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The neuroprotective potential of GLP-1 analogues with particular emphasis in Alzheimer's and Parkinson's diseases

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Abstract

Background: Alzheimer's and Parkinson's diseases are becoming more common as populations age, yet effective treatments remain elusive. People with type 2 diabetes face higher risks of developing these conditions, prompting researchers to explore whether diabetes medications might protect the brain. GLP-1 receptor agonists have emerged as promising candidates for this purpose.

Aim of the study: This systematic review evaluates the neuroprotective potential of GLP-1 analogues in treating Alzheimer's and Parkinson's diseases, examining clinical evidence and underlying molecular mechanisms.

Material and methods: A systematic literature search was conducted using PubMed, focusing on studies published from 2020 onwards. Search terms combined GLP-1 receptor agonists with neurodegenerative and neuroprotective terminology. From 38 initially identified articles, 5 studies were selected for detailed analysis based on their focus on GLP-1 analogues' therapeutic potential in neurodegeneration.

Results: The LIXIPARK trial demonstrated promising results in early Parkinson's disease, with lixisenatide showing significant benefits on motor symptom progression compared to placebo. However, evidence for Alzheimer's disease remains mixed, with smaller completed studies yielding disappointing outcomes while large-scale EVOKE trials are ongoing. In type 2 diabetes patients, liraglutide enhanced cognitive function and hippocampal activation, though DPP-4 inhibition showed no superior cognitive protection versus traditional diabetes medications.

Conclusions: GLP-1 receptor agonists show genuine promise as neuroprotective agents, with strongest evidence emerging from Parkinson's disease research. The therapeutic potential in Alzheimer's disease requires confirmation from ongoing large-scale trials. These findings suggest that personalized approaches considering disease stage, gender, and metabolic status may optimize therapeutic benefits.

Keywords: GLP-1 receptor agonists, Alzheimer's disease, Parkinson's disease, neurodegeneration, neuroprotection, lixisenatide, cognitive function

1. Introduction

Neurodegenerative diseases, particularly Alzheimer's disease (AD) and Parkinson's disease (PD), represent a growing global health challenge with significant socioeconomic implications. The epidemiological evidence reveals a striking association between type 2 diabetes mellitus (T2DM) and increased risk of neurodegeneration, with individuals with T2DM demonstrating a 1.7-fold higher risk of developing dementia compared to the general population (Sun et al., 2025). This relationship is further complicated by the aging population, making the prevention of T2DM-related dementia an urgent public health priority (Sun et al., 2025).

Epidemiological evidence demonstrates that T2DM not only increases the risk but also accelerates the rate of progression of PD (Cullinane et al., 2023). Interestingly, the incidence of PD in diabetic patients varies substantially depending on the antidiabetic treatment employed, with DPP4 inhibitors and GLP-1 mimetics showing protective effects compared to other oral antidiabetic medications (Bayram & Litvan, 2020). The underlying pathophysiological mechanisms linking these conditions involve insulin resistance and chronic inflammation, which contribute to the overlaying etiologies of T2D and PD (Ribarič, 2024).

Current therapeutic approaches for neurodegenerative disorders face significant limitations. Traditional strategies targeting individual aspects of disease pathogenesis have yielded limited success (Nowell et al., 2023), and disease-modifying treatments for major neurocognitive disorders remain among the main unmet needs in modern medicine (de Giorgi et al., 2025). The absence of effective disease-modifying treatments for both AD and PD, including the controversial approval of aducanumab, only emphasizes the urgent need for new neuroprotective interventions (Reich & Hölscher, 2022).

Against this backdrop, glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as promising therapeutic candidates beyond their established role in diabetes management. The incretin hormone GLP-1 demonstrates neuroprotective effects in animal models of PD, with clinical improvements observed in human PD patients treated with GLP-1 receptor agonists (Manfready et al., 2021). The cognitive protective effects of GLP-1RAs have attracted increasing attention, particularly given the association between T2DM and cognitive impairment (Dou et al., 2025). These agents, initially approved for diabetes and obesity, are now under investigation for their neuroprotective potential across a range of neurological disorders, with their receptors widely expressed in brain regions critical for cognition and metabolism (Roy et al., 2025).

It has been assessed that neurodegenerative diseases represent common complications of diabetes arising from insulin resistance, inflammation, and other pathological processes in the central nervous system (Hong et al., 2024). This convergence of metabolic pathways presents an opportunity for therapeutic intervention through the repurposing of GLP-1 analogs.

1.1. Biology of GLP-1 Analogs and Their Distribution to the CNS

GLP-1 is an incretin hormone secreted in response to food intake, exerting multiple actions conducive to glycemic control, including enhancing glucose-dependent insulin secretion, suppressing glucagon release, and delaying gastric emptying (Hong et al., 2024). The distribution of GLP-1 receptors (GLP-1R) throughout the central nervous system is extensive and strategically positioned in regions critical for neurological function.

