATIONAL PERSPECTIVES

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ABSTRACT

Background: Neurodegenerative diseases are increasingly linked to metabolic dysfunction, such as impaired insulin signaling, mitochondrial dysfunction, oxidative stress, and chronic neuroinflammation. These observations have contributed to the type 3 diabetes hypothesis, which describes AD as a disorder associated with brain insulin resistance. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual GLP-1/GIP receptor agonists have emerged as promising therapeutic candidates because of their metabolic and neuroprotective properties.

Objective: To evaluate the neuroprotective potential of GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists in neurodegenerative diseases.

Materials and Methods: A structured narrative review was conducted using PubMed, Scopus, and Web of Science databases. Studies published between 2015 and 2026 investigating incretin-based therapies in neurodegenerative disorders were included, encompassing randomized controlled trials, observational studies, meta-analyses, and mechanistic research.

Results: Preclinical studies consistently demonstrated neuroprotective effects of GLP-1RAs through modulation of neuroinflammation, oxidative stress, mitochondrial dysfunction, synaptic plasticity, and neuronal survival pathways. Observational studies suggested an association between incretin-based therapies and reduced dementia risk. Clinical trials in AD and PD have yielded heterogeneous results, with efficacy appearing to depend on disease stage and patient characteristics. Dual GLP-1/GIP receptor agonists showed promising mechanistic potential, although clinical evidence remains limited.

Conclusions: Incretin-based therapies represent a promising multi-target strategy for neurodegenerative diseases. Their effects extend beyond glycaemic regulation and may influence multiple pathways involved in neurodegeneration. Further large-scale clinical studies are required to determine their disease-modifying potential and optimal therapeutic use.

KEYWORDS

Brain Insulin Resistance, GLP-1 Receptor Agonists, Neuroinflammation, Alzheimer's Disease, Parkinson's Disease, Healthy Aging

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1. Introduction

Neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease are among the most significant challenges in modern medicine. Their rapid progression, coupled with increasing life expectancy, has resulted in a substantial rise in global prevalence and an escalating socioeconomic burden. Despite decades of research, current therapeutic approaches remain largely symptomatic and fail to modify disease progression. This limitation has fuelled growing interest in the development of disease-modifying approaches.

The growing body of evidence highlights the critical role of metabolic dysfunction in neurodegeneration. Central insulin resistance has been shown to impair synaptic plasticity, disrupt neuronal signalling, and contribute to cognitive decline. These findings have led to the development of the type 3 diabetes hypothesis or brain insulin resistance, which proposes that Alzheimer's disease represents a brain-specific form of insulin resistance characterized by impaired insulin signalling, reduced glucose utilization, and disrupted neuronal metabolism.

The growing prevalence of neurodegenerative diseases has also increased interest in preventive strategies associated with metabolic health, physical activity, and healthy aging. In this context, incretin-based therapies may represent an important interdisciplinary area linking metabolic medicine, neurology, and broader health-related quality of life research.

At the molecular level, insulin signalling plays a key role in regulating synaptic plasticity, neuronal survival, and mitochondrial function. Disruption of these pathways leads to elevated oxidative stress, enhanced neuroinflammation, and the accumulation of pathological protein aggregates, including amyloid- β and tau.

Epidemiological evidence further supports this relationship, demonstrating that individuals with type 2 diabetes have an increased risk of developing dementia. Shared pathological pathways include chronic inflammation, oxidative stress, mitochondrial dysfunction, and impaired cellular energy metabolism .

