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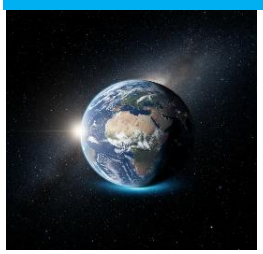

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GLP1 receptor agonists and their role in the therapy of neurodegenerative diseases - a literature review

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Abstract

Introduction: GLP-1 receptor agonists (GLP-1RAs) are drugs used in the treatment of type 2 diabetes and obesity, and are believed to have potential neuroprotective properties. Decreased glucose metabolism in the brain, the development of neuronal insulin resistance, and abnormal tau protein phosphorylation and amyloid-β deposition all play important roles in the pathogenesis of Alzheimer's disease (AD). Numerous preclinical studies in animal models have demonstrated that GLP-1 analogs, such as liraglutide and lixisenatide, are capable of crossing the blood-brain barrier, stimulating neurogenesis, limiting tau hyperphosphorylation, reducing amyloid-β deposition, and improving synaptic and cognitive functions. Data from clinical and observational studies suggest that GLP-1RA use in patients with type 2 diabetes is associated with a reduced risk of developing dementia, including AD. In large retrospective analyses, semaglutide therapy reduced the likelihood of a first diagnosis of Alzheimer's disease by 40–70% compared with other antidiabetic agents. In a randomized trial, liraglutide prevented the decline in brain glucose metabolism in patients with AD, but had no significant effect on amyloid-β levels or cognitive function. The neuroprotective effects of GLP-1RA are believed to result from, among other factors, improved insulin signaling, inhibited GSK-3β activity, reduced oxidative stress and inflammation, and promoted synaptic plasticity and neuronal survival.

Aim: The aim of this article is to explore the role of GLP1 receptor agonists in the therapy of neurodegenerative diseases.

Review methods: A comprehensive analysis of research papers available on PubMed and Google Scholar was conducted using keywords: Alzheimer's disease, neurodegeneration, GLP-1 analogues, liraglutide, dementia, tau, diabetes, obesity

Conclusion: Accumulating evidence suggests that GLP-1 agonists may be a promising therapeutic option for the prevention and treatment of neurodegenerative diseases. However, further randomized clinical trials are necessary to confirm their efficacy in patients with Alzheimer's disease.

Keywords: Alzheimer's disease, neurodegeneration, GLP-1 analogues, liraglutide, dementia, tau, diabetes, obesity

Introduction:

Alzheimer's disease (AD) is characterized by, among other things, impaired brain glucose metabolism, neuronal insulin resistance, hyperphosphorylation of tau protein, and amyloid-β accumulation, which leads to progressive synaptic dysfunction and cognitive decline. In recent years, GLP-1 receptor agonists (GLP-1RAs), primarily used to treat type 2 diabetes and obesity, have attracted increasing interest due to their potential neuroprotective effects. In a clinical study by Gejl et al. [1] 6 months of liraglutide therapy inhibited the decline in cerebral glucose metabolism, assessed by 8F-FDG PET, typically observed in patients with AD. Despite the lack of effect on amyloid β and cognitive outcomes, the authors suggest that GLP-1RA may stabilize brain energy function in the course of the disease. Furthermore, in patients with type 2 diabetes, a broad analysis of medical records (over 1 million people) showed that semaglutide use is associated with a 40–70% reduced risk of a first-time diagnosis of Alzheimer's disease compared with other antidiabetic drugs, with the strongest effect compared with insulin and a smaller but significant effect compared with other GLP-1RAs. Experiments on animal models provide further evidence: in the APP/PS1 transgenic mouse model (closing already complex amyloid plaques), administration of lixisenatide at doses ranging from 1 to 10 nmol/kg for 10 weeks improved memory and synaptic plasticity (LTP), inhibited synapse loss, limited amyloid burden and reduced microglial inflammation – the effect was stronger even at lower doses compared to liraglutide [2,3,4].