The highest concentrations of GLP-1R are found in the hippocampus and cerebral cortex, areas primarily responsible for cognitive function, memory improvement, and learning (Hammad et al., 2025). Additionally, these receptors are predominantly distributed in the brainstem, hypothalamus, cerebellum, and limbic system, as well as in microglia and astrocytes (Hammad et al., 2025).

The widespread expression of GLP-1 receptors also encompasses critical CNS regions involved in mood regulation, anxiety and reward processing, including amygdala, prefrontal cortex, ventral tegmental area (VTA), nucleus accumbens (NAc), and nucleus tractus solitarius (NTS) (al Qassab et al., 2025). Notably, genetic variability in GLP-1R and GIP receptors has been associated with increased odds of Alzheimer's disease and Parkinson's disease, correlating with elevated disease biomarkers such as amyloid-beta peptide 42 and tau proteins measured in cerebrospinal fluid (de Giorgi et al., 2025).

GLP-1 analogues demonstrate unique pharmacological properties that distinguish them from conventional therapeutic approaches. Unlike traditional treatments, GLP-1 analogues do not enhance insulin desensitization as they do not activate insulin receptors, instead re-sensitizing insulin signaling pathways (Hölscher, 2020). Importantly, these analogues do not affect blood glucose levels in normoglycemic individuals, allowing for safe administration to non-diabetic patients with Alzheimer's disease or Parkinson's disease (Hölscher, 2020). Liraglutide, the first GLP-1 analogue approved by the FDA for obesity treatment, achieves weight reduction through appetite suppression by directly stimulating anorexigenic pathways in the hypothalamic arcuate nucleus via GLP-1 receptor activation (Jasińska-Balwierz et al., 2024).

Different GLP-1 analogues exhibit varying kinetic profiles and mechanisms of central action. While lixisenatide and exenatide demonstrate relatively rapid and direct action within central circuits, liraglutide and semaglutide exert their effects more slowly or indirectly, potentially relying on longer systemic exposure, slow diffusion, or action through peripheral-central pathways (Marquez-Meneses et al., 2025).

The mechanisms enabling CNS access for GLP-1 analogues remain incompletely understood, though several routes have been proposed. One possibility involves receptor-mediated or adsorptive transcytosis across brain endothelial cells, although direct evidence for this process is limited (Marquez-Meneses et al., 2025). It is also speculated that they are capable of crossing the blood-brain barrier and exert anti-inflammatory, anti-apoptotic, and neurotrophic effects within the central nervous system (al Qassab et al., 2025). This neuroprotective capacity is directly associated with exendin-4 and DA-JC4 demonstrating the highest blood-brain barrier crossing capacity among non-acylated, non-PEGylated incretin receptor agonists (Kalinderi et al., 2024).

Specialized compounds like NLY01 bind GLP-1 receptors on microglia, suppressing pro-inflammatory cytokines and preventing astrocyte transformation into neurotoxic phenotypes, thereby reducing neuroinflammation and preserving synaptic integrity (Roy et al., 2025). However, some cognitive effects may result from indirect mechanisms rather than direct CNS entry, potentially mediated through peripheral functions across immune, endocrine-metabolic, and gut-brain axis pathways (de Giorgi et al., 2025).

1.2. Pathophysiology of Alzheimer's and Parkinson's Disease: Common Mechanisms

Alzheimer's disease (AD) and Parkinson's disease (PD) share several key pathophysiological mechanisms that contribute to neurodegeneration and disease progression. Central to both conditions is the disruption of insulin signaling and glucose metabolism in the brain, with insulin signaling being desensitized in affected patients (Hölscher, 2020). This metabolic dysfunction is particularly evident in PD, where postprandial GLP-1 responses are significantly attenuated compared to healthy controls (Manfready et al., 2021). The concept of AD as "type 3 diabetes" has emerged due to prominent insulin resistance and dysregulated insulin signaling pathways in the brain; reduced glucose metabolism may specifically result from decreased postsynaptic neurotransmission (Du et al., 2022).

Neuroinflammation represents another critical shared mechanism, characterized by glial cell activation and inflammatory cascades. Both diseases exhibit abnormal accumulation of toxic proteins, increased inflammation, decreased synaptic function, neuronal loss, and increased astrocyte activation, often occurring alongside insulin resistance (Nowell et al., 2023). The inflammatory responses are closely associated with insulin resistance development, creating conditions that promote amyloid plaque formation and deposition (Blázquez et al., 2022). GLP-1 receptor activation has demonstrated the ability to decrease both the number and reactivity of microglia in multiple neurodegenerative conditions including AD and PD, while also reducing microglia-induced astrocytosis (Diz-Chaves et al., 2022). Studies have shown that lower proportions of reactive microglia and astrocytes correlate with better neuronal preservation (Urkon et al., 2025). These common pathophysiological features highlight the interconnected nature of metabolic dysfunction, neuroinflammation, and neurodegeneration in both AD and PD, providing the importance of therapeutic targets for neuroprotective interventions.