GLP-1RAs have emerged as promising therapeutic candidates in this context. Originally developed for type 2 diabetes, these agents exhibit pleiotropic effects within the central nervous system, including potent anti-inflammatory (via NLRP3 inflammasome suppression), neurotrophic (promoting neurite outgrowth), and cytoprotective actions (improving mitochondrial bioenergetics) . These mechanisms are mediated through key signalling pathways such as PI3K/Akt and cAMP/PKA, which appear to bypass central insulin resistance to preserve neuronal integrity. Importantly, GLP-1 receptor signalling interacts with insulin signalling pathways, specifically via the PI3K/Akt/mTOR axis, which may restore impaired metabolic function in the brain . By bypassing dysfunctional insulin receptors to reestablish glucose homeostasis and mitochondrial efficiency, incretin-based therapies act as potential modulators of the pathological processes described in the type 3 diabetes hypothesis . Recent clinical data, including the ELAD trial, suggest that this metabolic stabilization can lead to a significant reduction in cortical atrophy, further supporting the brain-specific insulin resistance framework .

This review evaluates the neuroprotective efficacy of incretin-based therapies, specifically investigating their capacity to mitigate the metabolic and molecular deficits central to the type 3 diabetes hypothesis. Additionally, we examine how preserving these central bioenergetic pathways translates into maintaining motor function, physical mobility, and overall quality of life in neurodegenerative cohorts, thereby linking metabolic health directly to functional capacity and movement quality.

Although several reviews have explored the role of GLP-1 receptor agonists in neurodegenerative disorders, substantial new evidence has emerged from large observational studies and randomized clinical trials published between 2024 and 2026. Furthermore, increasing interest in dual GLP-1/GIP receptor agonists has expanded the therapeutic landscape beyond traditional incretin-based approaches. Therefore, an updated synthesis integrating mechanistic evidence, clinical trial outcomes, and translational perspectives is warranted.

2. Literature Search Strategy

A structured narrative review was conducted using PubMed, Scopus, and Web of Science databases. The literature search was performed up to March 2026. Studies published from January 2015 to March 2026 were considered for inclusion. The search strategy combined the following keywords and Medical Subject Headings (MeSH) where applicable: “GLP-1 receptor agonists”, “dual incretin agonists”, “GIP receptor”, “neuroprotection”, “Alzheimer’s disease”, “Parkinson’s disease”, “brain insulin resistance”, “type 3 diabetes”, “neuroinflammation”, and “mitochondrial dysfunction”.

Titles and abstracts were initially screened for relevance, followed by full-text assessment of potentially eligible studies. Randomized controlled trials, observational studies, systematic reviews, meta-analyses, and mechanistic experimental studies investigating incretin-based therapies in neurodegenerative diseases were included.

Studies not published in English, conference abstracts without available full texts, editorials, commentaries, and studies lacking sufficient methodological information were excluded.

Data extracted from eligible studies included molecular mechanisms, neuroprotective pathways, clinical outcomes, and translational implications of incretin-based therapies. Evidence was synthesized qualitatively with emphasis on identifying recurring mechanistic and clinical patterns across the literature.

Due to substantial heterogeneity regarding study design, patient populations, therapeutic interventions, and outcome measures, quantitative synthesis and formal meta-analysis were not performed.

Artificial intelligence-assisted language editing tools were used exclusively to improve grammatical accuracy, language clarity, and stylistic consistency under direct human supervision. All scientific interpretation, evidence selection, critical analysis, and conclusions were performed solely by the authors.

3. Biology of the Incretin System in the Central Nervous System

The incretin system, traditionally characterized by its role in peripheral glycaemic regulation, has emerged as a sophisticated neuroendocrine modulator of central nervous system (CNS) function. Glucagon-like peptide-1 (GLP-1) is uniquely positioned within the gut-brain axis, produced both by intestinal L-cells and preproglucagon neurons in the nucleus tractus solitarius (NTS) of the brainstem, allowing for a dual-origin signalling network. GLP-1 receptors (GLP-1R) are extensively distributed across regions critical to cognitive and motor function, including the hippocampus, cerebral cortex, and substantia nigra, which are areas that exhibit high vulnerability in Alzheimer's (AD) and Parkinson's diseases (PD).