GLP-1 Analogues and Brain Glucose Metabolism

Alzheimer's disease is associated with a decline in brain glucose metabolism. One study examined the effectiveness of liraglutide, a GLP-1 hormone analogue, in preventing this phenomenon. It examined its effects on the accumulation of amyloid beta in the brain, glucose metabolism levels (CMRglc), and cognitive performance in patients with Alzheimer's disease. Thirty-eight patients with Alzheimer's disease participated in this study, randomly divided into two groups: those receiving liraglutide (18 individuals) and those receiving a placebo (20 individuals) for six months. A PET scan was performed using the tracers 11C PIB for amyloid beta and 18F FDG as a marker of glucose metabolism. Cognitive outcomes were assessed using the WMS-IV test. Regarding glucose metabolism, a decline in placebo-treated patients, typical of Alzheimer's disease, was observed. This was noticeable in many brain regions, including the cerebral cortex, in the parietal, temporal, and occipital lobes, the cerebellum, and the precuneus, an area that plays a key role in, among other things, visual processing and episodic memory. [2,5]. In patients taking liraglutide, no decrease in CMRglc was observed, and even an increase in glucose metabolism, although statistically insignificant, was observed in some regions. Furthermore, it seems significant that changes in CMRglc were clearly noticeable in AD-sensitive areas, such as the precuneus, temporal, and parietal lobes. These results suggest that liraglutide may have the ability to halt the downward trend in glucose metabolism observed during the progression of Alzheimer's disease [5]. Regarding amyloid beta levels, no significant differences were found between groups, suggesting that liraglutide, although it significantly affects glucose metabolism, its effect on amyloid plaque deposition is uncertain. No significant differences were found in cognitive function between groups, while orientation deteriorated in the placebo group. This study excluded patients with diabetes, and none of the patients were taking antidiabetic medications [5].

GLP-1 Analogs and Their Impact on the Risk of Neurodegenerative Diseases

In the study by Sun et al. [6], a retrospective analysis of over 174,000 patients (87,229 in each group) was performed using the global TriNetX database, which covers data from 2004 to 2024. Patients were required to have a diagnosis of type 2 diabetes, initiate treatment with GLP-1 analogs or metformin as a first-line medication for at least 6 months, and were followed up for 24 months after treatment initiation. Exclusion criteria included prior use of a drug from the second group, diagnosis of dementia, cognitive impairment, neurological impairment,

psychiatric impairment, cerebrovascular disease, alcohol-related cognitive impairment, end-stage renal disease or dialysis within 6 months prior to treatment, or use of modern antidiabetic medications such as flozins or DPP-4 inhibitors prior to treatment. One group included patients who received a GLP-1 agonist as their first medication after being diagnosed with type 2 diabetes, while the other group included patients who began treatment for newly diagnosed T2DM with metformin. This analysis revealed that dementia occurred in 2.4% of patients taking a GLP-1 agonist, compared with 4.8% of patients taking metformin. This represents an absolute reduction of 2.4%. Regarding specific types of dementia, Alzheimer's disease was diagnosed in 1.2% of patients taking GLP-1 receptor agonists, compared to 2.6% of those taking metformin, corresponding to an AHR of 0.92, 95% CI 0.85-0.99. For other non-vascular dementias, the risk of their occurrence was 1% in the GLP-1-RA group and 2.4% in the metformin group (AHR 0.88, 95% CI 0.81-0.96).

For vascular dementia, the risk of its occurrence was 0.7% in the GLP-1 receptor agonist group and 1.3% in the metformin group, but the difference was not statistically significant. When analyzing patients by age, the greatest benefits were achieved by those aged 60-79 years (AHR 0.85) and those over 80 years (AHR 0.80). Gender-wise, women experienced greater benefits – AHR 0.83 for women and AHR 0.90 for men, respectively. Taking race into account, the greatest benefits were achieved by Caucasian patients.

