

Beyond Diabetes and Obesity: The Emerging Role of GLP-1 and GIP Agonists in Neurodegenerative Diseases—A Mini-Review

Andrei Emilian Popa ^{1,2}, Elena Popa ^{1,3*}, Mihaela Poroch ^{1,3}, Elena Adorata Coman ^{1,3}, Vladimir Poroch ^{1,3}

¹Faculty of Medicine, “Grigore T. Popa” University of Medicine and Pharmacy, 16 Universitatii Str., 700115 Iasi, Romania.

²“Prof. Dr. Nicolae Oblu” Emergency Clinic Hospital, 700309 Iasi, Romania.

³Department of Family Medicine, Preventive Medicine and Interdisciplinary, “Grigore T. Popa” University of Medicine and Pharmacy, Universitatii Str. 16, 700115 Iasi, Romania.

⁴2nd Internal Medicine Department, “Grigore T. Popa” University of Medicine and Pharmacy, 700115 Iasi, Romania.

***Corresponding Author:** Elena Popa, Faculty of Medicine, “Grigore T. Popa” University of Medicine and Pharmacy, 16 Universitatii Str., 700115 Iasi, Romania.

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Abstract

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP)-based therapies, originally developed for the treatment of type 2 diabetes mellitus and obesity, have attracted increasing interest for their potential role in neurodegenerative diseases. Beyond their established metabolic benefits, these agents may exert neuroprotective effects through modulation of neuroinflammation, improvement of mitochondrial function, enhancement of autophagy, preservation of neuronal energy homeostasis, and reduction of pathological protein accumulation, including beta-amyloid, hyperphosphorylated tau, and alpha-synuclein.

This mini-review summarizes current evidence regarding the role of incretin-based therapies in Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, amyotrophic lateral sclerosis, Huntington’s disease, and multiple system atrophy. The strongest clinical evidence is currently available for Alzheimer’s disease and Parkinson’s disease, although findings from large phase III trials have been inconsistent. In other neurodegenerative disorders, available data are derived predominantly from preclinical studies.

Emerging therapies, including dual GLP-1/GIP receptor agonists and GLP-2-based compounds, represent promising future directions and may offer broader neuroprotective benefits through simultaneous targeting of metabolic, inflammatory, and neurodegenerative pathways. While further clinical validation is required, incretin-based therapies may contribute to a more integrated approach to the management of patients with both metabolic and neurological disorders.

Keywords: GLP-1; GIP; incretin-based therapies; neurodegenerative diseases; Alzheimer’s disease; Parkinson’s disease; neuroinflammation; neuroprotection

1. Background. GLP-1 and GIP: from metabolic regulation to neuroprotection

Obesity has become one of the most significant chronic health challenges worldwide, affecting more than one billion individuals and contributing substantially to global morbidity and mortality. Rather than being viewed solely as a consequence of lifestyle factors, obesity is now recognized as a complex, chronic, and relapsing disease influenced by genetic, metabolic, behavioral, and environmental determinants. This modern perspective supports the need for early diagnosis, long-term monitoring, and individualized therapeutic strategies [1].

Recent international recommendations emphasize a comprehensive management approach that combines lifestyle interventions, behavioral therapy, pharmacological treatment, and bariatric surgery when clinically indicated. Within this framework, glucagon-like peptide-1 (GLP-1)-based therapies have emerged as an important therapeutic option, particularly for patients with obesity associated with cardiometabolic risk. Their long-term use may improve weight reduction, metabolic control, and cardiovascular outcomes, while also supporting better treatment adherence and sustain clinical benefits. [1].

In this context, glucagon-like peptide-1 (GLP-1)-based therapies and dual GLP-1/glucose-dependent insulintropic polypeptide (GIP) receptor agonists have become some of the most important modern therapeutic innovations in obesity and metabolic disease management [1]. Initially developed for the treatment of type 2 diabetes mellitus, these agents have demonstrated significant benefits in weight reduction, glycemic control, and cardiovascular risk reduction [2]. In September 2025, WHO added GLP-1 therapies to the Essential Medicines List for the management of type 2 diabetes mellitus in high-risk groups and subsequently published its first official guideline on their use in obesity treatment [3].