Central to the type 3 diabetes hypothesis, GLP-1R activation serves as a metabolic "rescue" mechanism. In neurodegenerative states, impaired insulin signalling disrupts the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), leading to synaptic dysfunction and energy deficits. GLP-1RAs bypass this resistance to restore intracellular signalling, facilitating hippocampal long-term potentiation (LTP) and enhancing synaptic plasticity. This metabolic restoration is further amplified by the emerging role of the glucose-dependent insulinotropic polypeptide (GIP). The GIP receptor (GIPR) represents an additional component of the incretin system that has gained increasing attention in recent years. Although less extensively studied in the brain, GIP receptors are expressed in several CNS regions and appear to play a role in neuronal metabolism and synaptic function. They are expressed in neurogenic niches like the hippocampal dentate gyrus, where they promote neuronal metabolism and synaptic integrity. The advent of dual GLP-1/GIP agonists (e.g., Tirzepatide) offers a synergistic approach, potentially providing a more comprehensive restoration of impaired metabolic signalling than monotherapy alone. Dual GLP-1/GIP receptor agonists simultaneously activate both incretin pathways, potentially leading to enhanced metabolic regulation and neuroprotection. These agents improve insulin sensitivity, reduce body weight, and modulate energy balance, all of which may influence brain function. Within the type 3 diabetes framework, dual agonism may provide a more comprehensive restoration of impaired metabolic signalling, addressing both systemic and central components of insulin resistance.

The central effects of GLP-1RAs depend partly on their ability to cross the blood-brain barrier (BBB). Several GLP-1 analogues have been shown to reach the brain and influence central metabolic processes. However, not all incretin-based therapies rely solely on direct BBB penetration. Peripheral actions, including improved insulin sensitivity, reduced systemic inflammation, and modulation of gut-brain signalling pathways, may indirectly influence brain function.

In neurodegenerative diseases, incretin signalling may be disrupted by chronic inflammation, oxidative stress, and metabolic dysfunction. These factors can alter receptor expression, impair intracellular signalling, and reduce responsiveness to endogenous hormones. This dysregulation may contribute to disease progression by exacerbating neuronal energy deficits and impairing cellular repair mechanisms. Pharmacological activation of incretin pathways may therefore restore disrupted signalling networks and improve neuronal resilience.

4. Molecular Mechanisms of Neuroprotection

GLP-1RAs exert neuroprotective effects through a network of interconnected molecular pathways that target key pathological processes underlying neurodegeneration. Importantly, these mechanisms intersect with both the amyloid cascade hypothesis and the type 3 diabetes hypothesis.

4.1. Neuroinflammation and Glial Regulation

Neuroinflammation and glial regulation are key targets in neurodegenerative processes. GLP-1 receptors on astrocytes and microglia, when activated, inhibit the NF- κ B pathway and the NLRP3 inflammasome. This shifts microglia from a pro-inflammatory M1-like state toward a neuroprotective M2-like phenotype, ultimately reducing the release of neurotoxic cytokines such as TNF- α . By restoring insulin signalling and reducing inflammation, GLP-1RAs may target both upstream metabolic dysfunction and downstream neurodegenerative processes.

4.2. Mitochondrial Dysfunction and Oxidative Stress

Mitochondrial dysfunction is a hallmark of neurodegeneration and a key component of the type 3 diabetes hypothesis. Neurons rely heavily on efficient mitochondrial function for energy production, and impairment of this system leads to cellular stress and degeneration. Incretin signalling enhances mitochondrial

function by activating AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) pathways, which stimulate mitochondrial biogenesis and lower the production of reactive oxygen species (ROS). GLP-1 receptor activation reduces ROS production and enhances antioxidant capacity, including upregulation of enzymes such as superoxide dismutase and catalase. Improved mitochondrial efficiency further contributes to reduced oxidative damage. These effects directly counteract the metabolic deficits associated with insulin resistance in the brain.

4.3. Amyloid- β and Tau Pathology

The accumulation of amyloid- β and tau proteins is a defining feature of Alzheimer's disease. Proteostasis and amyloid pathology are also influenced by incretin signalling. Incretin agonists bridge the metabolic and amyloid hypotheses by upregulating autophagy. This facilitates the clearance of amyloid- β plaques and phosphorylated tau, addressing the downstream proteinopathies that define AD.