Interestingly, the neuroprotective effect of GLP-1 receptor agonists was enhanced by the concomitant use of statins (AHR 0.82) and insulin (AHR 0.78). The authors emphasize that this is the largest study to date comparing these two therapies in terms of dementia risk. However, due to its retrospective nature and the limitations of using medical record data, further randomized trials are necessary, allowing confirmation of the results obtained in this study.[6]

In a study published by Lin et al. [7], a retrospective cohort study based on the analysis of electronic health record data from the TriNetX US network, 60,860 adults with type 2 diabetes and obesity who used the GLP-1 receptor agonists semaglutide and tirzepatide or other antidiabetic medications were observed for at least one year after initiation of treatment. Their impact on the risk of developing neurodegenerative diseases—Alzheimer's disease, vascular dementia, and other types of dementia—as well as mild cognitive impairment (MCI) and Parkinson's disease—was also examined. Their impact on overall mortality was also examined. Two groups were identified: a group taking GLP-1RA (semaglutide/tirzepatide), which comprised 30,430 patients, and a group taking other antidiabetic medications, including metformin, sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors Patients taking GLP-1RAs

had a 37% lower risk of overall dementia compared to the group taking other antidiabetic medications (HR = 0.63, 95% CI = 0.50-0.81). This was most evident in the so-called "other types of dementia," while for Alzheimer's disease and vascular dementia, this difference was not statistically significant.

No significant differences were found between the groups for mild cognitive impairment and Parkinson's disease. In the GLP-1 RA group, the risk of death was 30% lower compared to the control group (HR = 0.70, 95% CI = 0.63-0.78), while the risk of ischemic stroke was reduced by 19% in favor of GLP-1RA drugs. Analyzing the individual subgroups, we see that the greatest benefits were achieved by individuals ≥60 years of age, women, and patients with a BMI of 30-40. Additionally, in the case of dementia, a greater risk reduction was observed with semaglutide, while tirzepatide was more effective in reducing the risk of ischemic stroke and mortality. In summary, semaglutide and tirzepatide are superior to other antidiabetic medications in reducing the risk of overall dementia (due to a reduction in the risk of other types of dementia), ischemic stroke, and overall mortality, suggesting a potential neuroprotective profile of these medications. [7]. The meta-analysis by Seminer et al. [8], examined whether the use of cardioprotective medications, including GLP-1 receptor agonists, was associated with a lower risk of dementia and cognitive impairment compared to placebo. Both groups included approximately 80,000 participants. SGLT2 inhibitors, pioglitazone, and GLP-1 receptor agonists were studied, respectively. The minimum follow-up was 6 months, with a mean follow-up of 31 months. Only GLP-1 receptor agonists statistically significantly reduced the risk of overall dementia, with no statistically significant reduction for specific types of dementia. [8]

GLP-1 Analogues and Their Action at the Cellular Level

The McClean and Hölscher study [9] examined whether lixisenatide, a GLP-1 receptor agonist, crosses the blood-brain barrier and exerts neuroprotective effects in the presence of amyloid plaques in the brain. The results were compared to previous studies with liraglutide [10]. The study used APP/PS1 transgenic mice with Alzheimer's disease, which were administered lixisenatide daily at a dose of 1 nmol/kg or 10 nmol/kg for 10 weeks. Mice receiving saline served as the control group. Results were measured using memory and learning tests, a hippocampal synaptic plasticity (LTP) test, and analysis of synapse count, amyloid plaque count, and microglial activity. Mice receiving lixisenatide were shown to improve memory and

learning, enhance LTP, particularly at lower doses (1 nmol/kg), and prevent hippocampal synapse loss, reducing amyloid plaques and brain inflammation. Furthermore, these effects were observed at lower doses than those obtained with liraglutide. This may indicate a neuroprotective effect of lixisenatide in Alzheimer's disease. This suggests that GLP-1 agonists may be a potential treatment for Alzheimer's disease, but these studies are in animal studies and further clinical trials in humans are necessary. In a study by Parthsarathy and Hölscher [11], the effect of the GLP-1 analog liraglutide on neurogenesis in APP/PS1 mice with Alzheimer's disease and wild-type (WT) mice was examined. Forty-eight APP/PS1 mice and 48 wild-type mice were used in the study. We examined the effect of short-term (7 days) and long-term (37 days) intraperitoneal administration of liraglutide at a dose of 25 nmol/kg on the proliferation of progenitor cells and their differentiation into neurons in the hippocampus in different age groups (3, 6, 12, and 15 months). Saline was administered as a control.

