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The Neuroprotective Effects of GLP-1 Analogues on Alzheimer's Disease – A Literature Review

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Abstract

Alzheimer's disease (AD), often referred to as type 3 diabetes, is characterized by neuroinflammation, oxidative stress, mitochondrial dysfunction, and brain insulin resistance, leading to cognitive decline. GLP-1 receptor agonists, originally developed for type 2 diabetes, demonstrate neuroprotective properties that address these pathologies. They improve insulin sensitivity, reduce amyloid-beta deposition, tau hyperphosphorylation, and neuronal apoptosis while enhancing synaptic plasticity, autophagy, and neural stem cell proliferation. Studies highlight their potential as innovative AD therapies. However, further research is needed to confirm their efficacy and long-term safety in combating neurodegeneration.

Material and methods

This literature review aims to evaluate the potential of glucagon-like peptide-1 receptor agonists in reducing the risk and improving the treatment of Alzheimer's disease. A systematic search was conducted using the PubMed database with the following keywords: "Alzheimer's disease" AND ("glucagon-like peptide-1" OR GLP-1) AND neuroprotection. Only full-text studies published in English within the last ten years were included. Titles and abstracts were manually screened for relevance to the review objectives. Selected studies underwent qualitative analysis and were summarized to provide an overview of findings. Since this review is not designed as a meta-analysis, no statistical methods were applied.

Keywords: Alzheimer's disease (AD), glucagon like peptide 1 (GLP-1), neuroprotection

Introduction

Alzheimer's disease is one of the world's major health challenges and is the most common neurodegenerative disease.[1] Alzheimer's disease (AD) involves a gradual decline in brain functions, beginning with cognitive impairments such as difficulty remembering recent events, language problems, confusion and challenges in solving problems or thinking abstractly.[2] All of these features significantly reduce patient's quality of life. In 2021, approximately 50 million people worldwide suffered from Alzheimer's disease, which gradually leads to disability and death. With an aging global population and increasing life expectancy, the number of Alzheimer's patients is expected to triple by 2050.[3] The increasing number of AD patients requires an increased financial outlay on the health care system, which puts a strain on many countries' economies.[4] The progression of Alzheimer's disease is multifaceted and shaped by a combination of genetic predisposition, environmental factors, and lifestyle. Among genetic contributors, a family history of Alzheimer's holds particular significance. Early-onset AD (ages 30–50) is often linked to mutations in the PSEN1, PSEN2, or APP genes, while late-onset cases may be associated with the inheritance of the APOE gene. However, due to its polymorphic nature, the presence of APOE does not guarantee disease development but rather increases susceptibility. Nonetheless, inheritance patterns and the presence of mutations leading to the development of Alzheimer's disease remain incompletely

understood and require further research.[5, 6, 7, 8] Nevertheless, genetic factors are not the sole contributors to the risk of developing Alzheimer's disease. Numerous studies have identified insulin resistance, obesity, metabolic syndrome, and diabetes as risk factors for Alzheimer's disease, alongside aging. These conditions are closely associated with abnormalities in glucose and insulin metabolism.[9, 10] The development of Alzheimer's disease is driven by the accumulation of amyloid plaques and tau protein, alongside oxidative stress and inflammation, which damage neurons and advance the disease. Glucose and insulin are essential for proper neuronal function. Many studies have revealed that insulin resistance contributes to increased beta-amyloid deposition and tau protein hyperphosphorylation. Elevated insulin levels also heighten vascular reactivity and inflammation, leading to neurodegeneration. Insulin resistance is thus a key pathomechanism of AD. Moreover, hyperglycemia-induced pathological changes reduce neuronal autophagy and accelerate disease progression.[11, 12, 13, 14] Therefore, some authors refer to AD as type 3 diabetes.[15] Currently approved medications, such as memantine, rivastigmine, donepezil, galantamine, and tacrine, enhance cognitive functions and improve the quality of life for patients with Alzheimer's disease. However, they neither slow the progression of the disease nor offer a cure.[2, 16] Nevertheless, metabolic and molecular similarities and shared risk factors for the development of Alzheimer's disease (AD) and type 2 diabetes have prompted researchers to investigate the potential impact of antidiabetic drugs on the progression of AD. In recent years, particular attention has been drawn to novel medications, specifically glucagon-like peptide-1 (GLP-1) receptor agonists. Our primary objective will be to elucidate the role of GLP-1 analogues and their potential use in the treatment of Alzheimer's disease.