1.3 Mechanisms of Neuroprotective Action of GLP-1 Analogs

The neuroprotective effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) are mediated through multiple interconnected molecular pathways that collectively target brain incretin receptors to reduce inflammation, inhibit apoptosis, prevent toxic protein aggregation, enhance long-term potentiation and autophagy, while restoring dysfunctional insulin signaling (Nowell et al., 2023). Central to these mechanisms is the enhancement of cognitive function through key signal transduction pathways, where GLP-1 receptor activation increases cAMP levels, subsequently activating cAMP response element-binding protein (CREB) and inducing expression of brain-derived neurotrophic factor (BDNF), which acts via tropomyosin-related kinase B (TrkB) receptor (Dou et al., 2025). GLP-1RAs effectively alleviate central insulin resistance by decreasing serine phosphorylation of insulin receptor substrate 1 (IRS-1) and restoring downstream phosphoinositide 3-kinase/RAC serine/threonine–protein kinase (PI3K/Akt) signaling (Urkon et al., 2025), with receptor stimulation in the CNS impacting insulin receptor signaling pathways to enhance neuronal survival (Bayram & Litvan, 2020).

Notably, these cognitive benefits occur consistently in patients with type 2 diabetes mellitus even in the absence of metabolic improvements (Chuansangeam et al., 2025), with dulaglutide's protective effects on learning and memory occurring through reduction of tau and neurofilament protein hyperphosphorylation via PI3K/AKT/GSK3β signaling pathway (Zhao et al., 2021), and ADRD risk reduction occurring largely independent of HbA1c and BMI effects (Tang et al., 2025).

The anti-inflammatory properties of GLP-1RAs represent another crucial neuroprotective mechanism, as GLP-1 serves both as a target and mediator of inflammatory responses (Diz-Chaves et al., 2022). These effects are mediated through GLP-1 receptor stimulation on microglia (Bayram & Litvan, 2020). Antioxidant properties help reduce brain inflammation and oxidative stress, which are the key contributors to neurodegenerative diseases (Chuansangeam et al., 2025), while suppressing inflammatory cytokines and inhibiting microglial activation (al Qassab et al., 2025). GLP-1RAs facilitate M2 microglial polarization through both direct and indirect pathways while modulating CD4, CD8, and regulatory T cell quantities and functions (Sun et al., 2025), promoting M2 polarization and improving synapse growth and neuronal regeneration via cAMP/PKA pathway (Sun et al., 2025). Treatment with exendin-4 or linagliptin significantly reduces ROS levels, with linagliptin showing superior ROS reduction compared to exendin-4 (Yu et al., 2022).

Recent studies demonstrate that GLP-1RAs reduce amyloid-β deposition and tau hyperphosphorylation, hallmark pathologies of Alzheimer's disease (Chuansangeam et al., 2025). The toxic accumulation of amyloid β protein associated with Parkinson's disease disrupts long-term potentiation, but this can be reversed by exendin-4, leading to cognitive function and memory improvements (Hammad et al., 2025).

Finally, GLP-1RAs support neuronal survival, synaptic plasticity, and neurogenesis through enhanced BDNF expression, which is essential for proper neuronal functioning, inhibiting neural apoptosis while increasing survival and regeneration to form new connections (Hammad et al., 2025). GLP-1 receptor activation suppresses GABA_A receptor-mediated currents in retinal ganglion cells and affects glutamatergic signaling, indicating broader roles in neurotransmission modulation (Marquez-Meneses et al., 2025). These effects occur through restoration of neurite outgrowth, increased neurotrophic factors, and blood-brain barrier strengthening (Helal et al., 2025), with cardio- and neuroprotective effects reducing inflammation and apoptosis while influencing learning and memory processes (Jasińska-Balwierz et al., 2024). Exenatide may enhance synaptic dopamine levels providing benefits for Parkinson's disease symptoms (Helal et al., 2025), while semaglutide protects neurons from amyloid-β toxicity through autophagy enhancement and apoptosis inhibition (Zhao et al., 2021).

Research Objective

The primary objective of this study is to systematically evaluate the neuroprotective potential of glucagon-like peptide-1 (GLP-1) receptor agonists in the treatment and prevention of neurodegenerative diseases, with particular emphasis on Alzheimer's disease (AD) and Parkinson's disease (PD), through comprehensive analysis of current clinical evidence and underlying molecular mechanisms.