General practitioners (GPs) are often the first point of contact for individuals seeking help with weight management, making them essential in the early identification of obesity, associated metabolic complications, and disordered eating behaviors [2]. Their role is crucial not only in initiating effective therapeutic strategies, but also in providing long-term follow-up, monitoring treatment safety, and supporting lifestyle modifications such as healthy nutrition, physical activity, and behavioral interventions.

The inclusion of GLP-1 receptor agonists in major international therapeutic recommendations further reflects their growing importance in modern obesity management. [2]. Beyond their established metabolic benefits, these agents are increasingly investigated for their potential pleiotropic effects, including anti-inflammatory, cardiovascular, and neuroprotective actions, which may expand their role beyond traditional metabolic disease treatment [1,2] [4,5]. Semaglutide has been shown to reduce the risk of major adverse cardiovascular events (MACE) [4], including myocardial infarction, stroke, and cardiovascular death, while also promoting the resolution of metabolic dysfunction-associated steatohepatitis (MASH)[5]. These pleiotropic effects further support the role of incretin-based therapies not only in obesity management but also in reducing long-term cardiometabolic complications.

Disordered eating behaviors such as binge eating, emotional eating, and compulsive overeating are highly prevalent among individuals with obesity and significantly contribute to weight gain, psychological distress, reduced quality of life, and metabolic dysfunction. In addition to appetite suppression and increased satiety, GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists appear to reduce “food noise,” defined as persistent and intrusive thoughts about food, thereby providing important psychological benefits and improving long-term weight management adherence [2].

More recently, scientific interest has expanded beyond the metabolic field toward the neuroprotective potential of GLP-1 and GIP-based therapies, particularly in neurodegenerative diseases [6,7]. Their anti-inflammatory, antioxidant, and neuroprotective properties have generated considerable interest in conditions such as Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, and multiple sclerosis, where chronic neuroinflammation, mitochondrial dysfunction, and progressive neuronal loss play central pathogenic roles [8].

2. Aim

This mini-review aims to summarize the current evidence regarding the role of GLP-1 and GIP-based therapies in neurodegenerative diseases, with particular focus on their neuroprotective mechanisms, clinical relevance, therapeutic potential, current controversies, and future perspectives in multidisciplinary care

3. Materials and Methods

This mini-review was conducted to provide a concise and updated overview of the potential role of GLP-1 and GIP-based therapies in neurodegenerative diseases. The review focused on their neuroprotective effects, anti-inflammatory mechanisms, mitochondrial protection, modulation of pathological protein accumulation, and potential clinical applications in disorders such as Alzheimer’s disease, Parkinson’s

disease, multiple sclerosis, amyotrophic lateral sclerosis, Huntington’s disease, and multiple system atrophy.

A literature search was performed using PubMed, Scopus, Web of Science, and Google Scholar, including articles published in English during the past five years, while highly relevant landmark studies were included when necessary for contextual understanding. The search strategy included keywords such as “GLP-1,” “GIP,” “incretin-based therapies,” “neurodegenerative diseases,” “Alzheimer’s disease,” “Parkinson’s disease,” “multiple sclerosis,” “neuroinflammation,” and “neuroprotection.” Selected studies were analyzed based on their clinical relevance, mechanistic insights, and potential therapeutic implications.

