PPN

Personalized Psychiatry and Neurology

Review

Neuroprotective Activity of GLP-1 Analogues: General Understanding of Implementation Mechanisms

Eugenija L. Golovina *, Olga E. Vaizova and Julija G. Samojlova

Siberian State Medical University, 634050 Tomsk, Russia;
* Correspondence: e-mail: golovina.el@ssmu.ru (E.L.G.); Tel.: +7-913-801-08-06

Citation: Golovina, E.L.; Vaizova, O.E.; Samojlova, J.G. Neuroprotective Activity of GLP-1 Analogues: General Understanding of Implementation Mechanisms. *Personalized Psychiatry and Neurology* **2024**, *4 (3)*: 2-11. https://doi.org/10.52667/2712-9179-2024-4-3-2-11

Chief Editor: Nikolaj G. Neznanov, D Med Sci, Professor

Received: 2 August 2024
Accepted: 10 September 2024
Published: 15 September 2024

Publisher's Note: V.M. Bekhterev NMRC PN stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Glucagon-like peptide-1 (GLP-1) is a hormone possessing extensive pharmacologic potential. Additionally, to its multiple metabolic effects, GLP-1 also exhibits cardiac and neuroprotective effects. Native GLP-1 is not used as a medicinal agent, however, now GLP-1 analogues structurally similar to it and having a long-lasting effect have been developed and used in the treatment of type 2 diabetes mellitus (T2DM). The review focuses on the neuroprotective effect of these drugs and discusses possible mechanisms of this effect. Aim: To identify information about experimental and clinical evidence about the role of GLP-1 analogues in brain protection in neurodegenerative diseases. Materials and Methods: The review was performed in accordance with the PRISMA 2020 statement; publications were searched for in the PubMed, MedLine, Web of Science, Scopus, and Google Scholar databases covering the period from 2014 to 2024. Results: The publications provide strong evidence of the association between T2DM and cognitive impairment, as well as information on the effectiveness of GLP-1 analogues in the management of neurodegenerative diseases. Possible mechanisms are discussed. Conclusion: This review shows that GLP-1 can prevent cognitive and motor disorders. There is sufficient experimental evidence of the neurotropic activity of the drugs, and clinical trials are ongoing.

Keywords: *Alzheimer's disease; Parkinson's disease; glucagon-like peptide type 1; glucagon-like peptide type 1 receptor gene polymorphism; neuroprotective effect*

1. INTRODUCTION

Investigation of the glucagon-like peptide type 1 (GLP-1) role began at the early last century, when Sutherland E.W. and De Duve C. found that the extract of the gastrointestinal mucosa contained a substance producing the effect similar to glucagon. In the 60s of the XX century, cells similar to the pancreatic alpha cells were found in the intestinal mucosa and described [1].

GLP-1 is an incretin hormone and it plays an important role in glucose metabolism as well as glucose-dependent insulinotropic peptide (GIP) [2]. GLP-1 directly activates receptors present in different organs and tissues. GLP-1 receptor mRNA was found to express in multiple tissues with the highest expression observed in the lungs and pancreas, and lower expression in the stomach, intestines, kidneys, heart, and brain [3]. GLP-1 receptors belong to the group of stimulatory G protein-coupled receptors. Binding of GLP-1 to the receptor leads to activation of adenylate cyclase and higher production of cAMP. Protein kinase A and cAMP-regulated nucleotide exchange factors are activated under the influence of cAMP. This leads to changes in ion channel permeability, elevated intracellular calcium concentrations and intensified exocytosis of insulin-containing granules in beta cells [4]. GLP-1 is also synthesized in the brain where it acts as a mediator, as

it is involved in neuronal transmission [1]. However, endothelial cells ensuring the integrity of the blood-brain barrier are capable of transporting GLP-1 to the brain. GLP-1 receptors are abundantly present on the vascular endothelium [5]. The interaction of the receptor with GLP-1 ensures penetration of the latter through the blood-brain barrier via cAMP-dependent vesicular transport. Parenterally administered GLP-1 analogues are detected in the brain fairly rapidly [6].

All effects of GLP-1 can be conventionally divided into two groups - pancreatic (or the ones occurring within the gastrointestinal tract (GIT)) and extrapancreatic ones (including anti-inflammatory, neurotropic and cardiotropic effects). The review [7] describes the anti-inflammatory effect of GLP-1 in various diseases of the cardiovascular system, gastrointestinal tract (Crohn's disease, ulcerative colitis, and short bowel syndrome), liver, kidneys, and respiratory tract. In addition, it shows its role in reducing neurogenic inflammation in Alzheimer's disease (AD) and parkinsonism. The review [8] mentions cardioprotective effect of GLP-1 receptor agonists (GLP1R). GLP1R agonists have been found to be able to prevent ischemia-reperfusion injury of the heart. Long-term use of the drugs mitigates development of adverse cardiac remodeling in myocardial infarction, hypertension, and diabetes mellitus. Agonists can protect the heart from oxidative stress and reduce expression of proinflammatory cytokines (IL-1β, IL-6, TNF-α) in the myocardium.

The association between neurodegenerative disorders and metabolic disorders is supporting by growing evidence. The review [9] presents the results of epidemiological, non-clinical and clinical studies that establish a potential association between AD and T2DM. Studies have shown that insulin resistance and deficiency affect the phosphorylation of β-amyloid and tau protein, which can lead to AD onset and development. People with T2DM are at risk for cognitive impairment and dementia caused not only by AD but also by cerebral vascular damage. For example, a meta-analysis [10] showed that T2DM was associated with a 60% increased risk of dementia of any etiology. Possible mechanisms of dementia development include toxic effects of hyperglycemia, brain insulin resistance, formation of advanced glycation end products, and competition for the enzyme that destroys insulin leading to inhibition of β-amyloid degradation. Some publications refer AD as “type 3 diabetes” due to brain insulin resistance and dysregulation of insulin signaling in the brain [11]. The study [12] demonstrated that impaired glucose supply to the brain was closely associated with AD pathogenesis. Changes in brain glucose metabolism may begin long before the onset of AD clinical symptoms.