Could Antidiabetic Drugs Be Effective in Treating Alzheimer's Disease? The Relationship Between T2D and AD

The brain relies on glucose as its primary energy source, and insulin facilitates glucose uptake into cells. When cells become unresponsive to insulin signals, insulin resistance develops, causing glucose levels within cells, including neurons, to decline. This disrupts the formation of synapses—connections between neurons—impairing cognitive function and information transfer. Such effects are observed in both type 2 diabetes (T2D) patients and individuals with Alzheimer's disease (AD), highlighting a shared metabolic dysfunction that may contribute to cognitive decline.[17] Altmann et al. demonstrated that glucose hypometabolism in the brains of AD patients occurs 10–20 years before the onset of clinical symptoms.[18] Studies also revealed that insulin resistance contributes to brain atrophy in regions

characteristic of Alzheimer's disease, including the parietal, temporal, and frontal cortices.[19] Another negative impact of insulin resistance is the weakening of the blood-brain barrier (BBB). As a result, harmful substances can infiltrate the central nervous system, triggering inflammation and neurodegeneration.[20] It is also important to note that the disruption of the BBB is associated with gut dysbiosis—an imbalance in gut bacteria that regulate the balance between reactive oxygen species production and antioxidant defenses. Consequently, pro-inflammatory molecules enter the bloodstream and cross the BBB. Gut dysbiosis is observed in both T2D and AD.[21] Furthermore, certain bacteria can influence neurotransmitter metabolism, including GABA, which plays a role in brain aging.[22] Additionally, altered gut microbiota has been linked to β-amyloid accumulation in the brain.[23] Another connection between T2D and AD lies in the interaction between amylin and β-amyloid. These are two peptides with distinct roles but similar structures. Amylin, produced by pancreatic islets, forms amyloid deposits in T2D, impairing insulin secretion. Similar deposits have been observed in the brains of individuals with both T2D and AD.[24] Research suggests that amylin can cross the BBB and interact with β-amyloid, promoting its accumulation.[25] Furthermore, neurofibrillary tau protein tangles accumulate in the brains of AD patients. It has been observed that insulin resistance exacerbates tau hyperphosphorylation in the brains of patients with T2D.[11] Insulin resistance, hypercholesterolemia and dyslipidemia contribute to inflammation, which promotes β-amyloid formation and, in turn, amplifies the existing inflammation, creating a vicious cycle.[26] This inflammation triggers oxidative stress, leading to mitochondrial damage, cellular injury, and impaired neurogenesis, disrupting neurotransmitter balance. As result of this, acetylcholine levels decline in AD due to cholinergic neuron damage.[27] Moreover, studies on aging rats have shown that increasing IGF-1 levels in the hippocampus enhances learning and reduces cognitive deficits.[28] These findings highlight that T2D medications may serve as a therapeutic option for AD, often termed type 3 diabetes.

How Do GLP-1 Analogs Work?

GLP-1 analogs are medications primarily used in the treatment of type 2 diabetes. Their mechanism of action is based on mimicking the effects of the endogenous glucagon-like peptide-1 (GLP-1), a hormone secreted by the small intestine following food intake. This hormone acts as an incretin by stimulating insulin secretion from pancreatic β-cells in response to rising blood glucose levels. Additionally, GLP-1 inhibits the secretion of glucagon from pancreatic α-cells, but only when blood glucose levels are elevated above fasting levels. This

glucose-dependent mechanism minimizes the risk of hypoglycemia.[29, 30] GLP-1 plays a protective role in pancreatic β-cells by preventing their programmed cell death and promoting their growth and differentiation. These functions are vital for preserving pancreatic health.[31] Thus, GLP-1 plays a critical role in carbohydrate metabolism by regulating blood glucose levels and enhancing insulin sensitivity. GLP-1 influences gastric function by slowing gastric emptying, which delays digestion and the absorption of glucose into the bloodstream. This mechanism helps stabilize blood glucose levels after meals. Additionally, GLP-1 reduces gastric acid secretion. Collectively, these actions contribute to improved glycemic control and regulation of digestive processes.[32] GLP-1 has the ability to cross the blood-brain barrier, and its receptors are distributed throughout the central nervous system. These receptors are located in regions such as the hypothalamus, thalamus, hippocampus, cortex, and brainstem nuclei.[33] Moreover, studies have shown that GLP-1 can also be synthesized in the central nervous system by neurons within the nucleus of the solitary tract.[31, 34] Under normal physiological conditions, GLP-1 has a short half-life of approximately 1–2 minutes due to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). To address this limitation, scientists have developed two classes of drugs: DPP-4 inhibitors, such as linagliptin and sitagliptin, and GLP-1 analogs (also named GLP-1 receptor agonists), including semaglutide, liraglutide, exenatide, lixisenatide, and dulaglutide, which mimic GLP-1 while resisting DPP-4 degradation. (Table 1) GLP-1 analogs and their mechanisms of action form the focus of this review. Some GLP-1 analogs, similar to the native GLP-1 hormone, have the capacity to cross the blood brain barrier (BBB), allowing them to directly influence central nervous system functions.[35]