Research Problems

Primary Research Problem: To what extent do GLP-1 receptor agonists demonstrate clinically significant neuroprotective effects in patients with Alzheimer's disease and Parkinson's disease, and what are the underlying pathophysiological mechanisms mediating these therapeutic effects?

Secondary Research Problems:

1. What is the efficacy of GLP-1 receptor agonists in modifying disease progression in early-stage Parkinson's disease as measured by validated clinical outcome scales?
2. Do GLP-1 receptor agonists provide cognitive benefits in patients with Alzheimer's disease and mild cognitive impairment, and are these effects consistent across different patient populations?
3. What are the molecular and cellular mechanisms through which GLP-1 receptor activation exerts neuroprotective effects, including modulation of insulin signaling, neuroinflammation, oxidative stress, and protein aggregation?
4. Are there differential treatment responses based on patient characteristics, including disease stage, gender, metabolic status, and specific GLP-1 analog utilized?

Research Hypotheses

Hypothesis 1: GLP-1 receptor agonists demonstrate disease-modifying neuroprotective effects in neurodegenerative diseases through multi-mechanistic pathways involving restoration of insulin signaling, reduction of neuroinflammation, inhibition of pathological protein aggregation, and enhancement of synaptic plasticity.

Hypothesis 2: Administration of GLP-1 receptor agonists in patients with early Parkinson's disease results in significant attenuation of motor symptom progression compared to placebo, as measured by Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) scores.

Hypothesis 3: GLP-1 receptor agonists provide cognitive protection in patients with Alzheimer's disease and mild cognitive impairment through mechanisms independent of glycemic control, mediated by direct activation of GLP-1 receptors in hippocampal and cortical regions.

Hypothesis 4: The neuroprotective efficacy of GLP-1 receptor agonists varies according to specific pharmacological properties of individual analogs, including blood-brain barrier penetration capacity, receptor binding affinity, and duration of action.

Hypothesis 5: GLP-1 receptor agonist-mediated neuroprotection occurs through attenuation of microglial activation and promotion of M2 microglial polarization, resulting in reduced neuroinflammation and preservation of synaptic integrity in affected brain regions.

2. Research materials and methods

A systematic search of the scientific literature was conducted using the PubMed database. Multiple search strategies were employed using various combinations of terms related to GLP-1 receptor agonists (including "exenatide," "liraglutide," "semaglutide," and "dulaglutide") combined with neurological and neuroprotective terms such as "neurodegeneration," "cognitive function," "Parkinson disease," "Alzheimer disease," "neuroinflammation," "oxidative stress," and "central nervous system" effects. The search also included broader incretin-related terminology to capture relevant studies on neuroprotective mechanisms. A total of 38 articles were initially identified across all search queries. After screening for relevance and quality, 5 articles were selected for detailed analysis based on their focus on GLP-1 receptor agonists' neuroprotective effects and therapeutic potential in neurodegenerative disorders. To ensure the review reflects current evidence, only studies published from 2020 onwards were included in the final analysis.

3. Research results

3.1. Parkinson's Disease Studies

The investigation of GLP-1 receptor agonists in Parkinson's disease has yielded promising preliminary results. The most significant contribution to this field comes from the LIXIPARK trial (Meissner et al., 2024), which represents the largest randomized controlled trial evaluating a GLP-1 analog in early Parkinson's disease to date.

In this phase 2, double-blind, placebo-controlled study, Meissner et al. (2024) examined the effects of lixisenatide in 156 patients with early Parkinson's disease who had been diagnosed within three years of symptom onset. The trial employed a rigorous methodology with participants receiving either 20 μg subcutaneous lixisenatide daily or matching placebo for 12 months, followed by a 2-month washout period.

The primary endpoint focused on changes in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III scores in the on-medication state.

The results demonstrated a statistically significant difference favoring lixisenatide treatment. Participants receiving lixisenatide showed minimal worsening with a change of -0.04 points in MDS-UPDRS part III scores, while the placebo group experienced a progression of +3.04 points, resulting in a treatment difference of 3.08 points ($p=0.007$) (Meissner et al., 2024). This finding suggests a potential disease-modifying effect, as the benefit was sustained even after the 2-month washout period, indicating that the observed improvements were not merely symptomatic.

Importantly, cognitive function as measured by Montreal Cognitive Assessment (MoCA) scores remained similar between treatment groups, suggesting that the motor benefits occurred without significant cognitive enhancement or impairment (Meissner et al., 2024). The safety profile revealed predictable gastrointestinal side effects, with nausea occurring in 46% of lixisenatide-treated patients compared to 12% in the placebo group, and vomiting in 13% versus 3% respectively (Meissner et al., 2024).