Epidemiological studies also highlight the elevated risk of developing Parkinson's disease (PD) in T2DM patients. A retrospective cohort study of Taiwanese patients demonstrated the association between T2DM and PD risk. The high risk was noted in patients over 65 years of age. The authors believe that the association between T2DM and PD can be explained by the involvement of insulin in the regulation of dopaminergic activity of the brain [13]. A study involving a large population of elderly adults in the United States also established the association between T2DM and PD. Chronic inflammation or oxidative stress are considered one of mechanisms, which can lead to diabetes and years later to a high risk of PD [14].

Single publications indicate a genetic association of GLP1R gene polymorphisms and predisposition to PD. The most common GLP1R gene polymorphisms are rs3765467 and rs6923761. Changes of the amino acid sequence reduce sensitivity of the receptor to GLP-1 [15]. Analysis of polymorphisms in the Chinese Han population showed that frequency of the rs3765467 GG genotype was significantly higher in the PD group versus the control group. Genotype and allele frequencies for rs6923761 were not significantly different between PD patients and healthy subjects. That is, the GLP1R rs3765467 GG genotype presents a potential risk factor for PD [16].

This review focuses on studies and potential mechanisms of the neuroprotective activity of GLP-1 analogues.

2. MATERIAL AND METHODS

We analyzed articles in English devoted to this issue. Criteria for inclusion in search were the following: 1) full-text original articles and reviews cited in databases: PubMed, MedLine, Web of Science, Scopus, and Google Scholar, 2) articles in English, 3) search depth 10 years 4) keywords: Alzheimer's disease, Parkinson's disease, glucagon-like peptide type 1, glucagon-like peptide type 1 receptor gene polymorphism, neuroprotective effect. Exclusion criteria: abstracts, monographs, manuals, guidelines. The review was performed in accordance with the PRISMA 2020 statement.

3. RESULTS

The review focuses on the neurotropic activity of modified GLP-1 molecules (GLP-1 analogues). These agents provide a pharmacological effect due to direct activation of GLP-1 receptors (GLP-1 receptor agonists, incretin mimetics). GLP-1 receptor agonists enhance the functioning of beta cells, inhibit glucagon secretion by alpha cells, reduce hepatic glucose production, prolong satiation time (through central mechanisms), slow gastric emptying, and increase glucose uptake by peripheral tissues. Long-acting GLP-1 analogues (dulaglutide, semaglutide) and a sustained-release dosage form of exenatide are administered subcutaneously once a week [17]. Like incretin, GLP-1 analogues penetrate the blood-brain barrier and cause reduction of adipose tissue due to central effects at the level of arcuate nucleus neurons [18]. This has been demonstrated for exenatide [19] and liraglutide [20]..

3.1. Experimental Studies of Neuroprotective Activity of GLP-1 Analogues in Alzheimer's Disease Models

In a study [21], in mice with induced neurodegeneration, subcutaneous administration of liraglutide once daily for 8 weeks provided a significant protective effect on the central nervous system. Liraglutide was shown to improve aerobic glycolysis and reduce oxidative stress in astrocytes, probably through involvement of the intracellular PI3K/Akt pathway. This study suggests that altering the energetic phenotype may be effective in slowing AD progression. Liraglutide testing in a concurrent model of T2DM and AD in mice demonstrated promising results. Treatment with liraglutide not only eliminates metabolic changes and associated vascular damage in diabetic mice, but also simultaneously limits the pathological changes of β-amyloid and tau protein. A significant reduction in brain atrophy in animals was also noted [22]. Administration of liraglutide to 6-month-old AD mice improved mitochondrial dysfunction and prevented neuronal loss through activation of the cAMP/protein kinase A pathway. In the same *in vitro* study, GLP-1 was added to amyloid-β-treated astrocytes. It was demonstrated that GLP-1 reduced mitochondrial fragmentation in β-amyloid-treated astrocytes, reduced energy stress, and increased the production of brain-derived neurotrophic factor by astrocytes [23]. Based on the evidence of a higher risk of AD in older women suffering from T2DM, the authors of [24] examined brains of female mice with AD. Administration of liraglutide reduced β-amyloid levels and oxidative stress, and decreased the levels of inflammatory markers IL-1β and C-reactive protein. Streptozotocin administration into the lateral ventricles induces brain insulin resistance and it makes an AD model with several key neuropathological signs. Streptozotocin increases neuroinflammation, β-amyloid plaque deposition, and disrupts insulin signaling pathway [25]. Paladugu L et al. (2021) studied the effect of liraglutide on main pathological signs in the prodromal stage of AD induced in mice by the administration of streptozotocin. Liraglutide injections significantly reduced neuroinflammation, brain β-amyloid levels, and restored insulin sensitivity [26]. Insulin receptor changes are an important feature of the brain in AD that impairs the neuroprotective effect of central insulin signaling. Administration of β-amyloid oligomers into the lateral ventricle of non-human primate brain results in loss of insulin receptors and synapses in brain