4.4. Synaptic Plasticity and Neuronal Survival

Neuronal survival is further supported through the activation of pro-survival signalling pathways. GLP-1RAs enhance synaptic plasticity, improve long-term potentiation, and increase levels of neurotrophic factors such as BDNF. These effects contribute to improved cognitive function and neuronal resilience.

Table 1. Principal Neuroprotective Mechanisms of GLP-1 Receptor Agonists and Dual GLP-1/GIP Receptor Agonists

Mechanism	Major pathways involved	Potential neuroprotective effects
Anti-inflammatory activity	NF- κ B inhibition, NLRP3 inflammasome suppression	Reduced neuroinflammation and microglial activation
Improved insulin signalling	PI3K/Akt and MAPK/ERK pathways	Enhanced neuronal metabolism and survival
Mitochondrial protection	AMPK and PGC-1 α activation	Improved mitochondrial function and energy production
Reduction of oxidative stress	Increased antioxidant enzyme activity, reduced ROS generation	Lower oxidative damage
Synaptic plasticity enhancement	BDNF upregulation and long-term potentiation support	Improved cognition and neuronal resilience
Promotion of autophagy	Clearance of amyloid- β and phosphorylated tau	Reduced pathological protein accumulation
Metabolic regulation	Improved glucose utilization and insulin sensitivity	Restoration of brain metabolic homeostasis

Abbreviations: AMPK - AMP-activated protein kinase; BDNF - brain-derived neurotrophic factor; ERK - extracellular signal-regulated kinase; MAPK - mitogen-activated protein kinase; NF- κ B - nuclear factor kappa B; NLRP3 - NOD-like receptor family pyrin domain containing 3; PI3K/Akt - phosphoinositide 3-kinase/protein kinase B; PGC-1 α - peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ROS - reactive oxygen species.

The mechanisms described above are deeply interconnected, with metabolic dysfunction, inflammation, oxidative stress, and protein aggregation forming a self-reinforcing pathological network. While the amyloid cascade hypothesis focuses mainly on downstream protein aggregation, the type 3 diabetes hypothesis highlights upstream metabolic impairment. GLP-1RAs operate across multiple points within this network, offering a multi-target therapeutic strategy. This systems-level action sets incretin-based therapies apart from single-target approaches and helps explain their strong mechanistic potential in neurodegenerative diseases.

5. Clinical evidence and translational perspective

Despite strong mechanistic evidence, clinical studies evaluating incretin-based therapies in neurodegenerative diseases have produced heterogeneous results. These findings highlight the challenges associated with translating experimental neuroprotective effects into consistent clinical outcomes. While early results were heterogeneous, data emerging in 2024–2026 suggest that the efficacy of these agents is highly dependent on patient stratification and the stage of metabolic dysfunction at the time of intervention.

5.1. Observational studies

Large observational studies continue to provide the most consistent evidence linking GLP-1RAs to a reduced risk of neurodegeneration. In a landmark 2025 retrospective cohort analysis using data from a global health network, Sun and colleagues demonstrated that GLP-1RA initiation was associated with a 12% lower hazard of Alzheimer's disease compared to metformin, a finding that persisted across multiple sensitivity analyses.

Furthermore, in a pivotal 2024 retrospective cohort analysis of over 1 million patients, Wang and colleagues demonstrated that semaglutide was associated with a 40% to 70% lower risk of a first-time Alzheimer's diagnosis compared to other antidiabetic agents, including insulin and DPP-4 inhibitors.

However, recent comparative analyses have shown that this protective effect is not unique to GLP-1RAs. SGLT2 inhibitors have demonstrated similar, and in some cohorts superior, risk reduction for all-cause dementia.