3.2. Alzheimer's Disease and Mild Cognitive Impairment

The evidence for GLP-1 analogs in Alzheimer's disease and mild cognitive impairment presents a more complex picture with mixed results across different studies and patient populations.

Two ongoing phase 3 trials, EVOKE and EVOKE+, represent the most ambitious investigation of GLP-1 receptor agonists in Alzheimer's disease (Cummings et al., 2025). These large-scale studies are evaluating oral semaglutide 14 mg daily versus placebo in 3,680 participants with early-stage symptomatic Alzheimer's disease confirmed by amyloid abnormalities. The trials employ a robust design with 156 weeks of treatment including a 52-week extension period, with the primary endpoint being change in Clinical Dementia Rating-Sum of Boxes (CDR-SB) scores from baseline to week 104 (Cummings et al., 2025). Results are anticipated in September 2025 and will provide definitive evidence regarding the efficacy of GLP-1 receptor agonists in Alzheimer's disease prevention and treatment.

In contrast to these ongoing large-scale investigations, completed smaller studies have yielded disappointing results. The proof-of-concept trial by Dei Cas et al. (2024) examined long-acting exenatide in patients with mild cognitive impairment over 32 weeks. This open-label study of 32 participants found no beneficial effect on the primary endpoint of ADAS-Cog11 change ($p=0.17$). More concerning, a significant gender interaction was observed ($p=0.04$), with women experiencing cognitive worsening ($p=0.018$) while receiving exenatide treatment. The study's limitations include its small sample size, short duration, and open-label design, which may have influenced these negative findings.

3.3. Type 2 Diabetes and Cognitive Function

The CAROLINA-COGNITION study represents the most comprehensive long-term evaluation of cognitive outcomes with GLP-1-based therapy (Biessels et al., 2021). This randomized, double-blind, active-controlled trial compared linagliptin, a DPP-4 inhibitor that increases endogenous GLP-1 levels, with glimepiride in 6,033 participants with type 2 diabetes over a median duration of 6.1 years. The primary endpoint of accelerated cognitive decline occurrence showed no significant difference between treatment groups, with 27.8% of linagliptin-treated patients and 27.6% of glimepiride-treated patients experiencing this outcome (OR 1.01, 95% CI 0.86-1.18, $p>0.05$) (Biessels et al., 2021). This finding suggests that DPP-4 inhibition, while increasing GLP-1 activity, may not provide superior cognitive protection compared to traditional diabetes medications.

In contrast to these neutral findings, a smaller mechanistic study by Cheng et al. (2022) provided compelling evidence for direct brain effects of liraglutide. This 16-week randomized parallel comparative study examined 36 patients with type 2 diabetes, comparing liraglutide (titrated to 1.8 mg daily) with dapagliflozin and acarbose. The study employed functional magnetic resonance imaging to assess olfactory neural activation alongside comprehensive cognitive testing. Liraglutide treatment resulted in significant improvements across multiple cognitive domains, including delayed memory ($p<0.001$), attention ($p=0.001$), and executive function ($p=0.012$), while neither dapagliflozin nor acarbose showed similar benefits (Cheng et al., 2022). Critically, liraglutide enhanced impaired left hippocampal activation during olfactory tasks ($p<0.05$), suggesting direct neural effects beyond metabolic improvements (Cheng et al., 2022).

4. Discussion

4.1 Parkinson's Disease: Emerging Promise

The results from the LIXIPARK trial represent a significant advancement in Parkinson's disease research, providing the first robust evidence for potential disease-modifying effects of GLP-1 receptor agonists in this condition (Meissner et al., 2024). The observed 3.08-point difference in MDS-UPDRS part III progression between lixisenatide and placebo groups, sustained through a washout period, suggests mechanisms beyond symptomatic relief.

The fact that benefits were maintained after treatment discontinuation provides compelling evidence for true neuroprotection rather than symptomatic masking. However, the relatively short follow-up period and single-trial nature of this evidence necessitate replication in larger, longer-duration studies before definitive conclusions can be drawn.

4.2 Alzheimer's Disease: Mixed Signals and Methodological Challenges

The evidence for GLP-1 analogs in Alzheimer's disease and mild cognitive impairment presents a picture requiring careful interpretation. The negative results from the exenatide study in mild cognitive impairment (Dei Cas et al., 2024) contrast sharply with the mechanistic evidence supporting GLP-1 receptor activation as a potential therapeutic target in neurodegeneration. Several factors may contribute to these discordant findings.