regions associated with memory. Batista A.F. et al. treated non-human primates with liraglutide. The drug provided moderate protection against loss of synaptophysin and synapse density in the hippocampus, frontal cortex, and amygdala. The results also indicated that liraglutide reduced the abnormal phosphorylation of tau protein in primate brain [27]. In a study [28], the effect of liraglutide was tested in an *in vitro* model of neuronal insulin resistance using the SH-SY5Y human neuroblastoma cell line. The authors present the evidence that liraglutide alleviates neuronal insulin resistance, reduces β-amyloid formation and tau protein hyperphosphorylation. Additionally, liraglutide reduces the activity of beta-secretase 1, which is involved in generation of toxic β-amyloid [29]. An AD model in 3xTg-AD mice receiving high-fat diet demonstrated the effect of exenatide (a synthetic analogue of GLP-1). A high-fat diet caused significant weight gain in animals, with little change in blood glucose levels. In addition, such a diet significantly reduced cognitive function by disrupting brain-derived neurotrophic factor signaling. At the same time, exenatide increased the expression levels of brain-derived neurotrophic factor in the hippocampus and cortex and reduced neuroinflammation [30]. A study of the effect of exenatide on cognitive functions by modulating the activity of brain-derived neurotrophic factor was also performed in wild-type mice in [31]. After 2 months of treatment with exenatide, an improvement in long-term memory was noted. Administration of exenatide to 5xFAD transgenic mice significantly improved cognitive function after 16 weeks of treatment. At the cellular level, exenatide reduced β-amyloid deposition in the hippocampus and improved mitochondrial morphology by reducing oxidative damage [32]. In patients with T2DM, impaired brain insulin signaling may increase the risk of cognitive impairment. There is evidence of the effect of insulin monotherapy on improving memory and slowing AD progression [33]. In [34], intranasal administration of insulin with exenatide to AD mice had an effect on IRSP gene expression (a key mediator and effector of the insulin receptor signaling pathway), learning ability, and β-amyloid levels in the hippocampus

3.2. Experimental Studies of Neuroprotective Activity of GLP-1 Analogues in Parkinson's Disease Models

In [35], PD model in rats was induced by administration of the neurotoxin of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Animals treated with it showed a significant reduction in dopamine levels in the striatum. In addition, PD model induced by MPTP administration is characterized by increased levels of proinflammatory cytokines, in particular IL-1β and TNF-α which directly induced apoptosis in dopaminergic neurons. The use of exenatide significantly reduced the expression of IL-1β and TNF-α and increased the activity of antioxidant enzymes. It was shown that the neuroprotective effects resulted from the direct effect on the brain and were not related to blood glucose levels. Normal blood glucose levels were achieved even with a low dose of exenatide, while the neuroprotective effect increased with the increasing dose. The effect of oxyntomodulin analogue was demonstrated on the same model in mice. Oxyntomodulin is a hormone and growth factor and activates two receptors: GLP-1 and the glucagon receptor. D-Ser2-oxyntomodulin is a protease-resistant oxyntomodulin analogue that has been developed for diabetes treatment. Treatment with D-Ser2-oxyntomodulin prevented or reversed MPTP-induced motor impairment in animals. MPTP decreased tyrosine hydroxylase levels (in the substantia nigra and basal ganglia); synaptic marker synaptophysin, inactivated the growth factor kinase Akt/PKB and the anti-apoptotic signaling molecule Bcl-2. It also increased levels of the pro-inflammatory cytokine TNF-α. Administration of oxyntomodulin analogue prevented those effects [36]. A recent study [37] using a model of MPTP-induced neurodegeneration demonstrated the neuroprotective effect of liraglutide. Exposure to MPTP also causes changes in mitochondrial morphology and formation of megamitochondria. This can lead to loss of dopaminergic neurons and motor deficits in experimental animals. Liraglutide protects dopaminergic neurons by reducing apoptosis, rebalancing mitochondrial changes, reducing oxidative stress, and reducing α-synuclein

in the substantia nigra. The study [38] evaluates the effect of liraglutide on the mitochondrial system. Administration of various doses of the drug to animals with PD model induced by MPTP demonstrated a protective effect in the substantia nigra. The neuroprotective effect was shown to be associated with the PGC-1α activation pathway. Encoded by the same gene, this protein regulates the biogenesis and changes of mitochondria, as well as autophagy and cell apoptosis. Using the PD model induced by MPTP, Zhang L. et al. demonstrated the effect semaglutide, the long-acting GLP-1 receptor agonist, versus liraglutide. Both drugs reduced motor disorders caused in mice by MPTP administration. Semaglutide and liraglutide increased tyrosine hydroxylase levels and reduced the inflammatory response and lipid peroxidation. Semaglutide was superior to liraglutide in most parameters [39]. Later, the same authors showed the effect of semaglutide versus liraglutide in a chronic PD model induced by MPTP administration. Both drugs increased tyrosine hydroxylase levels, decreased α-synuclein accumulation, mitigated chronic inflammatory response in the brain, decreased lipid peroxidation, and inhibited the mitochondrial mitophagy signaling pathway. Additionally, the drugs were shown to influence the expression of glial neurotrophic factor protecting dopaminergic neurons in the substantia nigra and striatum. This study also demonstrated the superiority of semaglutide over liraglutide [40]. PD in animals is also induced by administration of rotenone. It is a neurotoxin that primarily inhibits mitochondrial complex I with ATP depletion, leading to the death of nigrostriatal dopaminergic neurons and increased formation of Lewy bodies [41]. Administration of exenatide to rats with a rotenone-induced PD model caused lower levels of malondialdehyde and TNF-α. In addition, exenatide treatment significantly reduced the loss of dopaminergic neurons in the striatum [42]. The use of dulaglutide in rotenone-induced PD model in mice revealed its antioxidant and anti-inflammatory properties as well as the ability to inhibit the formation of alpha-synuclein [43]. SH-SY5Y human neuroblastoma cell line treated with 6-hydroxydopamine can be considered to be an *in vitro* PD model. 6-hydroxydopamine can freely enter dopaminergic neurons where it increases oxidative stress levels and triggers apoptosis. In addition, it can cause accumulation of α-synuclein [44]. Liu D.X. et al. studied the effect of semaglutide and liraglutide on SH-SY5Y cell cultures. The result confirmed the neuroprotective effect of both drugs. The authors believed that semaglutide and liraglutide reduced oxidative stress and reversed mitochondrial dysfunction. Semaglutide was demonstrated to be superior in most parameters [45].