Table 1.[36, 37]

GLP-1 receptor agonists					
Parameters	Liraglutide	Semaglutide	Dulaglutide	Exenatide	Lixisenatide
Tmax [h]	9-12	165-184	90	2.4	3
Bioavailability [%]	55	89	47-65	22-25	N/A
Ability to cross the BBB	YES	NO	NO	YES	YES

Explanation of abbreviations: Tmax: time to reach maximum concentration; NA: not available.

GLP-1 receptor agonists act directly on the hypothalamus, targeting brain regions that regulate hunger and satiety. Studies have shown that these drugs reduce snacking, enhance feelings of fullness, and decrease overall energy intake. This leads to weight loss in individuals,

including those with diabetes or obesity, as well as in healthy populations.[32, 38] Research indicates that GLP-1 receptor agonists may exhibit neuroprotective effects, enhancing neuronal function and survival. These agents could potentially mitigate the risk or slow the progression of neurodegenerative conditions. Evidence suggests that GLP-1 receptor agonists support synaptic integrity by preserving existing connections and promoting the formation of new synapses, underscoring their therapeutic potential for Alzheimer's disease.[39, 40]

The Effect of GLP-1 in Type 3 Diabetes

Neuroinflammation is a hallmark of Alzheimer's disease, compromising the blood-brain barrier and allowing harmful substances and signaling molecules like TNF-a and Il-b to infiltrate the brain. This inflammatory state damages neurons and can lead to cells death. Research indicates that GLP-1 analogues such as liraglutide, exenatide, and lixisenatide possess neuroprotective properties.[41–43] Astrocytes and microglia play a significant role in triggering neuroinflammation. Studies have demonstrated that liraglutide treatment reduces microglial activation and decreases levels of pro-inflammatory cytokines, such as IL-6 and IL-1β.[44] Additionally, another study found that administering liraglutide mitigates neuroinflammation while preventing memory impairment in APP-PS1 mice models of Alzheimer's disease.[45] These drugs have been shown to reduce neuroinflammation and enhance cognitive function, making them promising candidates for addressing both the symptoms and progression of Alzheimer's disease.

GLP-1 receptor agonists have shown the ability to reduce beta-amyloid accumulation and tau hyperphosphorylation in the brain, thereby improving cognitive functions. Studie by Perry et al. demonstrated that GLP-1 reduces endogenous beta-amyloid levels.[46] Other research highlighted that lixisenatide decreases neurofibrillary tangles and amyloid plaques,[47,48] while liraglutide and dulaglutide have been shown to lower tau hyperphosphorylation.[49–51] These mechanisms collectively enhance memory and cognitive abilities, suggesting the therapeutic potential of GLP-1 analogs in neurodegenerative diseases such as AD.

One of the key functions of GLP-1 is to regulate cell growth and differentiation while interrupting pro-apoptotic processes.[52] Studies have shown that intraperitoneal injection of GLP-1 analogs enhances neural stem cells and neurogenesis in the dentate gyrus.[53] Additionally, prolonged administration of liraglutide has been found to stimulate the proliferation of stem cells and their differentiation into mature neurons.[54] Moreover, research indicates that GLP-1 analogs enhance synaptic plasticity. Liraglutide has been shown to prevent synapse loss in the

hippocampus of APP/PS1 mice and improve synaptic plasticity in control mice.[55] Another study demonstrated that liraglutide protects synapses from damage caused by beta-amyloid.[56] These findings highlight the potential of GLP-1 analogs to support synaptic function and positively influence neural stem cell proliferation and differentiation, both of which are critical factors in preserving cognitive abilities and addressing neurodegenerative diseases such as AD.