4. GLP-1 and GIP in neurodegenerative diseases

4.1. General Neuroprotective Effects of GLP-1 Receptor Agonists in Neurodegenerative Disorders

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), originally introduced for the management of type 2 diabetes mellitus (T2DM) and obesity, have recently gained considerable attention for their potential role in neurodegenerative diseases due to their pleiotropic effects on the central nervous system [10]. Experimental studies indicate that GLP-1RAs may attenuate neuroinflammation, improve cerebral glucose utilization, preserve mitochondrial integrity, stimulate autophagic processes, and reduce the accumulation of abnormal proteins such as beta-amyloid (A β), hyperphosphorylated tau, and alpha-synuclein [11,12]. These observations have reinforced the “Type 3 diabetes” hypothesis, which links impaired cerebral insulin signaling and brain insulin resistance to the pathogenesis of neurodegenerative disorders, particularly Alzheimer’s disease [13].

One of the principal mechanisms involved is the regulation of chronic neuroinflammatory activity. Persistent activation of microglia and astrocytes leads to excessive production of pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6), which contribute to synaptic dysfunction, neuronal damage, tau hyperphosphorylation, beta-amyloid deposition, and progressive neurodegeneration [6,15]. Simultaneously, sustained activation of the nuclear factor kappa B (NF- κ B) pathway and the NLRP3 inflammasome promotes oxidative stress, mitochondrial dysfunction, and apoptotic signaling, further accelerating neuronal loss [8].

GLP-1RAs may counteract these pathological processes by restoring neuronal energy balance through improved insulin and growth factor signaling, supporting mitochondrial biogenesis, and facilitating autophagy and cellular repair mechanisms [15]. In addition, they may reduce inflammatory damage by suppressing cytokine release, limiting microglial M1 polarization, promoting the anti-inflammatory M2 phenotype, and decreasing NLRP3 inflammasome activation [14]. Through these combined effects, GLP-1RAs may help preserve neuronal viability and delay disease progression.

Observational evidence also supports this broader neuroprotective potential [12]. A large propensity-matched cohort study involving more than five million adults with obesity demonstrated that GLP-1RA therapy was associated with a lower incidence of several neurodegenerative conditions, including Alzheimer’s disease, Lewy body dementia, and vascular dementia [12]. Although the overall reduction in Parkinson’s disease risk did not reach statistical significance, semaglutide users showed a significant protective association [12]. Among available agents, semaglutide demonstrated the most consistent benefits and was also associated with reduced all-cause mortality [12].

Taken together, these findings suggest that GLP-1RAs may provide clinical benefits that extend beyond weight reduction and cardiometabolic improvement, potentially contributing to long-term neurocognitive preservation across multiple neurodegenerative disorders. Although most available evidence currently focuses on GLP-1 receptor agonists,

emerging experimental data suggest that GIP signaling may also exert neuroprotective effects through modulation of neuroinflammation, neuronal energy metabolism, and synaptic function. These observations have stimulated growing interest in dual GLP-1/GIP receptor agonists as potential therapeutic strategies for neurodegenerative disorders. This

broad neuroprotective profile provides the rationale for further investigation of incretin-based therapies in specific neurodegenerative diseases and highlights their potential relevance for clinicians managing patients with both metabolic and neurological disorders (Figure 1).