A sufficient number of studies have been devoted to studying the effect of dual GLP-1/GIP agonists on various parameters in neurodegenerative disorders [46, 47, 48]. Dual GLP-1/GIP agonists demonstrate distinct neuroprotective effects, reducing inflammation, oxidative stress and apoptosis, and improving motor performance, dopaminergic neuron function, and energy utilization in the brain [46]. In PD model induced by MPTP, new dual agonists eliminated dopamine deficiency, increasing the level of tyrosine hydroxylase, decreased the levels of proinflammatory cytokines, and increased the amount of glial neurotrophic factor. The effects were more pronounced compared to liraglutide [47]. In AD models both *in vivo* and *in vitro*, the compounds demonstrate greater activity versus liraglutide activity [48]. Thus, dual agonists may represent a promising new treatment for neurodegenerative diseases.

3.3. Clinical Trials of GLP-1 Analogues for Treatment of Neurodegenerative Diseases

A pilot study enrolling T2DM patients demonstrated the effect of liraglutide on cognitive function. Forty obese patients treated with metformin and having prediabetes or newly diagnosed T2DM were divided into 2 groups. Half of them received liraglutide (1.8 mg/day), while the remaining subjects received lifestyle counseling (diet and exercise) until weight loss was achieved (-7% of baseline body weight). Neuropsychological assessments before and after weight loss were performed in 16 patients in each group using seven psychological tests, assessing attention and memory. Following weight loss and improvement in insulin sensitivity, participants taking liraglutide experienced a significant

improvement of short-term memory [49]. Mullins R.J. et al. conducted a pilot study of exenatide in AD patients (2019). This small, randomized, double blind, placebo-controlled study of 21 patients was designed to assess tolerability and, secondarily, to evaluate treatment responses by clinical, cognitive, MRI, and biomarker outcomes. Exenatide demonstrated a good safety and tolerability profile in all participants reducing body mass index and improving glucose tolerance. Treatment with exenatide had no differences compared to placebo in clinical and cognitive parameters, MRI cortical thickness and volume, and biomarkers in cerebrospinal fluid, plasma, and plasma neuronal extracellular vesicles. There was only a slight decrease in β-amyloid levels in neuronal-enriched extracellular vesicles. The authors were unable to draw definitive conclusions due to the small cohort size and early termination of the study [50]. A randomized, placebo-controlled, double blind clinical trial of 38 asthma patients was completed. 18 patients took liraglutide and 20 took placebo. Liraglutide prevented the reduction of brain glucose uptake, but no effect was found on β-amyloid accumulation or cognitive function. The authors suggested that the cohort size and duration of the study did not allow drawing definitive clinical conclusions but the results could be used for further research [51]. Enrollment to the ELAD study is currently ongoing. This is a 12-month, multicenter, randomized, double blind, placebo-controlled, phase 2 study of liraglutide in participants with mild AD dementia. The primary objective of the ELAD study is to evaluate changes in brain glucose metabolic rate after 12 months of treatment with liraglutide versus placebo. Secondary objectives include assessing changes in cognitive performance, MRI changes, microglial activation, changes in β-amyloid and tau protein, and the frequency and severity of side effects occurring during treatment. The authors are optimistic that if the study is successful, liraglutide could be a step forward in the treatment of AD. The potential of the drug can subsequently be further assessed in larger studies [52].

In a study [53], patients with PD were randomized to self-administer 2 mg exenatide (n = 31) or placebo (n = 29) once weekly for 48 weeks. Patients were assessed using the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS). The results showed that compared to placebo treatment with exenatide was associated with positive and durable effects on motor activity parameters. It remains unclear whether exenatide provides impact on PD pathogenesis or simply causes long-term symptomatic effects. Another article described the testing serum parameters in the patients from study [53]. It demonstrated that treatment with exenatide might be associated with enhancement of insulin signaling pathways in the brain, as evidenced by IRS-1 tyrosine phosphorylation and activated Akt and mTOR signaling. It was also found that the improvement in motor performance observed on 48 and 60 weeks in the exenatide group could be explained by activation of mTOR signaling [54]. A phase 2, double blind, randomized, placebo-controlled study assessed the effect of lixisenatide on the progression of motor disorders in PD subjects. A total of 156 subjects participated in the study, they were randomized into two equal groups to receive subcutaneous lixisenatide or placebo for 12 months followed by a 2-month break. Baseline MDS-UPDRS Part III scores were approximately 15 in both groups. After a year of treatment, the lixisenatide group showed a decrease in scores (-0.04) indicating an improvement in motor functions. Whereas in the placebo group there was a change of 3.04 points which indicated the progression of motor disorders. That is, in patients with early PD, 12-month treatment with lixisenatide led to slower progression of motor impairment versus the placebo group [55].

4. DISCISSION

GLP1R agonists present a promising class of antidiabetic drugs, and their popularity as weight loss agents is growing every day [56]. However, the properties of agonists go beyond the control of glucose levels and body mass index in patients with T2DM. Published data indicate that GLP-1 and its analogues possess certain additional effects. Anti-inflammatory, cardiotropic and neuroprotective effects are the most studied ones. Reports of association between T2DM and cognitive impairment are increasingly common [9–14].

Source [16] indicates a genetic association of GLP1R gene polymorphisms and predisposition to PD. In this regard, drugs for T2DM management including GLP-1 analogues, may bring certain benefit for protection against neurodegenerative disorders.