Immunohistochemical staining was used: BrdU and Ki67 to assess cell proliferation, DCX as a marker of immature neurons, NeuN as a marker of mature neurons, GFAP as a marker of astrocytes, and Iba1 as a marker of microglia. Brain sections including the hippocampus were used. It was shown that the proliferation of camellae (BrdU and Ki67 markers) decreased with age and was lower in APP/PS1 mice than in wild-type mice. In mice treated with liraglutide for a short period, cell proliferation increased in APP/PS1 mice and partially in WT mice. The number of neuroblasts (a marker of DCX) also increased, but there was no effect on the number of mature neurons. Chronic treatment with liraglutide significantly increased proliferation and the number of new neurons in both wild-type and Alzheimer's disease mice, particularly in the older groups. There was no effect on the number of new glial cells. Chronic liraglutide administration (37 days) was shown to be significantly more effective than short-term liraglutide administration (7 days). [11] This study concluded that chronic liraglutide administration more effectively supports neurogenesis and the maturation of new neurons, indicating the potential of this drug in the treatment of neurodegenerative diseases, including Alzheimer's disease.

In the study by Hansen et al. [12], transgenic mice with a tau mutation (hTauP301L) were used. From the age of 3 months, they develop age-dependent tau protein phosphorylation and neurofibrillary tangles, which leads to the development of movement problems – so-called clasping – a motor symptom that is indicative of motor dysfunction and nervous system damage, particularly in diseases such as tauopathies, Huntington's disease, and neurodegenerative diseases that damage motor neurons and the cerebellum. Three groups of mice were identified:

hTauP301L mice treated with liraglutide (n=18), hTauP301L mice treated with placebo (n=18), and wild-type mice serving as controls (n=17). In the placebo-treated hTauP301L mice, 61% of mice showed clasping, and survival was 55% by 9 months of age. In the liraglutide group, clasping occurred in 39% of mice, and survival increased to 89% by 9 months of age. This study provides strong preclinical evidence for the neuroprotective effect of the GLP-1 analog liraglutide in the treatment of taupotence. [12]

In a study [13] examining the relationship between type 2 diabetes and Alzheimer's disease and the possibility of preventing abnormal tau protein phosphorylation—one of the key pathogenic factors in Alzheimer's disease, researchers used db/db mice, a well-known animal model of type 2 diabetes. Eighty male db/db mice aged 3-3.5 weeks were enrolled in the study and divided into three groups: liraglutide-treated group – 27 mice (0.1 mg/kg subcutaneously daily); insulin-treated group – 27 mice (0.67 U/kg subcutaneously daily); and control group (saline) – 26 mice. Every two weeks (weeks 0, 2, 4, 6, and 8), 5-7 mice from each group were sacrificed to collect samples for biochemical analyses. Treatment lasted 8 weeks, and doses were administered daily subcutaneously just before the onset of the dark cycle. The materials studied included blood, cerebrospinal fluid, and hippocampal formation. Every two weeks, blood, CSF, and hippocampal tissue samples were collected from 5–7 mice for analysis of glucose levels, insulin levels, and protein phosphorylation (tau, Akt, GSK-3β).[13]

Insulin functions in the brain similarly to other tissues. Binding to its receptor activates the PI3K-PIP3-Akt pathway. Active Akt, a kinase, phosphorylates many proteins, including GSK-3β, inhibiting their activity. GSK-3β, in turn, phosphorylates many proteins, including bail-on tau, a significant pathogenetic factor in Alzheimer's disease. Thanks to Akt's inhibitory effect on GSK-3β, proper tau protein phosphorylation and cytoskeletal stability are maintained. In Alzheimer's disease, insulin resistance occurs in the brain. Insulin signaling is weakened, which leads to decreased Akt activity, which in turn leads to increased GSK-3β activity, leading to excessive tau protein phosphorylation, the formation of neurofibrillary tangles, and the destabilization of microtubules and intracellular transport in neurons. [14]

The study results show that in the control and insulin groups, hyperphosphorylation of tau was observed with age from weeks 4-6 of the experiment, while liraglutide completely prevented this increase, maintaining a low ratio of phosphorylated tau to total tau protein.