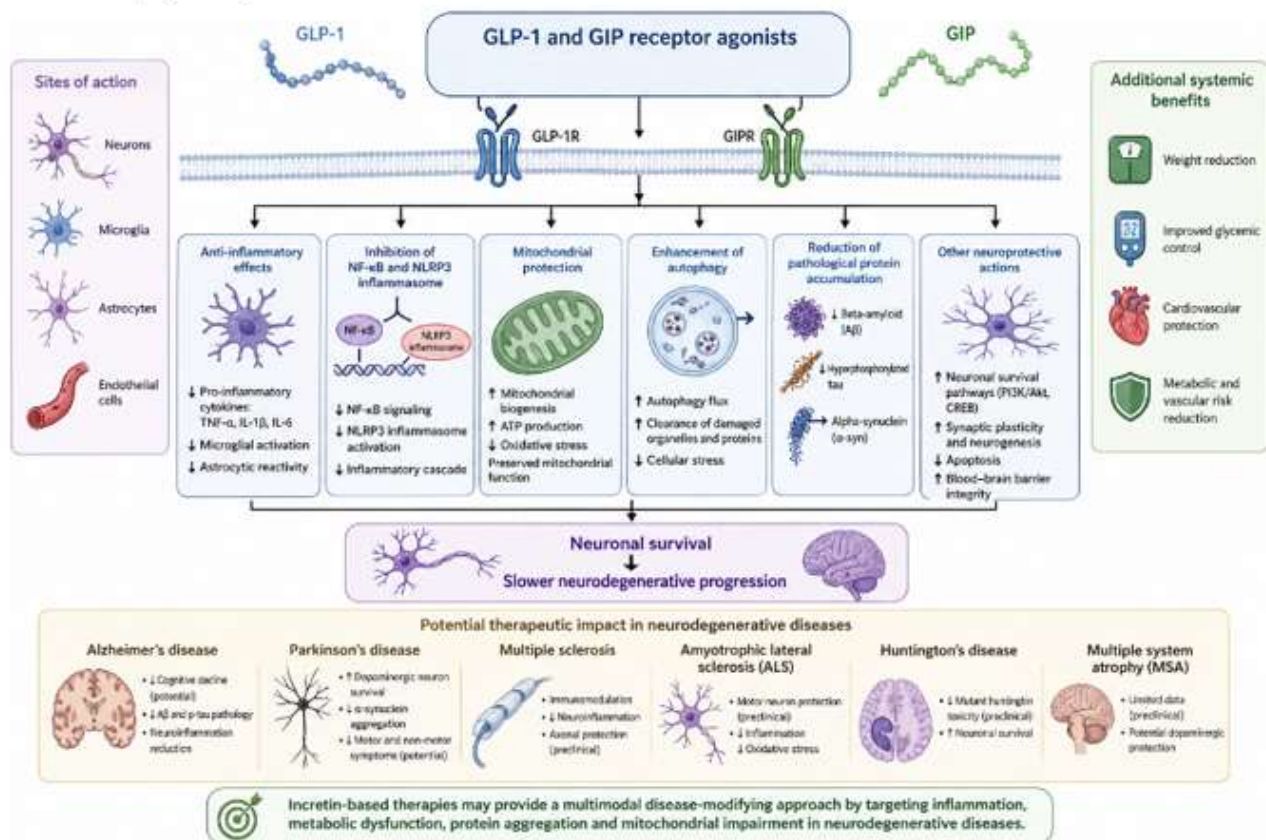


Figure 1: Incretins in neurodegenerative diseases.

GLP-1 and GIP receptor agonists exert neuroprotective effects through multiple mechanisms, including reduction of neuroinflammation, inhibition of NF- κ B signaling and NLRP3 inflammasome activation, improvement of mitochondrial function, enhancement of autophagy, and reduction of pathological protein accumulation, such as beta-amyloid, hyperphosphorylated tau, and alpha-synuclein. These mechanisms promote neuronal survival, delay neurodegenerative progression, and may contribute to disease modification in Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, and multiple system atrophy.

4.2. Alzheimer's Disease (AD)

Liraglutide, one of the most extensively studied GLP-1 receptor agonists in AD, demonstrated promising neuroprotective effects in preclinical models (18), (19). The ELAD trial (Evaluating Liraglutide in Alzheimer's Disease), a multicenter, randomized, double-blind, placebo-controlled phase 2b study, evaluated liraglutide in 204 non-diabetic patients with mild to moderate AD over 52 weeks [20].

The primary outcome was the change in cerebral glucose metabolism assessed by FDG-PET. Although no significant difference was observed between liraglutide and placebo regarding cerebral glucose metabolic rate, liraglutide-treated patients showed better performance in executive cognitive function, particularly in the ADAS-Exec (Alzheimer's Disease Assessment Scale-Executive Function) score. No significant improvements were observed in activities of daily living or overall dementia severity. Importantly, liraglutide was generally safe and well tolerated [20].