According to Yaribeygi H. et al. (2021), the neuroprotective effect of GLP-1 is realized through at least 8 mechanisms that may explain improvement of cognitive functions in neurodegenerative diseases [57]. They include reduction of oxidative stress, prevention of neuronal apoptosis, stimulation of neurogenesis and neuronal plasticity, reduction of neuronal inflammation, prevention of phosphorylation and aggregation of tau proteins and β-amylode, reduction of neurotoxic effects, improvement of the sensitivity of nervous tissue to the action of insulin, and direct neurotropic effects [1, 57]. The data from the analyzed publications partially confirm these findings. Thus, liraglutide improves aerobic glycolysis and reduces oxidative stress in astrocytes, limits pathological changes in β-amyloid and tau protein, improves mitochondrial dysfunction, and reduces neuroinflammation in various models of AD [21–24, 26–28]. In AD, exenatide increases the level of expression of brain-derived neurotrophic factor, reduces neuroinflammation and β-amyloid deposition in the hippocampus, and changes mitochondrial dynamics [30–32]. In PD, GLP-1 analogues also reduce neuroinflammation, increase the level of tyrosine hydroxylase, reduce the accumulation of α-synuclein, and exhibit antioxidant properties. All this contributes to the protection of dopaminergic neurons in the substantia nigra and striatum [35–40, 42, 43, 45]. There is increasing evidence of clinical trials of GLP-1 receptor agonists. Findings about clinical trials of these agents in PD patients seem to be more optimistic. The use of exenatide and lixisenatide in PD partially stopped the progression of motor disorders [53, 55].

5. CONCLUSION

This review demonstrates that additionally to improvement of glycemic parameters, GLP-1 can also prevent cognitive and motor disorders. There are convincing experimental data proving that these agents, in addition to their main effect, also exert certain neuroprotective effect. The main mechanisms of neurotropic action include reduction of oxidative stress, neuroinflammation, apoptosis, improvement of mitochondrial dysfunction, and antioxidant action. Clinical data on the effect of GLP-1 analogues on cognitive and motor functions in AD and PD patients are still insufficient, as well as information on individual differences in the treatment of neurogenerative disorders with these drugs.

Author Contributions: : The study concept and design, data analysis and interpretation, review of critical intellectual content, E.L.G; development of the study concept and design, review of critical intellectual content, approval of the final version of the manuscript, responsibility for the integrity of the manuscript content, O.E.V.; the study concept and design, final approval for manuscript publication, J.G.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

1. Müller, T.D.; Finan, B.; Bloom, S.R.; D'Alessio, D.; Drucker, D.J.; Flatt, P.R.; Fritsche, A.; Gribble, F.; Grill, H.J.; Habener, J.F. Glucagon-like peptide 1 (GLP-1). *Mol Metab.* **2019**, 30:72-130. doi: 10.1016/j.molmet.2019.09.010.

2. Campbell, J.E.; Müller, T.D.; Finan, B.; DiMarchi, R.D.; Tschöp, M.H.; D'Alessio, D.A. GIPR/GLP-1R dual agonist therapies for diabetes and weight loss-chemistry, physiology, and clinical applications. *Cell Metab*. **2023,** 35(9):1519-1529. doi: 10.1016/j.cmet.2023.07.010.

3. Wei, Y.; Mojsov, S. Tissue-specific expression of the human receptor for glucagon-like peptide-I: brain, heart and pancreatic forms have the same deduced amino acid sequences. *FEBS Lett*. **1995**, 358(3):219-24. doi: 10.1016/0014-5793(94)01430-9.