Research suggests that GLP-1 analogs may reduce oxidative stress and associated mitochondrial dysfunction. Spielman et al. demonstrated that these drugs decrease oxidative stress in microglia by inhibiting the accumulation of reactive oxygen species and nitric oxide (NO).[57] Additionally, Xie et al. reported that liraglutide alleviates mitochondrial dysfunction,[58] while other studies have shown similar effects for exenatide.[59] A significant pathological mechanism in neurodegenerative diseases is neuronal apoptosis. Numerous studies have shown that GLP-1 analogs can inhibit signaling pathways leading to apoptosis.[60–62] Perry et al. demonstrated that GLP-1 and exendin-4 protects hippocampal neurons in cultured rats by preventing apoptosis.[63] Similarly, other research revealed that exendin-4 counteracts apoptosis induced by amyloid-b.[64] On the other hand, GLP-1 analogs possess the ability to enhance autophagy, which serves to protect neurons from damage. Research has shown that treatment with exenatide-4 in diabetic rats induced autophagy in cortical cells.[65] Similarly, other studies have demonstrated comparable effects for semaglutide and liraglutide,[66, 67] highlighting their role in promoting neuronal resilience. These findings further emphasize the therapeutic potential of GLP-1 analogs in addressing neurodegenerative conditions.

Insulin resistance in the brain, which is observed in AD (sometimes referred to as "type 3 diabetes"), plays a significant role in its pathology. Studies have demonstrated that treatment with liraglutide improves neuronal insulin sensitivity. This improvement is accompanied by a reduction in amyloid-beta formation and decreased tau hyperphosphorylation, which are key features of AD.[68] Liraglutide improves insulin signaling by reducing phosphorylation of the ERK and JNK pathways, which are linked to tau hyperphosphorylation.[69] Exendin-4 increases insulin levels and enhances insulin receptor signaling in the hippocampus, but its ability to reduce tau hyperphosphorylation depends on the presence of insulin.[70] This suggests that the neuroprotective effects of GLP-1 receptor agonists require proper insulin signaling. Gejl et al. demonstrated that 26 weeks of liraglutide treatment in AD patients prevented a decline in glucose metabolism, which is often linked to cognitive impairment and disease progression.[71] Furthermore, patients with T2DM, who are at higher risk of developing AD, showed a reduced risk of AD when treated with liraglutide, exenatide, or dulaglutide.[72] Studies show that GLP-1

analogs demonstrate therapeutic potential associated with the development and progression of AD, known as type 3 diabetes.

Conclusion

In conclusion, GLP-1 analogs exhibit a multifaceted neuroprotective potential in Alzheimer's disease, a condition often referred to as type 3 diabetes due to its association with brain insulin resistance. These therapies address key pathological processes, including reducing neuroinflammation, mitigating oxidative stress, and enhancing mitochondrial function. They also support synaptic plasticity, prevent neuronal apoptosis, and promote neural stem cell proliferation and differentiation. Furthermore, GLP-1 analogs improve brain insulin sensitivity, reducing tau hyperphosphorylation and amyloid-beta accumulation - hallmarks of AD pathology. Collectively, these effects contribute to preserving cognitive function and slowing disease progression. These therapies represent a new hope in the treatment of AD. However, further extensive research is necessary to fully understand their mechanisms and long-term efficacy.

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References:

1. Talbot K, Wang HY. The nature, significance, and glucagon-like peptide-1 analog treatment of brain insulin resistance in Alzheimer's disease. *Alzheimers Dement J Alzheimers Assoc*. 2014;10(1 Suppl):S12-25. doi:10.1016/j.jalz.2013.12.007

2. Nguyen TT, Nguyen TTD, Nguyen TKO, Vo TK, Vo VG. Advances in developing therapeutic strategies for Alzheimer's disease. *Biomed Pharmacother Biomedecine Pharmacother*. 2021;139:111623. doi:10.1016/j.biopha.2021.111623

3. The Epidemiology of Alzheimer's Disease Modifiable Risk Factors and Prevention - PubMed. Accessed December 9, 2024. https://pubmed.ncbi.nlm.nih.gov/34101789/

4. Abeysinghe AADT, Deshapriya RDUS, Udawatte C. Alzheimer's disease; a review of the pathophysiological basis and therapeutic interventions. *Life Sci*. 2020;256:117996. doi:10.1016/j.lfs.2020.117996