More recently, the large phase 3 EVOKE and EVOKE+ trials [21] investigated oral semaglutide in patients with early AD, including individuals with mild cognitive impairment (MCI) or mild dementia and amyloid-confirmed disease. These multicenter, randomized, double-blind, placebo-controlled studies included more than 3,800 participants across 40 countries [21].

The primary endpoint was the change in Clinical Dementia Rating-Sum of Boxes (CDR-SB) score over 104 weeks. Despite strong expectations, semaglutide failed to demonstrate significant clinical efficacy. In both EVOKE and EVOKE+, there was no meaningful difference between semaglutide and placebo in slowing cognitive decline or disease progression, and both trials were discontinued due to negative clinical outcomes [21].

These findings represented a major setback for the therapeutic use of GLP-1RAs in AD and highlight the challenges of translating encouraging preclinical findings into clinical efficacy. Further studies are needed to clarify the role of incretin-based therapies in AD and identify patient subgroups most likely to benefit [13].

4.3. Parkinson's Disease

Parkinson's disease (PD) is characterized by progressive dopaminergic neuronal loss in the substantia nigra, α -synuclein accumulation, mitochondrial dysfunction, oxidative stress, and chronic neuroinflammation. Increased levels of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, together with persistent activation of the NF- κ B pathway and the NLRP3 inflammasome, contribute to neuronal

degeneration and disease progression [11]. Because GLP-1 receptor agonists (GLP-1RAs) can reduce neuroinflammation, improve mitochondrial function, protect dopaminergic neurons, and potentially slow α -synuclein pathology, they have attracted considerable interest as potential disease-modifying therapies in Parkinson's disease [22]. Early clinical evidence was encouraging. In a phase 2 trial [23], lixisenatide was evaluated in 156 patients with early PD, and after one year, patients receiving lixisenatide showed less progression of motor symptoms compared with placebo, suggesting a possible neuroprotective effect. However, gastrointestinal adverse events such as nausea and vomiting were frequent, and larger, longer-term studies are still needed to confirm whether this benefit is sustained over time [23].

Exenatide has been one of the most extensively studied GLP-1 receptor agonists in Parkinson's disease. Early phase 2 studies suggested possible motor benefits and a potential disease-modifying effect, with a randomized double-blind trial showing that patients treated with exenatide had a mean 3.5-point advantage in MDS-UPDRS Part III motor scores after 48 weeks, and these benefits persisted after the washout period, suggesting possible neuroprotection [24].

However, the larger phase 3 Exenatide-PD3 trial did not confirm these findings, as no significant benefit of once-weekly exenatide over placebo was observed in slowing PD progression or improving secondary clinical outcomes, raising important questions regarding its clinical efficacy [25].

Semaglutide is currently being evaluated in the MOST-ABLE study, the first phase 2 randomized trial of oral semaglutide in PD. This study investigates whether 7 mg or 14 mg oral semaglutide can improve motor symptoms and provide disease-modifying effects after 48 weeks of treatment [22].

Overall, GLP-1RAs represent a promising but still controversial therapeutic strategy in PD. While early studies suggest neuroprotective effects, larger clinical trials are still needed to confirm their long-term efficacy and identify which patients may benefit most (26,27). Ongoing studies of semaglutide and emerging dual GLP-1/GIP receptor agonists may further clarify the therapeutic potential of incretin-based therapies in Parkinson's disease (26), [27].

4.4. Other Neurodegenerative Disorders

Although most clinical evidence focuses on Alzheimer's disease and Parkinson's disease, incretin-based therapies may also have potential benefits in other neurodegenerative and neuroinflammatory disorders, including multiple system atrophy (MSA), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS) [28].

In MSA, GLP-1 receptor agonists may have disease-modifying potential by reducing brain insulin resistance, α -synuclein accumulation, neuroinflammation, and mitochondrial dysfunction [28,29]. Preclinical studies showed that exendin-4 improved insulin signaling, reduced α -synuclein load, and preserved dopaminergic neurons [29]. Clinical data remain limited; weekly exenatide showed slower worsening of UMSARS scores compared with controls, although no significant differences were observed in objective secondary outcomes such as gait analysis, imaging, or biomarkers, indicating that further controlled studies are needed [30].