First, the heterogeneity in study populations, intervention duration, and outcome measures makes direct comparisons challenging. The exenatide trial enrolled participants with mild cognitive impairment without requiring biomarker confirmation of underlying Alzheimer's disease pathology (Dei Cas et al., 2024), potentially including individuals with non-Alzheimer's cognitive impairment who might not respond to amyloid-targeting or neuroprotective interventions. In contrast, the ongoing EVOKE trials specifically require amyloid positivity, ensuring that participants have the underlying pathophysiology that GLP-1 receptor agonists are hypothesized to address (Cummings et al., 2025).

Second, the concerning gender differences observed in the exenatide study (Dei Cas et al., 2024), with women experiencing cognitive worsening, highlight the importance of considering sex-specific effects in neurodegeneration research.

The ongoing EVOKE trials will provide critical insights into the true potential of GLP-1 receptor agonists in Alzheimer's disease (Cummings et al., 2025). The large sample size, biomarker-confirmed population, and extended treatment duration should provide definitive evidence regarding the efficacy of this therapeutic approach. The inclusion of cerebrospinal fluid biomarker assessments will also elucidate potential mechanisms of action and identify predictive biomarkers for treatment response.

5. Conclusions

The current evidence suggests that GLP-1 receptor agonists represent a promising therapeutic approach for neurodegenerative diseases, with the strongest support emerging from Parkinson's disease research. The LIXIPARK trial provides compelling evidence for disease-modifying effects of lixisenatide in early Parkinson's disease (Meissner et al., 2024), with benefits sustained beyond treatment cessation. This finding warrants further investigation in larger, longer-duration trials to confirm these promising preliminary results.

In contrast, the evidence for Alzheimer's disease remains inconclusive, with small completed studies showing mixed or negative results (Dei Cas et al., 2024) while large-scale phase 3 trials are ongoing (Cummings et al., 2025). The upcoming results from the EVOKE trials will be crucial in determining whether GLP-1 receptor agonists have a role in Alzheimer's disease prevention and treatment.

The apparent differential effects across neurodegenerative conditions suggest that personalized approaches may be necessary to maximize therapeutic benefits. Additionally, the potential for gender-specific effects (Dei Cas et al., 2024) requires careful consideration in future trial designs and clinical implementation.

Overall, GLP-1 receptor agonists show promise as neuroprotective agents, particularly in Parkinson's disease, but definitive evidence of clinical efficacy awaits completion of ongoing large-scale trials and replication of positive findings in independent study populations.

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All authors have read and approved the final version of the manuscript for publication

Supplementary Materials

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The authors declare no conflict of interest.

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References

al Qassab, M., Mneimneh, M., Jradi, A., Derbas, B., Dabboussi, D., Khoury Baini, J., Katrib, N., Chaarani, N., Attieh, P., Kanaan, A., Harb, F., Azar, S., & Ghadieh, H. E. (2025). The Expanding Role of GLP-1 Receptor Agonists: Advancing Clinical Outcomes in Metabolic and Mental Health. Current Issues in Molecular Biology, 47(4). https://doi.org/10.3390/cimb47040285

Bayram, E., & Litvan, I. (2020). Lowering the risk of Parkinson's disease with GLP-1 agonists and DPP4 inhibitors in type 2 diabetes. Brain, 143(10), 2868–2871. https://doi.org/10.1093/brain/awaa287

Biessels, G. J., Verhagen, C., Janssen, J., van den Berg, E., Zinman, B., Rosenstock, J., George, J. T., Passera, A., Schnaidt, S., Johansen, O. E., & CAROLINA Investigators. (2021). Effects of linagliptin vs glimepiride on cognitive performance in type 2 diabetes: results of the randomised double-blind, active-controlled CAROLINA-COGNITION study. Diabetologia, 64(5), 1235–1245. https://doi.org/10.1007/s00125-021-05393-8

Blázquez, E., Hurtado-Carneiro, V., LeBaut-Ayuso, Y., Velázquez, E., García-García, L., Gómez-Oliver, F., Ruiz-Albusac, J. M., Ávila, J., & Pozo, M. Á. (2022). Significance of Brain Glucose Hypometabolism, Altered Insulin Signal Transduction, and Insulin Resistance in Several Neurological Diseases. Frontiers in Endocrinology, 13. https://doi.org/10.3389/fendo.2022.873301

Cheng, B., Yang, J., Cai, R., Zhou, H., Xu, Y., Sun, C., He, Q., Pan, J., Chen, W., Fang, Q., Gu, H., & Gao, F. (2022). Enhancement of Impaired Olfactory Neural Activation and Cognitive Capacity by Liraglutide, but Not Dapagliflozin or Acarbose, in Patients With Type 2 Diabetes: A 16-Week Randomized Parallel Comparative Study. Diabetes Care, 45(9), 2090–2100. https://doi.org/10.2337/dc21-2064