5.2. Clinical Trial Outcomes in Alzheimer's Disease

Clinical studies investigating incretin-based therapies in Alzheimer's disease have produced heterogeneous results despite encouraging mechanistic evidence. The Phase IIb ELAD trial, led by Paul Edison, evaluated the efficacy of liraglutide in 204 non-diabetic patients with mild Alzheimer's disease. While the study did not meet its primary endpoint of significantly altering cerebral glucose metabolism, notable neuroprotective signals were observed in secondary measures. Specifically, MRI analysis revealed that liraglutide treatment resulted in a reduction in the rate of cortical atrophy compared to placebo. Furthermore, while broad cognitive measures remained unchanged, a statistically significant preservation of executive function (ADAS-Exec) was recorded. These findings suggest that metabolic dysfunction associated with the type 3 diabetes hypothesis may be challenging to fully restore during symptomatic stages of the disease, incretin mimetics may still provide structural neuroprotection and stabilize specific cognitive domains. This complexity was further corroborated by the global EVOKE and EVOKE+ Phase III programs. Evaluating oral semaglutide in participants with early-stage disease, these trials did not demonstrate consistent clinical benefit on the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score across the general study population. While directional trends toward slowed cognitive decline were noted, the lack of robust clinical significance suggests that by the time Alzheimer's reaches a symptomatic stage, the window for metabolic rescue may be partially compromised by advanced tau pathology and irreversible synaptic loss. Specifically, post-hoc analyses suggested that efficacy may be phenotype-specific, with more pronounced responses observed in patients with coexisting small vessel disease, supporting the potential contribution of metabolic and neurovascular dysfunction to disease progression.

5.3. Clinical trials in Parkinson's Disease

In contrast to the challenges observed in Alzheimer's, Parkinson's disease trials have provided the first definitive signals of disease modification using incretin mimetics. The 2024 LixiPark trial led by Meissner and colleagues reported that lixisenatide significantly slowed the progression of motor disability over twelve months in patients with early-stage disease. This effect was notably sustained even after a washout period, suggesting potential sustained neuroprotective effects.

However, a major setback occurred in 2025 with the results of the large Phase III trial Exenatide-PD3. In contrast to earlier Phase II findings suggesting potential benefit, this multicentre study demonstrated that once-weekly exenatide did not produce a statistically significant improvement in motor function compared with placebo over a 96-week follow-up period. These findings underscore the difficulties associated with converting promising metabolic therapies into consistent clinical outcomes and indicate that the effectiveness of GLP-1RAs may depend on factors such as disease stage, timing of intervention, and patient-specific characteristics.

5.4. Clinical trials in acute neurology

The application of incretin-based therapies in acute neurology, specifically ischemic stroke, also demonstrates the challenges associated with translating preclinical neuroprotective findings into clinical practice. According to a comprehensive 2025 systematic review and meta-analysis of 35 studies (31 preclinical and 4 clinical), GLP-1RAs demonstrated significant neuroprotective effects in animal models, significantly reducing infarct volume and improving functional recovery through the attenuation of oxidative stress, neuroinflammation, and hypoxia-triggered cell death.

Despite these compelling mechanistic foundations, the meta-analysis reveals that clinical demonstration in non-diabetic human cohorts remains a challenge. Recent randomized trials have failed to show a significant effect on acute neurological recovery or long-term functional independence in patients without diabetes. These findings underscore that while GLP-1RAs are safe and well-tolerated in the acute post-stroke window, their clinical role as neuroprotective therapies requires more precise patient stratification and potentially different dosing regimens to overcome the threshold of human ischemic damage.

Beyond cognitive outcomes, incretin-based therapies may also influence functional capacity, mobility, and quality of life in aging populations. Improvements in insulin sensitivity, mitochondrial efficiency, vascular function, and systemic inflammation may contribute not only to neuroprotection, but also to preservation of motor performance and physical independence. Emerging evidence suggests that metabolic interventions targeting central and peripheral energy regulation may become increasingly relevant in interdisciplinary approaches combining neurology, preventive medicine, rehabilitation, and physical activity research.