5. Clark K, Leung YY, Lee WP, Voight B, Wang LS. Polygenic Risk Scores in Alzheimer's Disease Genetics: Methodology, Applications, Inclusion, and Diversity. *J Alzheimers Dis*. 89(1):1-12. doi:10.3233/JAD-220025

6. Uddin MS, Hasana S, Hossain MF, et al. Molecular Genetics of Early- and Late-Onset Alzheimer's Disease. *Curr Gene Ther*. 2021;21(1):43-52. doi:10.2174/1566523220666201123112822

7. Cacace R, Sleegers K, Van Broeckhoven C. Molecular genetics of early-onset Alzheimer's disease revisited. *Alzheimers Dement*. 2016;12(6):733-748. doi:10.1016/j.jalz.2016.01.012

8. Lanoiselée HM, Nicolas G, Wallon D, et al. APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. *PLoS Med*. 2017;14(3):e1002270. doi:10.1371/journal.pmed.1002270

9. Wang XF, Lin X, Li DY, et al. Linking Alzheimer's disease and type 2 diabetes: Novel shared susceptibility genes detected by cFDR approach. *J Neurol Sci*. 2017;380:262-272. doi:10.1016/j.jns.2017.07.044

10. Li L, Cavuoto M, Biddiscombe K, Pike KE. Diabetes Mellitus Increases Risk of Incident Dementia in APOEε4 Carriers: A Meta-Analysis. *J Alzheimers Dis JAD*. 2020;74(4):1295-1308. doi:10.3233/JAD-191068

11. Li X, Song D, Leng SX. Link between type 2 diabetes and Alzheimer's disease: from epidemiology to mechanism and treatment. *Clin Interv Aging*. 2015;10:549-560. doi:10.2147/CIA.S74042

12. Miao Y, Guo D, Li W, Zhong Y, Guo Y. Diabetes Promotes Development of Alzheimer's Disease Through Suppression of Autophagy. *J Alzheimer's Dis*. 2019;69(1):289-296. doi:10.3233/JAD-190156

13. Kellar D, Craft S. Brain insulin resistance in Alzheimer's disease and related disorders: mechanisms and therapeutic approaches. *Lancet Neurol*. 2020;19(9):758-766. doi:10.1016/S1474-4422(20)30231-3

14. Akhtar A, Sah SP. Insulin signaling pathway and related molecules: Role in neurodegeneration and Alzheimer's disease. *Neurochem Int*. 2020;135:104707. doi:10.1016/j.neuint.2020.104707

15. Nguyen TT, Ta QTH, Nguyen TKO, Nguyen TTD, Van Giau V. Type 3 Diabetes and Its Role Implications in Alzheimer's Disease. *Int J Mol Sci*. 2020;21(9):3165. doi:10.3390/ijms21093165

16. Kevadiya BD, Ottemann BM, Thomas MB, et al. Neurotheranostics as Personalized Medicines. *Adv Drug Deliv Rev*. 2019;148:252-289. doi:10.1016/j.addr.2018.10.011

17. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat Rev Neurol*. 2018;14(3):168-181. doi:10.1038/nrneurol.2017.185

18. Altmann A, Ng B, Landau SM, Jagust WJ, Greicius MD. Regional brain hypometabolism is unrelated to regional amyloid plaque burden. *Brain*. 2015;138(12):3734-3746. doi:10.1093/brain/awv278

19. Baker LD, Cross D, Minoshima S, Belongia D, Watson GS, Craft S. INSULIN RESISTANCE IS ASSOCIATED WITH ALZHEIMER-LIKE REDUCTIONS IN

REGIONAL CEREBRAL GLUCOSE METABOLISM FOR COGNITIVELY NORMAL ADULTS WITH PRE-DIABETES OR EARLY TYPE 2 DIABETES. *Arch Neurol*. 2011;68(1):51-57. doi:10.1001/archneurol.2010.225

20. Park SA. A Common Pathogenic Mechanism Linking Type-2 Diabetes and Alzheimer's Disease: Evidence from Animal Models. *J Clin Neurol Seoul Korea*. 2011;7(1):10-18. doi:10.3988/jcn.2011.7.1.10