Chuansangeam, M., Phadungsaksawasdi, P., Park, H. J., & Yang, Y.-H. (2025). Exploring the link between GLP-1 receptor agonists and dementia: A comprehensive review. Journal of Alzheimer's Disease Reports, 9. https://doi.org/10.1177/25424823251342182

Cullinane, P. W., de Pablo Fernandez, E., König, A., Outeiro, T. F., Jaunmuktane, Z., & Warner, T. T. (2023). Type 2 Diabetes and Parkinson's Disease: A Focused Review of Current Concepts. Movement Disorders, 38(2), 162–177. https://doi.org/10.1002/mds.29298

Cummings, J., Hamann, G. F., Aarsland, D., Bråthen, G., Vigen, C., Barrett, N. J., Cummings, B., Tummolo, A. M., Berent-Spillson, A., Sjöström, C. D., Ericsson, Å., Hey-Hadavi, J., & Buse, J. B. (2025). EVOKE and EVOKE+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer's disease. Alzheimer's Research & Therapy, 17(1). https://doi.org/10.1186/s13195-024-01666-7

de Giorgi, R., Ghenciulescu, A., Yotter, C., Taquet, M., & Koychev, I. (2025). Glucagon-like peptide-1 receptor agonists for major neurocognitive disorders. Journal of Neurology, Neurosurgery and Psychiatry. https://doi.org/10.1136/jnnp-2024-335593

Dei Cas, A., Spigoni, V., Cito, M., Aldigeri, R., Ridolfi, V., Ziveri, V., Baccarini, F., Antenucci, P., Orso, M., Rinaldi, E., Voltini, L., Gnudi, L., Dall'Asta, M., Brighenti, F., Zavaroni, I., Riccardi, G., Bonadonna, R. C., & Derlindati, E. (2024). Long-acting exenatide does not prevent cognitive decline in mild cognitive impairment: a proof-of-concept clinical trial. Journal of Endocrinological Investigation, 47(5), 1121–1129. https://doi.org/10.1007/s40618-024-02320-7

Diz-Chaves, Y., Mastoor, Z., Spuch, C., González-Matías, L. C., & Mallo, F. (2022). Anti-Inflammatory Effects of GLP-1 Receptor Activation in the Brain in Neurodegenerative Diseases. International Journal of Molecular Sciences, 23(17). https://doi.org/10.3390/ijms23179583

Dou, X., Zhao, L., Li, J., & Jiang, Y. (2025). Effect and mechanism of GLP-1 on cognitive function in diabetes mellitus. Frontiers in Neuroscience, 19. https://doi.org/10.3389/fnins.2025.1537898

Du, H., Meng, X., Yao, Y., & Xu, J. (2022). The mechanism and efficacy of GLP-1 receptor agonists in the treatment of Alzheimer's disease. Frontiers in Endocrinology, 13. https://doi.org/10.3389/fendo.2022.1033479

Hammad, B. F., Zafar, N., Ullah, M., Faisal, S. J., Iftikhar, F., Waheed, H., Muzaffar, M. W., Ahmed, K., Ashraf, F., Zahid, K., Akhtar, M., & Mahmmoud Fadelallah Eljack, M. (2025). Exploring the multifaceted roles of GLP-1 receptor agonists; a comprehensive review. Frontiers in Clinical Diabetes and Healthcare, 6. https://doi.org/10.3389/fcdhc.2025.1590530

Helal, M. M., AbouShawareb, H., Abbas, O. H., Haddad, R., Zain, Y., Osman, A. S. A., & Hassan, A. K. (2025). GLP-1 receptor agonists in Parkinson's disease: an updated comprehensive systematic review with meta-analysis. Diabetology and Metabolic Syndrome, 17(1). https://doi.org/10.1186/s13098-025-01888-1

Hölscher, C. (2020). Brain insulin resistance: role in neurodegenerative disease and potential for targeting. Expert Opinion on Investigational Drugs, 29(4), 333–348. https://doi.org/10.1080/13543784.2020.1738383

Hong, C. T., Chen, J. H., & Hu, C. J. (2024). Role of glucagon-like peptide-1 receptor agonists in Alzheimer's disease and Parkinson's disease. Journal of Biomedical Science, 31(1). https://doi.org/10.1186/s12929-024-01090-x

Jasińska-Balwierz, A., Balwierz, R. J., Biernat, P., Makieieva, N., Tomkow, M., Cesarz, K., Osowski, M., Dorożyński, B., Skotnicka-Graca, U., & Lipok, J. (2024). GLP-1 and GIP analogues in the treatment of obesity. Pediatria i Medycyna Rodzinna, 20(2), 162–167. https://doi.org/10.15557/PiMR.2024.0023

Kalinderi, K., Papaliagkas, V., & Fidani, L. (2024). GLP-1 Receptor Agonists: A New Treatment in Parkinson's Disease. International Journal of Molecular Sciences, 25(7). https://doi.org/10.3390/ijms25073812