In the control and insulin groups, Akt phosphorylation (Thr 308) and GSK-3β phosphorylation (Ser9) decreased with age, indicating a decrease in Akt activity and GSK-3β inhibition. Liraglutide completely prevented these changes, maintaining Akt activation and GSK-3β

inhibition. Summarizing the results of this study, it appears that liraglutide, unlike insulin, prevented Tau protein hyperphosphorylation and maintained Akt activation and GSK-3B inhibition, which in turn was associated with protection against neurodegenerative processes. [13]

In a study [15] using a mouse model combining Alzheimer's disease and type 2 diabetes, the effects of liraglutide on vascular damage, neuronal loss, and cognitive impairment were described by crossing APP/PS1 mice (a model of Alzheimer's disease) with db/db mice (a model of diabetes). Four groups were formed: a control group of 9-10 mice, an APP/PS1 group (a model of Alzheimer's disease) of 9-10 mice, a db/db group (a model of type 2 diabetes) of 7-9 mice, and an APP/PS1 x db/db model (a model combining Alzheimer's disease and type 2 diabetes) of 5-7 mice. Liraglutide was administered subcutaneously for 20 weeks, starting at 6 weeks of age. The final dose was 500 µg/kg/day, followed by a weekly dose escalation. Control animals received phosphate-buffered saline (PBS). In the Morris Water Maze (MWM) test, a behavioral test for assessing spatial memory and learning in rodents, untreated APP/PS1 x db/db mice had significantly longer platform finding times from day 1. After treatment, this time decreased significantly, although not identical to that of the control group.

Regarding brain weight, the db/db and APP/PS1 x db/db groups were significantly lower than in controls. After treatment, brain weight in the diseased groups returned to values similar to those in the control groups. Untreated APP/PS1 x db/db mice had significantly fewer neurons in the cortex near amyloid plaques ($p = 0.008$), while treatment significantly increased the number of neurons.

Regarding amyloid plaques, liraglutide significantly reduced their number and size in the cortex. The level of amyloid beta aggregates decreased by approximately 30%. Tau protein phosphorylation increased in APP/PS1 x db/db mice ($p=0.009$ vs. control). Treatment led to a reduction in this index close to the control level. [15]

In a study [16], in which researchers used the human neuroblastoma cell line SH-SY5Y and induced insulin resistance by administering high doses of insulin, the effect of liraglutide was analyzed in conditions of neuronal insulin resistance. As previously noted, insulin resistance in the brain is associated with the development of Alzheimer's disease by leading to, among other things, excessive tau protein phosphorylation [13,14,16]. We examined whether liraglutide could restore proper insulin signaling in the brain, reduce tau protein hyperphosphorylation, and influence the activity of the BACE-1 enzyme, which is responsible for the production of beta amyloid. During the experiment, cells were incubated for 48 hours in high insulin

concentrations (100nM) to induce neuronal insulin resistance. Liraglutide (500nM) was then administered for 24 hours to some cells (IL), while the remaining cells were left drug-free (group I). Control groups were also created: C- in normal medium, and L- in normal medium with liraglutide. After incubation, phosphorylation of IR, IRS-1, AKT, and GSK-3β, protein levels of Aβ, APP, and p-tau, BACE-1 activity, glucose uptake, and the presence of protein deposits were assessed. It was found that 24-hour incubation of insulin-resistant cells with liraglutide restored phosphorylation of IR, IRS-1, AKT, and GSK-3β, resulting in improved insulin signaling. There was also a decrease in Aβ and p-tau levels and a reduction in BACE-1 activity. The study suggests that liraglutide may have potential use in treating Alzheimer's disease associated with insulin resistance in the brain by improving insulin signaling and inhibiting the formation of abnormal proteins (Aβ and tau).[16]