Table 2. Selected Clinical Trials Evaluating GLP-1 Receptor Agonists in Neurodegenerative Diseases

Trial	Population	Main Outcome	Key Finding	Clinical Interpretation
LixiPark	Early-stage Parkinson's disease	Motor progression	Slower motor progression with lixisenatide	Potential benefit in early-stage PD
ELAD	Mild Alzheimer's disease	Cortical atrophy and cognition	Reduced cortical atrophy compared with placebo	Possible structural neuroprotective effect
EVOKE / EVOKE+	Early-stage Alzheimer's disease	Phase III clinical evaluation	Preliminary reports suggest heterogeneous treatment response	Further clinical data required
Exenatide-PD3	Advanced Parkinson's disease	Motor disability progression	No significant improvement versus placebo	Limited efficacy in advanced disease
Michaelsen et al.	Experimental and clinical stroke studies	Stroke-related outcomes	Significant neuroprotective effects in experimental models	Limited clinical evidence in human studies

6. Discussion

The growing body of evidence linking metabolic dysfunction with neurodegenerative disorders has generated substantial interest in incretin-based therapies as potential disease-modifying interventions. Beyond their established role in glucose regulation, GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists influence multiple biological pathways implicated in neurodegeneration, including insulin signalling, neuroinflammation, oxidative stress, mitochondrial dysfunction, and protein aggregation (Kellar & Craft, 2020; Gandhi & Parhizgar, 2025; Athauda et al., 2026; Hölscher, 2020).

One of the most important concepts supporting the investigation of incretin-based therapies in neurodegenerative diseases is the type 3 diabetes hypothesis. According to this framework, impaired insulin signalling within the central nervous system contributes to synaptic dysfunction, reduced neuronal energy metabolism, and progressive cognitive decline (Kellar & Craft, 2020; De La Monte & Wands, 2008). By

activating intracellular pathways that overlap with insulin signalling, GLP-1 receptor agonists may partially restore metabolic homeostasis and improve neuronal resilience (Gandhi & Parhizgar, 2025; Athauda et al., 2026; Hölscher, 2020).

Preclinical evidence has consistently demonstrated beneficial effects of incretin-based therapies across experimental models of Alzheimer's disease, Parkinson's disease, and other neurological disorders. These studies have shown reductions in neuroinflammatory activity, attenuation of oxidative stress, enhancement of mitochondrial function, and improvement of synaptic plasticity (Gandhi & Parhizgar, 2025; Athauda et al., 2026; Ros-Madrid et al., 2025; Du et al., 2022).

Furthermore, incretin signalling appears to influence the clearance of pathological protein aggregates, including amyloid- β and phosphorylated tau, suggesting potential disease-modifying properties (Du et al., 2022).

Despite these promising mechanistic findings, clinical evidence remains less consistent. While observational studies frequently report associations between incretin-based therapies and reduced dementia risk, randomized clinical trials have produced heterogeneous results (Edison et al., 2025; Sun et al., 2025; Wang et al., 2024; Tang et al., 2025). Several factors may explain this discrepancy. First, neurodegenerative diseases are typically diagnosed after substantial neuronal loss has already occurred, potentially limiting the effectiveness of interventions targeting metabolic dysfunction. Second, patient populations differ considerably regarding disease stage, metabolic status, vascular comorbidities, and genetic susceptibility. Finally, treatment duration may be insufficient to detect meaningful disease-modifying effects in slowly progressive neurological disorders (Edison et al., 2025; Scheltens et al., 2026; Vijiaratnam et al., 2025).

Recent clinical trials suggest that therapeutic efficacy may depend on early intervention. The beneficial findings observed in selected Parkinson's disease cohorts and the structural neuroprotective signals reported in Alzheimer's disease studies support the possibility that incretin-based therapies may be most effective during earlier stages of neurodegeneration, when neuronal reserve remains relatively preserved and metabolic abnormalities are potentially reversible (Edison et al., 2025; Meissner et al., 2024).