4. Holz, G.G. New insights concerning the glucose-dependent insulin secretagogue action of glucagon-like peptide-1 in pancreatic beta-cells. *Horm Metab Res*. **2004**, 36(11-12):787-94. doi: 10.1055/s-2004-826165.
5. Laurindo, L.F.; Barbalho, S.M.; Guiguer, E.L.; da Silva Soares de Souza, M.; de Souza, G.A.; Fidalgo, T.M.; Araújo, A.C.; de Souza Gonzaga, H.F.; de Bortoli Teixeira, D.; de Oliveira Silva Ullmann, T. GLP-1a: Going beyond traditional use. *Int J Mol Sci.* **2022**, 23(2):739. doi: 10.3390/ijms23020739.
6. Abdulhameed, N.; Babin, A.; Hansen, K.; Weaver, R.; Banks, W.A.; Talbot, K.; Rhea, E.M. Comparing regional brain uptake of incretin receptor agonists after intranasal delivery in CD-1 mice and the APP/PS1 mouse model of Alzheimer's disease. *Alzheimers Res Ther*. **2024**, 16(1):173. doi: 10.1186/s13195-024-01537-1.
7. Mehdi, S.F.; Pusapati, S.; Anwar, M.S.; Lohana, D.; Kumar, P.; Nandula, S.A.; Nawaz, F.K.; Tracey, K.; Yang, H.; LeRoith, D.; Glucagon-like peptide-1: a multi-faceted anti-inflammatory agent. *Front Immunol*. **2023**, 14:1148209. doi: 10.3389/fimmu.2023.1148209.
8. Boshchenko, A.A.; Maslov, L.N.; Mukhomedzyanov, A.V.; Zhuravleva, O.A.; Slidnevskaya, A.S.; Naryzhnaya, N.V.; Zinovieva, A.S.; Ilinykh, P.A. Peptides are cardioprotective drugs of the future: the receptor and signaling mechanisms of the cardioprotective effect of glucagon-like peptide-1 receptor agonists. *Int J Mol Sci.* **2024**, 25(9):4900. doi: 10.3390/ijms25094900.
9. Li, X.; Song, D.; Leng, S.X. Link between type 2 diabetes and Alzheimer's disease: from epidemiology to mechanism and treatment. *Clin Interv Aging*. **2015**, 10:549-60. doi: 10.2147/CIA.S74042.
10. Gudala, K.; Bansal, D.; Schifano, F.; Bhansali, A. Diabetes mellitus and risk of dementia: A meta-analysis of prospective observational studies. *J Diabetes Investig*. **2013**, 4(6):640-50. doi: 10.1111/jdi.12087.
11. Zheng, M.; Wang, P. Role of insulin receptor substance-1 modulating PI3K/Akt insulin signaling pathway in Alzheimer's disease. *3 Biotech*. **2021**, 11(4):179. doi: 10.1007/s13205-021-02738-3.
12. An, Y.; Varma, V.R.; Varma, S.; Casanova, R.; Dammer, E.; Pletnikova, O.; Chia, C.W.; Egan, J.M.; Ferrucci, L.; Troncoso, J.; Evidence for brain glucose dysregulation in Alzheimer's disease. *Alzheimers Dement.* **2018**, 14(3):318-329. doi: 10.1016/j.jalz.2017.09.011.
13. Yang, Y.W.; Hsieh, T.F.; Li, C.I.; Liu, C.S.; Lin, W.Y.; Chiang, J.H.; Li, T.C.; Lin, C.C. Increased risk of Parkinson disease with diabetes mellitus in a population-based study. *Medicine (Baltimore)* **2017**, 96(3):e5921. doi: 10.1097/MD.0000000000005921.
14. Xu, Q.; Park, Y.; Huang, X.; Hollenbeck, A.; Blair, A.; Schatzkin, A.; Chen, H. Diabetes and risk of Parkinson's disease. *Diabetes Care* **2011**, 34(4):910-5. doi: 10.2337/dc10-1922.
15. Sathananthan, A.; Man, C.D.; Micheletto, F.; Zinsmeister, A.R.; Camilleri, M.; Giesler, P.D.; Laugen, J.M.; Toffolo, G.; Rizza, R.A.; Cobelli, C. Common genetic variation in GLP1R and insulin secretion in response to exogenous GLP-1 in nondiabetic subjects: a pilot study. *Diabetes Care* **2010**, 33(9):2074-6. doi: 10.2337/dc10-0200.
16. Qiu, X.; Huang, Y.; Cen, L.; Chen, X.; Lu, T.; Shen, Y.; Xu, P.; Wang, J.; Xiao, Y. Association of GLP-1 receptor gene polymorphisms with sporadic Parkinson's disease in Chinese Han population. *Neurosci Lett*. **2020**, 728:135004. doi: 10.1016/j.neulet.2020.135004.
17. Cornell, S. A review of GLP-1 receptor agonists in type 2 diabetes: A focus on the mechanism of action of once-weekly agents. *J Clin Pharm Ther.* **2020**, 45 (1):17-27. doi: 10.1111/jcpt.13230.
18. Morieri, M.L.; Avogaro, A.; Fadini, G.P. Long-acting injectable GLP-1 receptor agonists for the treatment of adults with type 2 diabetes: perspectives from clinical practice. diabetes *Metab Syndr Obes*. **2020**, 13:4221-4234. doi: 10.2147/DMSO.S216054.
19. Göke, R.; Larsen, P.J.; Mikkelsen, J.D.; Sheikh, S.P. Distribution of GLP-1 binding sites in the rat brain: evidence that exendin-4 is a ligand of brain GLP-1 binding sites. *Eur J Neurosci*. **1995**, 7(11):2294-300. doi: 10.1111/j.1460-9568.1995.tb00650.x.
20. Secher, A.; Jelsing, J.; Baquero, A.F.; Hecksher-Sørensen, J.; Cowley, M.A.; Dalbøge, L.S.; Hansen, G.; Grove, K.L.; Pyke, C.; Raun, K. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J Clin Invest.* **2014**, 124(10):4473-88. doi: 10.1172/JCI75276.
21. Zheng, J.; Xie,Y.; Ren, L.; Qi, L.; Wu, L.; Pan, X.; Zhou, J.; Chen, Z.; Liu, L. GLP-1 improves the supportive ability of astrocytes to neurons by promoting aerobic glycolysis in Alzheimer's disease. *Mol Metab*. **2021**, 47:101180. doi: 10.1016/j.molmet.2021.101180.
22. Carranza-Naval, M.J.; Del Marco, A.; Hierro-Bujalance, C.; Alves-Martinez, P.; Infante-Garcia, C.; Vargas-Soria, M.; Herrera, M.; Barba-Cordoba, B.; Atienza-Navarro, I.; Lubian-Lopez, S. Liraglutide reduces vascular damage, neuronal loss, and cognitive impairment in a mixed murine model of Alzheimer's disease and type 2 diabetes. *Front Aging Neurosci*. **2021**, 13:741923. doi: 10.3389/fnagi.2021.741923.
23. Xie, Y.; Zheng, J.; Li, S.; Li, H.; Zhou, Y.; Zheng, W.; Zhang, M.; Liu, L.; Chen, Z. GLP-1 improves the neuronal supportive ability of astrocytes in Alzheimer's disease by regulating mitochondrial dysfunction via the cAMP/PKA pathway. *Biochem Pharmacol.* **2021**, 188:114578. doi: 10.1016/j.bcp.2021.114578.
24. Duarte, A.I.; Candeias, E.; Alves, I.N.; Mena, D.; Silva, D.F.; Machado, N.J.; Campos, E.J.; Santos, M.S.; Oliveira, C.R.; Moreira, P.I. Liraglutide protects against brain amyloid-β_{1-42} accumulation in female mice with early Alzheimer's disease-like pathology by partially rescuing oxidative/nitrosative stress and inflammation. *Int J Mol Sci.* **2020**, 21(5):1746. doi: 10.3390/ijms21051746.
25. Mehla, J.; Pahuja, M.; Gupta, Y.K. Streptozotocin-induced sporadic Alzheimer's disease: selection of appropriate dose. *J Alzheimers Dis*. **2013**, 33(1):17-21. doi: 10.3233/JAD-2012-120958.
26. Paladugu, L.; Gharaibeh, A.; Kolli, N.; Learman, C.; Hall, T.C.; Li, L.; Rossignol, J.; Maiti, P.; Dunbar, G.L. Liraglutide has anti-inflammatory and anti-amyloid properties in streptozotocin-induced and 5xFAD mouse models of Alzheimer's disease. *Int J Mol Sci.* **2021**, 22(2):860. doi: 10.3390/ijms22020860.