ALS is also associated with neuroinflammation, glial overactivation, oxidative stress, and progressive motor neuron loss [31]. GLP-1 signaling may exert important neuroprotective effects by reducing neuronal apoptosis, improving neuroplasticity, and modulating inflammatory pathways [31], [32]. Experimental studies demonstrated that exendin-4 and other GLP-1 activators preserved motor neurons, reduced oxidative stress, and improved neuronal survival [32,33]. Restoration of impaired IGF-1/GLP-1 signaling [33] may therefore represent a promising disease-modifying strategy in ALS, although robust clinical evidence is still lacking.

Huntington's disease (HD) is a progressive neurodegenerative disorder caused by CAG repeat expansion in the huntingtin (HTT) gene, leading to mutant huntingtin accumulation, impaired autophagy, oxidative stress, and neuronal apoptosis [34]. Studies in animal models demonstrated that liraglutide restored insulin signaling, reduced oxidative stress, activated AMPK-dependent autophagy, and decreased mutant huntingtin aggregation [35,36], while exendin-4 improved motor performance, reduced brain pathology, and significantly prolonged survival in HD models [37].

Multiple sclerosis (MS) may also benefit from GLP-1 receptor agonists. In EAE models, exendin-4, liraglutide, and dulaglutide reduced oxidative stress, suppressed microglial activation, promoted remyelination, and improved neurological function through immunomodulation, NLRP3 inflammasome suppression, and blood-brain barrier stabilization [38-40]. Early clinical data suggest that GLP-1RAs are generally well tolerated and may improve metabolic outcomes without worsening disease activity [41]. However, no large, randomized trials have confirmed significant benefits on relapse rates, MRI outcomes, or long-term disability progression.

Although most available data in these disorders involve GLP-1 receptor agonists, emerging experimental evidence suggests that GIP signaling and dual GLP-1/GIP receptor agonists may also exert neuroprotective effects; however, their role in individual neurodegenerative diseases remains insufficiently explored.

Overall, outside Alzheimer's disease and Parkinson's disease, the available evidence is predominantly preclinical. Further biomarker-driven studies and early-phase clinical trials are needed to determine whether GLP-1 and GIP-based therapies can provide meaningful neuroprotection across a broader spectrum of neurodegenerative diseases.

5. Future Perspectives: Novel Incretin-Based Therapies and Dual Receptor Agonists

Recent research has increasingly focused on dual incretin receptor agonists, particularly combined GLP-1/GIP therapies such as tirzepatide, which may offer broader neuroprotective benefits compared with single GLP-1 receptor agonists. Simultaneous activation of multiple incretin pathways could result in more effective metabolic regulation, stronger control of inflammatory responses, improved mitochondrial stability, and better support of neuronal survival pathways [11].

A recent real-world retrospective cohort study compared tirzepatide and semaglutide in adults with type 2 diabetes mellitus without baseline dementia [42]. Tirzepatide, a dual GLP-1/GIP receptor agonist, was associated with a lower incidence of dementia compared with both semaglutide and sodium-glucose cotransporter 2 (SGLT2) inhibitors. In addition, tirzepatide was linked to reduced all-cause mortality, suggesting that combined incretin receptor stimulation may provide additional neurocognitive benefits beyond metabolic control alone [42].

These potential advantages may be related to reductions in systemic inflammation, improved insulin sensitivity, better vascular function, preservation of blood-brain barrier integrity, and lower production of pro-inflammatory cytokines involved in neuronal injury [43].

Another promising direction involves glucagon-like peptide-2 (GLP-2) analogues [44], which are currently used mainly in the treatment of short bowel syndrome and intestinal failure rather than neurological disorders. Although traditionally associated with intestinal mucosal growth and epithelial repair, accumulating evidence suggests that GLP-2 may also exert neuroprotective effects within the central nervous system [45,46].