Manfready, R. A., Engen, P. A., Verhagen Metman, L., Sanzo, G., Goetz, C. G., Hall, D. A., Forsyth, C. B., Raeisi, S., Voigt, R. M., & Keshavarzian, A. (2021). Attenuated Postprandial GLP-1 Response in Parkinson's Disease. Frontiers in Neuroscience, 15. https://doi.org/10.3389/fnins.2021.660942

Marquez-Meneses, J. D., Olaya-Bonilla, S. A., Barrera-Carreño, S., Tibaduiza-Arévalo, L. C., Forero-Cárdenas, S., Carrillo-Vaca, L., Rojas-Rodríguez, L. C., Calderon-Ospina, C. A., & Rodríguez-Quintana, J. (2025). GLP-1 Analogues in the Neurobiology of Addiction: Translational Insights and Therapeutic Perspectives. International Journal of Molecular Sciences, 26(11). https://doi.org/10.3390/ijms26115338

Meissner, W. G., Remy, P., Giordana, C., Maltête, D., Derkinderen, P., Houéto, J.-L., Anheim, M., Benatru, I., Boraud, T., Brefel-Courbon, C., Carrière, N., Catala, H., Colin, O., Corvol, J.-C., Damier, P., Dellapina, E., Devos, D., Drapier, S., Fabbri, M., … Rascol, O. (2024). Trial of Lixisenatide in Early Parkinson's Disease. New England Journal of Medicine, 390(13), 1176–1185. https://doi.org/10.1056/nejmoa2312323

Nowell, J., Blunt, E., Gupta, D., & Edison, P. (2023). Antidiabetic agents as a novel treatment for Alzheimer's and Parkinson's disease. Ageing Research Reviews, 89. https://doi.org/10.1016/j.arr.2023.101979

Reich, N., & Hölscher, C. (2022). The neuroprotective effects of glucagon-like peptide 1 in Alzheimer's and Parkinson's disease: An in-depth review. Frontiers in Neuroscience, 16. https://doi.org/10.3389/fnins.2022.970925

Ribarič, S. (2024). The Contribution of Type 2 Diabetes to Parkinson's Disease Aetiology. International Journal of Molecular Sciences, 25(8). https://doi.org/10.3390/ijms25084358

Roy, A., Dawson, V. L., & Dawson, T. M. (2025). From metabolism to mind: The expanding role of the GLP-1 receptor in neurotherapeutics. Neurotherapeutics. https://doi.org/10.1016/j.neurot.2025.e00712

Sun, H., Hao, Y., Liu, H., & Gao, F. (2025). The immunomodulatory effects of GLP-1 receptor agonists in neurogenerative diseases and ischemic stroke treatment. Frontiers in Immunology, 16. https://doi.org/10.3389/fimmu.2025.1525623

Sun, M., Wang, X., Lu, Z., Yang, Y., Lv, S., Miao, M., Chen, W. M., Wu, S. Y., & Zhang, J. (2025). Evaluating GLP-1 receptor agonists versus metformin as first-line therapy for reducing dementia risk in type 2 diabetes. BMJ Open Diabetes Research and Care, 13(4). https://doi.org/10.1136/bmjdrc-2025-004902

Tang, H., Donahoo, W. T., DeKosky, S. T., Lee, Y. A., Svensson, M., Bian, J., & Guo, J. (2025). Glycated hemoglobin and body mass index as mediators of GLP-1RAs and Alzheimer's disease and related dementias in patients with type 2 diabetes. Alzheimer's and Dementia, 21(4). https://doi.org/10.1002/alz.70161

Urkon, M., Ferencz, E., Szász, J. A., Szabo, M. I. M., Orbán-Kis, K., Szatmári, S., & Nagy, E. E. (2025). Antidiabetic GLP-1 Receptor Agonists Have Neuroprotective Properties in Experimental Animal Models of Alzheimer's Disease. Pharmaceuticals, 18(5). https://doi.org/10.3390/ph18050614

Yu, H.-Y., Sun, T., Wang, Z., Li, H., Xu, D., An, J., Wen, L.-L., Li, J.-Y., Li, W., & Feng, J. (2022). Exendin-4 and linagliptin attenuate neuroinflammation in a mouse model of Parkinson′s disease. Neural Regeneration Research, 0(0), 0. https://doi.org/10.4103/1673-5374.360242

Zhao, X., Wang, M., Wen, Z., Lu, Z., Cui, L., Fu, C., Xue, H., Liu, Y., & Zhang, Y. (2021). GLP-1 Receptor Agonists: Beyond Their Pancreatic Effects. Frontiers in Endocrinology, 12. https://doi.org/10.3389/fendo.2021.721135