27. Batista, A.F.; Forny-Germano, L.; Clarke, J.R.; Lyra, E.; Silva, N.M.; Brito-Moreira, J.; Boehnke, S.E.; Winterborn, A.; Coe, B.C.; Lablans, A.; Vital, J.F.; The diabetes drug liraglutide reverses cognitive impairment in mice and attenuates insulin receptor and synaptic pathology in a non-human primate model of Alzheimer's disease. *J Pathol.* **2018**, 245(1):85-100. doi: 10.1002/path.5056

28. Jantrapirom, S.; Nimlamool, W.; Chattipakorn, N.; Chattipakorn, S.; Temviriyanukul, P.; Inthachat, W.; Govitrapong, P.; Potikanond, S. Liraglutide suppresses tau hyperphosphorylation, amyloid beta accumulation through regulating neuronal insulin signaling and BACE-1 activity. *Int J Mol Sci.* **2020**, 21(5):1725. doi: 10.3390/ijms21051725.

29. Vassar, R. BACE1: the beta-secretase enzyme in Alzheimer's disease. *J Mol Neurosci*. **2004**, 23(1-2):105-14. doi: 10.1385/JMN:23:1-2:105.

30. Bomba, M.; Granzotto, A.; Castelli, V.; Onofrj, M.; Lattanzio, R.; Cimini, A.; Sensi, S.L. Exenatide reverts the high-fat-diet-induced impairment of BDNF signaling and inflammatory response in an animal model of Alzheimer's disease. *J Alzheimers Dis.* **2019**, 70(3):793-810. doi: 10.3233/JAD-190237.

31. Bomba, M.; Granzotto, A.; Castelli, V.; Massetti, N.; Silvestri, E.; Canzoniero, L.M.T.; Cimini, A.; Sensi, S.L. Exenatide exerts cognitive effects by modulating the BDNF-TrkB neurotrophic axis in adult mice. *Neurobiol Aging.* **2018**, 64:33-43. doi: 10.1016/j.neurobiolaging.2017.12.009.

32. An, J.; Zhou, Y.; Zhang, M.; Xie, Y.; Ke, S.; Liu, L.; Pan, X.; Chen, Z. Exenatide alleviates mitochondrial dysfunction and cognitive impairment in the 5×FAD mouse model of Alzheimer's disease. *Behav Brain Res.* **2019**, 370:111932. doi: 10.1016/j.bbr.2019.111932.

33. Craft, S.; Asthana, S.; Cook, D.G.; Baker, L.D.; Cherrier, M.; Purganan, K.; Wait, C.; Petrova, A.; Latendresse, S.; Watson, G.S.; Insulin dose-response effects on memory and plasma amyloid precursor protein in Alzheimer's disease: interactions with apolipoprotein E genotype. *Psychoneuroendocrinology* **2003**, 28(6):809-22. doi: 10.1016/s0306-4530(02)00087-2.

34. Robinson, A.; Lubitz, I.; Atrakchi-Baranes, D.; Licht-Murava, A.; Katsel, P.; Leroith, D.; Liraz-Zaltsman, S.; Haroutunian, V.; Beeri, M.S. Combination of insulin with a GLP1 agonist is associated with better memory and normal expression of insulin receptor pathway genes in a mouse model of Alzheimer's disease. *J Mol Neurosci*. **2019**, 67(4):504-510. doi: 10.1007/s12031-019-1257-9.

35. Elbassuoni, E.A.; Ahmed, R.F. Mechanism of the neuroprotective effect of GLP-1 in a rat model of Parkinson's with pre-existing diabetes. *Neurochem Int.* **2019**, 131:104583. doi: 10.1016/j.neuint.2019.

36. Liu, W.; Li, Y.; Jalewa, J.; Saunders-Wood, T.; Li, L.; Hölscher, C. Neuroprotective effects of an oxyntomodulin analogue in the MPTP mouse model of Parkinson's disease. *Eur J Pharmacol*. **2015**, 765:284-90. doi: 10.1016/j.ejphar.2015.08.038.

37. Lin, T.K.; Lin, KJ.; Lin, H.Y.; Lin, K.L.; Lan, M.Y.; Wang, P.W.; Wang, T.J.; Wang, F.S.; Tsai, P.C.; Liou, C.W. Glucagon-like peptide-1 receptor agonist ameliorates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity through enhancing mitophagy flux and reducing α-synuclein and oxidative stress. *Front Mol Neurosci.* **2021**, 14:697440. doi: 10.3389/fnmol.2021.697440.

38. Wu, P.; Dong, Y.; Chen, J.; Guan, T.; Cao, B.; Zhang, Y.; Qi, Y.; Guan, Z.; Wang, Y. Liraglutide regulates mitochondrial quality control system through PGC-1α in a mouse model of Parkinson's disease. *Neurotox Res*. **2022**, 40(1):286-297. doi: 10.1007/s12640-021-00460-9

39. Zhang, L.; Zhang, L.; Li, L.; Hölscher, C. Neuroprotective effects of the novel GLP-1 long acting analogue semaglutide in the MPTP Parkinson's disease mouse model. *Neuropeptides* **2018**, 71:70-80. doi: 10.1016/j.npep.2018.07.003.

40. Zhang, L.; Zhang, L.; Li, L.; Hölscher, C. Semaglutide is neuroprotective and reduces α-synuclein levels in the chronic MPTP mouse model of Parkinson's disease. *J Parkinsons Dis.* **2019**, 9(1):157-171. doi: 10.3233/JPD-181503.

41. Thirugnanam, T.; Santhakumar, K. Chemically induced models of Parkinson's disease. *Comp Biochem Physiol C Toxicol Pharmacol***. 2022**, 252:109213. doi: 10.1016/j.cbpc.2021.109213.