21. Chen C, Ahn EH, Kang SS, Liu X, Alam A, Ye K. Gut dysbiosis contributes to amyloid pathology, associated with C/EBPβ/AEP signaling activation in Alzheimer's disease mouse model. *Sci Adv*. 2020;6(31):eaba0466. doi:10.1126/sciadv.aba0466

22. Strandwitz P, Kim KH, Terekhova D, et al. GABA Modulating Bacteria of the Human Gut Microbiota. *Nat Microbiol*. 2019;4(3):396-403. doi:10.1038/s41564-018-0307-3

23. Kowalski K, Mulak A. Brain-Gut-Microbiota Axis in Alzheimer's Disease. *J Neurogastroenterol Motil*. 2019;25(1):48-60. doi:10.5056/jnm18087

24. Oskarsson ME, Paulsson JF, Schultz SW, Ingelsson M, Westermark P, Westermark GT. In Vivo Seeding and Cross-Seeding of Localized Amyloidosis: A Molecular Link between Type 2 Diabetes and Alzheimer Disease. *Am J Pathol*. 2015;185(3):834-846. doi:10.1016/j.ajpath.2014.11.016

25. Amyloid-β and islet amyloid pathologies link Alzheimer's disease and type 2 diabetes in a transgenic model. doi:10.1096/fj.201700431R

26. Michailidis M, Moraitou D, Tata DA, Kalinderi K, Papamitsou T, Papaliagkas V. Alzheimer's Disease as Type 3 Diabetes: Common Pathophysiological Mechanisms between Alzheimer's Disease and Type 2 Diabetes. *Int J Mol Sci*. 2022;23(5):2687. doi:10.3390/ijms23052687

27. Terry AV, Buccafusco JJ. The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. *J Pharmacol Exp Ther*. 2003;306(3):821-827. doi:10.1124/jpet.102.041616

28. Carro E, Trejo JL, Gomez-Isla T, LeRoith D, Torres-Aleman I. Serum insulin-like growth factor I regulates brain amyloid-beta levels. *Nat Med*. 2002;8(12):1390-1397. doi:10.1038/nm1202-793

29. Reed J, Bain SC, Kanamarlapudi V. Recent advances in understanding the role of glucagon-like peptide 1. *F1000Research*. 2020;9:F1000 Faculty Rev-239. doi:10.12688/f1000research.20602.1

30. Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. *Cell Metab*. 2018;27(4):740-756. doi:10.1016/j.cmet.2018.03.001

31. Yildirim Simsir I, Soyaltin UE, Cetinkalp S. Glucagon like peptide-1 (GLP-1) likes Alzheimer's disease. *Diabetes Metab Syndr Clin Res Rev*. 2018;12(3):469-475. doi:10.1016/j.dsx.2018.03.002

32. Baggio LL, Drucker DJ. Biology of Incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131-2157. doi:10.1053/j.gastro.2007.03.054

33. Cork SC, Richards JE, Holt MK, Gribble FM, Reimann F, Trapp S. Distribution and characterisation of Glucagon-like peptide-1 receptor expressing cells in the mouse brain. *Mol Metab*. 2015;4(10):718-731. doi:10.1016/j.molmet.2015.07.008

34. Vrang N, Larsen PJ. Preproglucagon derived peptides GLP-1, GLP-2 and oxyntomodulin in the CNS: Role of peripherally secreted and centrally produced peptides. *Prog Neurobiol*. 2010;92(3):442-462. doi:10.1016/j.pneurobio.2010.07.003

35. Hunter K, Hölscher C. Drugs developed to treat diabetes, liraglutide and lixisenatide, cross the blood brain barrier and enhance neurogenesis. *BMC Neurosci*. 2012;13:33. doi:10.1186/1471-2202-13-33

36. Złotek M, Kurowska A, Herbet M, Piątkowska-Chmiel I. GLP-1 Analogs, SGLT-2, and DPP-4 Inhibitors: A Triad of Hope for Alzheimer's Disease Therapy. *Biomedicines*. 2023;11(11):3035. doi:10.3390/biomedicines11113035

37. Dong M, Wen S, Zhou L. The Relationship Between the Blood-Brain-Barrier and the Central Effects of Glucagon-Like Peptide-1 Receptor Agonists and Sodium-Glucose Cotransporter-2 Inhibitors. *Diabetes Metab Syndr Obes Targets Ther*. 2022;15:2583-2597. doi:10.2147/DMSO.S375559

38. Turton MD, O'Shea D, Gunn I, et al. A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature*. 1996;379(6560):69-72. doi:10.1038/379069a0