Preclinical studies indicate that GLP-2 may have therapeutic relevance in both Alzheimer's disease and Parkinson's disease. In Alzheimer's disease, altered plasma GLP-2 levels have been observed in affected patients compared with cognitively healthy individuals, supporting a possible relationship between GLP-2 signaling, metabolic regulation, and

neurodegeneration [47]. In Parkinson's disease, a GLP-2 analogue improved motor performance, preserved dopaminergic neurons, reduced α -synuclein accumulation, and decreased neuroinflammation by lowering inflammatory mediators such as TNF- α and NF- κ B in the MPTP mouse model [48].

More recently, a novel GLP-2/GIP dual receptor agonist demonstrated stronger protective effects than GLP-2 alone, with significant reductions in TNF- α and NF- κ B expression, lower Bcl-2-associated X protein (Bax) levels, increased B-cell lymphoma 2 (Bcl-2) expression, and improved motor activity. These findings suggest that combined receptor targeting may offer a more effective strategy for limiting neuronal damage in Parkinson's disease [49].

While current evidence remains largely preclinical, these findings indicate that GLP-2-based therapies and novel dual receptor agonists may represent important future directions in neurodegenerative disease management. Prospective clinical studies are required to determine whether these emerging incretin-based therapies can provide meaningful long-term therapeutic benefits in Alzheimer's disease and Parkinson's disease.

6. Conclusions

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP)-based therapies may offer benefits that extend beyond metabolic control, influencing key mechanisms involved in neurodegeneration, including chronic inflammation, mitochondrial dysfunction, impaired autophagy, and pathological protein accumulation.

The strongest clinical evidence is currently available for Alzheimer's disease and Parkinson's disease, although large phase III trials have yielded mixed results. In multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, and multiple system atrophy, available evidence remains limited and is derived predominantly from preclinical studies.

Beyond their established role in diabetes and obesity management, incretin-based therapies represent a promising area of investigation in neurodegenerative diseases. By targeting shared metabolic, inflammatory, and neurodegenerative pathways, these agents may contribute to a more integrated approach to patient care. Further clinical studies are needed to clarify their disease-modifying potential, identify the patients most likely to benefit, and define their future role in neurological practice.

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Abbreviations:

AD — Alzheimer's disease

ADAS-Exec — Alzheimer's Disease Assessment Scale-Executive Function

ALS — Amyotrophic lateral sclerosis

A β — Beta-amyloid

Bax — Bcl-2-associated X protein

BBB — Blood-brain barrier

Bcl-2 — B-cell lymphoma 2

CDR-SB — Clinical Dementia Rating-Sum of Boxes

CREB — cAMP response element-binding protein

EAE — Experimental autoimmune encephalomyelitis

FDG-PET — Fluorodeoxyglucose positron emission tomography

GIP — Glucose-dependent insulintropic polypeptide

GLP-1 — Glucagon-like peptide-1

GLP-1RA — Glucagon-like peptide-1 receptor agonist

GLP-2 — Glucagon-like peptide-2

GP — General practitioner

HD — Huntington's disease

HTT — Huntingtin gene

IGF-1 — Insulin-like growth factor 1

IL-1 β — Interleukin-1 beta

IL-6 — Interleukin-6

MACE — Major adverse cardiovascular events

MASH — Metabolic dysfunction-associated steatohepatitis

MCI — Mild cognitive impairment

MS — Multiple sclerosis

MSA — Multiple system atrophy

NF- κ B — Nuclear factor kappa B

NLRP3 — NOD-like receptor family pyrin domain containing 3

SGLT2 — sodium-glucose cotransporter 2

PD — Parkinson's disease

PI3K — Phosphoinositide 3-kinase

T2DM — Type 2 diabetes mellitus

TNF- α — Tumor necrosis factor-alpha

UMSARS — Unified Multiple System Atrophy Rating Scale

WHO — World Health Organization

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