42. Aksoy, D.; Solmaz, V.; Çavuşoğlu, T.; Meral, A.; Ateş, U.; Erbaş, O. Neuroprotective effects of exenatide in a rotenone-induced rat model of Parkinson's disease. *Am J Med Sci.* **2017,** 354(3):319-324. doi: 10.1016/j.amjms.2017.05.002.

43. Khalaf, M.M.; El-Sayed, M.M.; Kandeil, M.A.; Ahmed, S. A novel protective modality against rotenone-induced Parkinson's disease: A pre-clinical study with dulaglutide. *Int Immunopharmacol*. **2023**, 119:110170. doi: 10.1016/j.intimp.2023.110170.

44. Yang, G.; Li, J.; Cai, Y.; Yang, Z.; Li, R.; Fu, W. Glycyrrhizic acid alleviates 6-hydroxydopamine and corticosterone-induced neurotoxicity in SH-SY5Y cells through modulating autophagy. *Neurochem Res*. **2018**, 43(10):1914-1926. doi: 10.1007/s11064-018-2609-5.

45. Liu, D.X.; Zhao, C.S.; Wei, X.N.; Ma, Y.P.; Wu, J.K. Semaglutide protects against 6-OHDA toxicity by enhancing autophagy and inhibiting oxidative stress. *Parkinsons Dis.* **2022**, 2022:6813017. doi: 10.1155/2022/6813017.

46. Hölscher, C. Novel dual GLP-1/GIP receptor agonists show neuroprotective effects in Alzheimer's and Parkinson's disease models. *Neuropharmacology* **2018**, 136(Pt B):251-259. doi: 10.1016/j.neuropharm.2018.01.040.

47. Feng, P.; Zhang, X.; Li, D.; Ji, C.; Yuan, Z.; Wang, R.; Xue, G.; Li, G.; Hölscher, C. Two novel dual GLP-1/GIP receptor agonists are neuroprotective in the MPTP mouse model of Parkinson's disease. *Neuropharmacology* **2018**, 133:385-394. doi: 10.1016/j.neuropharm.2018.02.012.

48. Salles, G.N.; Calió, M.L.; Hölscher, C.; Pacheco-Soares, C.; Porcionatto, M.; Lobo, A.O. Neuroprotective and restorative properties of the GLP-1/GIP dual agonist DA-JC1 compared with a GLP-1 single agonist in Alzheimer's disease. *Neuropharmacology* **2020**, 162:107813. doi: 10.1016/j.neuropharm.2019.107813.

49. Vadini, F.; Simeone, P.G.; Boccatonda, A.; Guagnano, M.T.; Liani, R.; Tripaldi, R.; Di Castelnuovo, A.; Cipollone, F.; Consoli, A.; Santilli, F. Liraglutide improves memory in obese patients with prediabetes or early type 2 diabetes: a randomized, controlled study. *Int J Obes (Lond).* **2020**, 44(6):1254-1263. doi: 10.1038/s41366-020-0535-5.
50. Mullins, R.J.; Mustapic, M.; Chia, C.W.; Carlson, O.; Gulyani, S.; Tran, J.; Li, Y.; Mattson, M.P.; Resnick, S.; Egan, J.M. A pilot study of exenatide actions in Alzheimer's disease. *Curr Alzheimer Res.* **2019**, 16(8):741-752. doi: 10.2174/1567205016666190913155950.
51. Gejl, M.; Gjedde, A.; Egefjord, L.; Møller, A.; Hansen, S.B.; Vang, K.; Rodell, A.; Brændgaard, H.; Gottrup, H.; Schacht, A. In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. *Front Aging Neurosci.* **2016**, 8:108. doi: 10.3389/fnagi.2016.00108.
52. Femminella, G.D.; Frangou, E.; Love, S.B.; Busza, G.; Holmes, C.; Ritchie, C.; Lawrence, R.; McFarlane, B.; Tadros, G.; Ridha, B.H. Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer's disease: study protocol for a randomised controlled trial (ELAD study). *Trials* **2019**, 20(1):191. doi: 10.1186/s13063-019-3259-x.
53. Athauda, D.; Maclagan, K.; Skene, S.S.; Bajwa-Joseph, M.; Letchford, D.; Chowdhury, K.; Hibbert, S.; Budnik, N.; Zampedri, L.; Dickson, J. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet* **2017**, 390(10103):1664-1675. doi: 10.1016/S0140-6736(17)31585-4.
54. Athauda, D.; Gulyani, S.; Karnati, H.K.; Li, Y.; Tweedie, D.; Mustapic, M.; Chawla, S.; Chowdhury, K.; Skene, S.S.; Greig, N.H. Utility of neuronal-derived exosomes to examine molecular mechanisms that affect motor function in patients with Parkinson disease: a secondary analysis of the exenatide-PD trial. *JAMA Neurol.* **2019**, 76(4):420-429. doi: 10.1001/jamaneurol.2018.4304ю
55. Meissner, W.G.; Remy, P.; Giordana, C.; Maltête, D.; Derkinderen, P.; Houéto, J.L.; Anheim, M.; Benatru, I.; Boraud, T.; Brefel-Courbon, C. Trial of lixisenatide in early Parkinson's disease. *N Engl J Med.* **2024**, 390(13):1176-1185. doi: 10.1056/NEJMoa2312323.
56. Kluger, A.Y.; McCullough, P.A. Semaglutide and GLP-1 analogues as weight-loss agents. *Lancet* **2018**, 392(10148):615-616. doi: 10.1016/S0140-6736(18)31826-9.
57. Yaribeygi, H.; Rashidy-Pour, A.; Atkin, S.L.; Jamialahmadi, T.; Sahebkar, A. GLP-1 mimetics and cognition. *Life Sci.* **2021**, 264:118645. doi: 10.1016/j.lfs.2020.118645.