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

40. Monti G, Gomes Moreira D, Richner M, Mutsaers HAM, Ferreira N, Jan A. GLP-1 Receptor Agonists in Neurodegeneration: Neurovascular Unit in the Spotlight. *Cells*. 2022;11(13):2023. doi:10.3390/cells11132023

41. Reich N, Hölscher C. The neuroprotective effects of glucagon-like peptide 1 in Alzheimer's and Parkinson's disease: An in-depth review. *Front Neurosci*. 2022;16:970925. doi:10.3389/fnins.2022.970925

42. Lee CH, Jeon SJ, Cho KS, et al. Activation of Glucagon-Like Peptide-1 Receptor Promotes Neuroprotection in Experimental Autoimmune Encephalomyelitis by Reducing

Neuroinflammatory Responses. *Mol Neurobiol*. 2018;55(4):3007-3020. doi:10.1007/s12035-017-0550-2

43. Bomba M, Granzotto A, Castelli V, et al. 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 JAD*. 2019;70(3):793-810. doi:10.3233/JAD-190237

44. Parthsarathy V, Hölscher C. The type 2 diabetes drug liraglutide reduces chronic inflammation induced by irradiation in the mouse brain. *Eur J Pharmacol*. 2013;700(1-3):42-50. doi:10.1016/j.ejphar.2012.12.012

45. McClean PL, Jalewa J, Hölscher C. Prophylactic liraglutide treatment prevents amyloid plaque deposition, chronic inflammation and memory impairment in APP/PS1 mice. *Behav Brain Res*. 2015;293:96-106. doi:10.1016/j.bbr.2015.07.024

46. Perry T, Lahiri DK, Sambamurti K, et al. Glucagon-like peptide-1 decreases endogenous amyloid-beta peptide (Abeta) levels and protects hippocampal neurons from death induced by Abeta and iron. *J Neurosci Res*. 2003;72(5):603-612. doi:10.1002/jnr.10611

47. Cai HY, Yang JT, Wang ZJ, et al. Lixisenatide reduces amyloid plaques, neurofibrillary tangles and neuroinflammation in an APP/PS1/tau mouse model of Alzheimer's disease. *Biochem Biophys Res Commun*. 2018;495(1):1034-1040. doi:10.1016/j.bbrc.2017.11.114

48. McClean PL, Hölscher C. Lixisenatide, a drug developed to treat type 2 diabetes, shows neuroprotective effects in a mouse model of Alzheimer's disease. *Neuropharmacology*. 2014;86:241-258. doi:10.1016/j.neuropharm.2014.07.015

49. Zhang Y, Xie JZ, Xu XY, et al. Liraglutide Ameliorates Hyperhomocysteinemia-Induced Alzheimer-Like Pathology and Memory Deficits in Rats via Multi-molecular Targeting. *Neurosci Bull*. 2019;35(4):724-734. doi:10.1007/s12264-018-00336-7

50. Qi L, Ke L, Liu X, et al. Subcutaneous administration of liraglutide ameliorates learning and memory impairment by modulating tau hyperphosphorylation via the glycogen synthase kinase-3β pathway in an amyloid β protein induced alzheimer disease mouse model. *Eur J Pharmacol*. 2016;783:23-32. doi:10.1016/j.ejphar.2016.04.052

51. Chen S, An FM, Yin L, et al. Glucagon-like peptide-1 protects hippocampal neurons against advanced glycation end product-induced tau hyperphosphorylation. *Neuroscience*. 2014;256:137-146. doi:10.1016/j.neuroscience.2013.10.038

52. Holst JJ, Burcelin R, Nathanson E. Neuroprotective properties of GLP-1: theoretical and practical applications. *Curr Med Res Opin*. 2011;27(3):547-558. doi:10.1185/03007995.2010.549466

53. McGovern SFJ, Hunter K, Hölscher C. Effects of the glucagon-like polypeptide-1 analogue (Val8)GLP-1 on learning, progenitor cell proliferation and neurogenesis in the C57B/16 mouse brain. *Brain Res*. 2012;1473:204-213. doi:10.1016/j.brainres.2012.07.029

54. Parthsarathy V, Hölscher C. Chronic treatment with the GLP1 analogue liraglutide increases cell proliferation and differentiation into neurons in an AD mouse model. *PloS One*. 2013;8(3):e58784. doi:10.1371/journal.pone.0058784