An additional area of interest involves dual GLP-1/GIP receptor agonists. By simultaneously activating complementary incretin pathways, these agents may provide broader metabolic and neuroprotective effects than GLP-1 receptor agonist monotherapy (Fukuda, 2021; Sánchez-Garrido et al., 2017). Although clinical evidence remains limited, their favourable effects on insulin sensitivity, body weight, systemic inflammation, and energy homeostasis make them promising candidates for future investigation in neurodegenerative disorders (Sánchez-Garrido et al., 2017).

From a broader preventive medicine perspective, incretin-based therapies may complement non-pharmacological interventions such as physical activity and lifestyle modification. Both approaches influence overlapping biological pathways associated with healthy aging, including improved insulin sensitivity, enhanced mitochondrial function, reduced inflammation, and increased neurotrophic support (Hölscher, 2020; Yang et al., 2025). Consequently, integrated strategies combining pharmacological and lifestyle interventions may represent a promising direction for future neuroprotective approaches.

Overall, current evidence supports the concept that incretin-based therapies represent a promising multi-target strategy in neurodegenerative diseases. However, additional large-scale randomized trials with longer follow-up periods are required to determine their true disease-modifying potential and identify patient populations most likely to benefit from treatment (Athauda et al., 2026; Edison et al., 2025; Scheltens et al., 2026; Vijiaratnam et al., 2025).

6.1. Limitations of the Review

Several limitations of the present review should be acknowledged. First, this study was conducted as a narrative review rather than a systematic review, which may increase the risk of selection bias despite the structured literature search strategy employed. Second, the included studies demonstrated substantial heterogeneity regarding study design, patient populations, therapeutic interventions, outcome measures, and duration of follow-up, limiting direct comparison between findings.

Third, a considerable proportion of the currently available evidence originates from preclinical and observational studies, whereas high-quality randomized controlled trial data remain relatively limited (Athauda et al., 2026; Sun et al., 2025; Wang et al., 2024; Tang et al., 2025). Consequently, the translation of experimental neuroprotective effects into clinical practice remains uncertain. Fourth, only English-language publications were included, which may have resulted in the exclusion of relevant studies published in other languages.

Finally, the field of incretin-based therapies in neurodegenerative diseases is evolving rapidly, with several ongoing clinical trials expected to provide additional evidence in the coming years (Scheltens et al., 2026). Therefore, some conclusions presented in this review may require reassessment as new clinical data become available. Publication bias should also be considered, as studies reporting positive therapeutic effects are more likely to be published than studies with neutral or negative findings.

7. Conclusions

Incretin-based therapies have emerged as promising therapeutic candidates in neurodegenerative diseases due to their pleiotropic metabolic, anti-inflammatory, and neuroprotective properties. Increasing evidence supports the concept that impaired insulin signalling and metabolic dysfunction contribute substantially to the pathogenesis of disorders such as Alzheimer's disease and Parkinson's disease, strengthening the relevance of the type 3 diabetes hypothesis.

Preclinical studies consistently demonstrate neuroprotective effects of GLP-1 receptor agonists, while observational and clinical studies suggest potential benefits in selected patient populations. However, clinical outcomes remain heterogeneous across available studies, indicating that therapeutic efficacy may depend on factors such as disease stage, metabolic status, and timing of intervention.

Dual GLP-1/GIP receptor agonists represent a particularly promising therapeutic direction for future research because of their broader metabolic and potentially complementary neuroprotective effects. Nevertheless, current clinical evidence remains limited, and further large-scale longitudinal studies are necessary to determine their long-term therapeutic value in neurodegenerative disorders.

The growing interest in incretin-based therapies also highlights the increasing importance of metabolic health, healthy aging, and preventive medicine in contemporary neurological research. In this context, therapies targeting metabolic dysfunction may contribute not only to neuroprotection, but also to preservation of cognitive and functional performance during aging.

Overall, incretin-based therapies represent a promising multi-target therapeutic strategy in neurodegenerative diseases. Future research should focus on optimizing patient selection, therapeutic timing, and long-term evaluation of neuroprotective outcomes.

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