In the study [17], the researchers used primary cultures of rat hippocampal neurons, which were then incubated with Aβ oligomers and/or liraglutide. Each neuronal culture was divided into groups: a control group, an AβOs group exposed to 500nM AβOs for 3 hours, a liraglutide + AβOs group in which liraglutide was added 40 minutes before AβOs administration, a group in which liraglutide was administered alone without AβOs, and an AβOs + liraglutide + GLP-1 receptor antagonist group, which was added 15 minutes before liraglutide, to check whether the effect was indeed mediated by the GLP-1 receptor. In some trials, researchers used Forskolin (10 μM), an adenylate cyclase activator, and 8-Br-cAMP (10 μM), a stable cAMP analog that activates PKA, instead of liraglutide. Immunofluorescence measurements were performed on synaptic proteins: Synaptophysin and PSD-95. The NU4 antibody, specific for AβOs, was used to determine whether liraglutide reduced their binding to neurons. It was observed that AβOs caused a decrease in synaptic protein levels, while liraglutide reversed this trend and reduced AβOs binding to neurons. This effect was simultaneously blocked by a GLP-1 receptor antagonist, demonstrating that this effect was dependent on the GLP-1 receptor. Forskolin and 8-Br-cAMP produced a similar protective effect – the mechanism was confirmed to depend on activation of the cAMP/PKA pathway, while PKA inhibitors neutralized the effect of liraglutide.[17]

In the study [18], the researchers aimed to determine whether GLP-1 receptor agonists, a drug used in diabetes, could cross the blood-brain barrier, activate receptors, and influence neurogenesis. Female mice of the C57/BL6 strain were used in the study. Mice were administered liraglutide intraperitoneally at doses of 2.5/25/250 nmol/kg or saline. They were then sacrificed 5 minutes, 30 minutes, and 3 hours after drug administration. Brain samples

were collected, weighed, frozen in liquid nitrogen, and subjected to acid-ethanol extraction. Subsequently, the amount of liraglutide in the brain was assessed using ELISA, and the level of cAMP, the second messenger of the GLP-1 receptor in the brain, was measured. In the case of liraglutide, no significant increase in brain concentration was observed after 5 minutes for all doses. However, after 30 minutes, a significant increase was observed at the two highest concentrations – 25 nmol/kg ($p < 0.05$) and 250 nmol/kg ($p < 0.01$), respectively. No significant increase was observed for the 2.5 nmol/kg dose. After 3 hours, a significant increase was observed only for the 250 nmol/kg dose ($p < 0.05$). Regarding cAMP levels, after administration of 25nmol/kg liraglutide, a significant increase in cAMP levels in the brain was observed 30 minutes after injection ($p < 0.05$), which indicates that liraglutide crosses the blood-brain barrier and activates GLP-1 receptors. In the second experiment, lixisenatide was used. In addition to the part assessing drug penetration into the brain (similar to the experiment with liraglutide), mice were administered lixisenatide intraperitoneally at doses of 2.5/25/250 nmol/kg or saline, and the animals were analyzed 30 minutes and 3 hours after administration. Additionally, lixisenatide was administered chronically at a dose of 25 nmol/kg daily for 3 weeks in the experimental trial (n=6) and in the control trial, where saline was administered for the same period. In this part, the number of proliferating cells (BrdU+) and young neurons (DCX+) in the dentate gyrus of the hippocampus was assessed.

When assessing lixisenatide penetration into the brain, a significant increase was observed after 30 minutes for all doses (2.5/25/250 nmol/kg) – $p < 0.05$ or $p < 0.01$, while after 3 hours, a significant increase occurred for the 2.5 nmol/kg and 25 nmol/kg doses ($p < 0.05$).

When assessing cAMP after the 25 nmol/kg dose, a significant increase in cAMP was observed 30 minutes after administration ($p < 0.01$), indicating activation of GLP-1 receptors.