55. McClean PL, Parthsarathy V, Faivre E, Hölscher C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. *J Neurosci Off J Soc Neurosci*. 2011;31(17):6587-6594. doi:10.1523/JNEUROSCI.0529-11.2011

56. Batista AF, Forny-Germano L, Clarke JR, et al. 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

57. Spielman LJ, Gibson DL, Klegeris A. Incretin hormones regulate microglia oxidative stress, survival and expression of trophic factors. *Eur J Cell Biol*. 2017;96(3):240-253. doi:10.1016/j.ejcb.2017.03.004

58. Xie Y, Zheng J, Li S, et al. 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

59. Garabadu D, Verma J. Exendin-4 attenuates brain mitochondrial toxicity through PI3K/Akt-dependent pathway in amyloid beta (1-42)-induced cognitive deficit rats. *Neurochem Int*. 2019;128:39-49. doi:10.1016/j.neuint.2019.04.006

60. Kimura R, Okouchi M, Fujioka H, et al. Glucagon-like peptide-1 (GLP-1) protects against methylglyoxal-induced PC12 cell apoptosis through the PI3K/Akt/mTOR/GCLc/redox signaling pathway. *Neuroscience*. 2009;162(4):1212-1219. doi:10.1016/j.neuroscience.2009.05.025

61. Zhang H, Song B, Zhu W, et al. Glucagon-like peptide-1 attenuated carboxymethyl lysine induced neuronal apoptosis via peroxisome proliferation activated receptor-γ. *Aging*. 2021;13(14):19013-19027. doi:10.18632/aging.203351

62. Chen S, Yin L, Xu Z, et al. Inhibiting receptor for advanced glycation end product (AGE) and oxidative stress involved in the protective effect mediated by glucagon-like peptide-1 receptor on AGE induced neuronal apoptosis. *Neurosci Lett*. 2016;612:193-198. doi:10.1016/j.neulet.2015.12.007

63. Perry T, Haughey NJ, Mattson MP, Egan JM, Greig NH. Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. *J Pharmacol Exp Ther*. 2002;302(3):881-888. doi:10.1124/jpet.102.037481

64. Qiu C, Wang YP, Pan XD, Liu XY, Chen Z, Liu LB. Exendin-4 protects Aβ(1-42) oligomer-induced PC12 cell apoptosis. *Am J Transl Res*. 2016;8(8):3540-3548.

65. Candeias E, Sebastião I, Cardoso S, et al. Brain GLP-1/IGF-1 Signaling and Autophagy Mediate Exendin-4 Protection Against Apoptosis in Type 2 Diabetic Rats. *Mol Neurobiol*. 2018;55(5):4030-4050. doi:10.1007/s12035-017-0622-3

66. Chang YF, Zhang D, Hu WM, Liu DX, Li L. Semaglutide-mediated protection against Aβ correlated with enhancement of autophagy and inhibition of apotosis. *J Clin Neurosci Off J Neurosurg Soc Australas*. 2020;81:234-239. doi:10.1016/j.jocn.2020.09.054

67. Panagaki T, Michael M, Hölscher C. Liraglutide restores chronic ER stress, autophagy impairments and apoptotic signalling in SH-SY5Y cells. *Sci Rep*. 2017;7(1):16158. doi:10.1038/s41598-017-16488-x

68. Jantrapirom S, Nimlamool W, Chattipakorn N, et al. 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

69. Xiong H, Zheng C, Wang J, et al. The neuroprotection of liraglutide on Alzheimer-like learning and memory impairment by modulating the hyperphosphorylation of tau and neurofilament proteins and insulin signaling pathways in mice. *J Alzheimers Dis JAD*. 2013;37(3):623-635. doi:10.3233/JAD-130584

70. Yang Y, Ma D, Xu W, et al. Exendin-4 reduces tau hyperphosphorylation in type 2 diabetic rats via increasing brain insulin level. *Mol Cell Neurosci*. 2016;70:68-75. doi:10.1016/j.mcn.2015.10.005

71. Gejl M, Gjedde A, Egefjord L, et al. 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

72. Akimoto H, Negishi A, Oshima S, et al. Antidiabetic Drugs for the Risk of Alzheimer Disease in Patients With Type 2 DM Using FAERS. *Am J Alzheimers Dis Other Demen*. 2020;35:1533317519899546. doi:10.1177/1533317519899546