Assessing the effect of lixisenatide on neurogenesis by administering a 25 nmol/kg dose once daily for 3 weeks, it was found that it caused a 1.8-fold increase in cell proliferation (BrdU+) compared to the control group ($p < 0.01$) and a 1.7-fold increase in the number of young neurons (DCX+) compared to the control group ($p < 0.05$).

In summary, we note that GLP-1 receptor agonists cross the barrier. Blood-brain agonists activate GLP-1 receptors, and long-term administration increases neuronal cell proliferation and neurogenesis in the hippocampus.[18]

In the study [19], the authors focused on analyzing the available literature describing common mechanisms of type 2 diabetes and Alzheimer's disease. It was shown that in the course of Alzheimer's disease and diabetes, a state of insulin resistance in the brain, impaired glucose metabolism, and oxidative stress develop. GLP-1 agonists, on the other hand, may reduce

inflammation and, by improving mitochondrial function, reduce oxidative stress. Additionally, it was noted that by reducing amyloid-beta deposition and tau protein hyperphosphorylation, they simultaneously support neurogenesis, neuronal survival, and neural plasticity. This demonstrates the neuroprotective effect of this class of drugs, which raises hopes for their potential use in patients with Alzheimer's disease. In the study [20], the authors focused on the association between the use of semaglutide, a GLP-1 receptor agonist, and the risk of Alzheimer's disease diagnosis in patients with type 2 diabetes, compared to other antidiabetic medications.

Data from the medical records of 1.09 million patients in the US were analyzed. The study found that semaglutide use was associated with a 40-70% reduction in the first diagnosis of Alzheimer's disease compared to other medications. The greatest risk reduction was observed when combined with insulin (HR = 0.33), and the smallest when compared to other GLP-1 receptor agonists (HR = 0.59). The results were similar in individuals with and without obesity, in men and women, and across age groups. These data show that GLP-1 analogues may not only improve cognitive functions in people already diagnosed with Alzheimer's disease, but also reduce the risk of its development in patients with type 2 diabetes.

Summary:

GLP-1 receptor agonists (GLP-1RAs), used in the treatment of type 2 diabetes and obesity, demonstrate potential neuroprotective effects in Alzheimer's disease (AD). Neuronal insulin resistance, impaired glucose metabolism in the brain, oxidative stress, chronic inflammation, and pathological changes in amyloid-β and tau proteins play important roles in the pathogenesis of AD. Numerous preclinical studies have demonstrated that GLP-1 analogues, such as liraglutide and lixisenatide, can cross the blood-brain barrier, activate GLP-1 receptors in the central nervous system, support neurogenesis, improve synaptic plasticity, limit tau hyperphosphorylation, reduce amyloid-β deposition, and improve cognitive function and neuronal survival. Data from clinical and observational studies indicate that in patients with type 2 diabetes, GLP-1RA use is associated with a lower risk of developing dementia, including AD. In a randomized trial, liraglutide inhibited the decline in brain glucose metabolism in individuals with AD, although it did not significantly affect amyloid-β deposition or cognitive function. Extensive retrospective analyses, including those using the TriNetX database, have shown that patients treated with GLP-1RAs had a significantly lower risk of dementia, and semaglutide use was associated with a 40–70% reduction in the risk of a first AD diagnosis

compared with other antidiabetic medications. The neuroprotective effects of GLP-1RAs are explained by, among other factors, improved insulin signaling in the brain, inhibition of GSK-3β activity, reduction of oxidative stress and inflammation, and promotion of neuronal survival and synaptic plasticity. The results of preclinical and observational studies are consistent and underscore the potential of this class of drugs as a therapy that can modify the course of Alzheimer's disease. Despite encouraging results, there are still no large, long-term randomized clinical trials that would unequivocally confirm the efficacy of GLP-1RAs in the prevention and treatment of AD. Further research is needed to determine the optimal use of these drugs and identify the patient groups that could benefit most from them.

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All authors have read and agreed with the published version of the manuscript.

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this review.

Informed Consent Statement

Not applicable.

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