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Review

Exploring the Role of GLP-1 Receptor Agonists in Alzheimer's Disease: A Review of Preclinical and Clinical Evidence

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Abstract: Glucagon-like peptide-1 receptor agonists (GLP-1RAs), including dulaglutide, liraglutide, semaglutide, and exenatide, are effective treatments for type 2 diabetes mellitus (T2DM) and obesity. These agents mimic the action of the endogenous incretin glucagon-like peptide-1 (GLP-1) by enhancing insulin secretion, inhibiting glucagon release, and promoting weight loss through appetite suppression. GLP-1RAs have recently been suggested to have neuroprotective effects, suggesting their potential as treatment for neurodegenerative disorders, such as Alzheimer's disease (AD). AD and T2DM share several common pathophysiological mechanisms, including insulin resistance, chronic inflammation, oxidative stress, and mitochondrial dysfunction. These shared mechanisms suggest that therapeutic agents targeting metabolic dysfunction may also be beneficial for neurodegenerative conditions. Preclinical studies on GLP-1RAs in AD models, both in vitro and in vivo, have demonstrated promising neuroprotective effects, including reductions in amyloid-beta accumulation, decreased tau hyperphosphorylation, improved synaptic plasticity, and enhanced neuronal survival. Despite the encouraging results from preclinical models, several challenges need to be addressed before GLP-1RAs can be widely used for AD treatment. Ongoing clinical trials are investigating the potential cognitive benefits of GLP-1RAs in AD patients, aiming to establish their role as a therapeutic option for AD. This review aimed to examine the current literature on preclinical and clinical studies investigating GLP-1 receptor agonists as potential therapeutic agents for AD.

Keywords: GLP-1 receptor; GLP-1 receptor agonists; Alzheimer's disease; type 2 diabetes mellitus

Academic Editor: Zhanguo Gao

Received: 28 October 2024
Revised: 26 November 2024
Accepted: 20 January 2025
Published: 26 January 2025

Citation: Teixeira, L.C.R.; Luizon, M.R.; Gomes, K.B. Exploring the Role of GLP-1 Receptor Agonists in Alzheimer's Disease: A Review of Preclinical and Clinical Evidence. *Receptors* **2025**, *4*, 2. https://doi.org/10.3390/receptors4010002

1. Introduction

The glucagon-like peptide-1 receptor (GLP-1R) is a member of the G-protein-coupled receptor (GPCR) family, which participates in numerous physiological processes [1]. The GLP-1R is mainly found in pancreatic beta cells and is activated by glucagon-like peptide-1 (GLP-1), an incretin hormone secreted by intestinal L-cells in response to nutrient intake [2]. This receptor regulates a variety of metabolic responses, including the potentiation of glucose-dependent insulin secretion, the suppression of glucagon release, and the slowing of gastric emptying [3]. Through these effects, GLP-1 plays a critical role in maintaining glucose homeostasis, particularly in the postprandial state [4]. The GLP-1R is also expressed in several other tissues, including the brain, the heart, and endothelial vascular tissues, among others [2], suggesting that this receptor is involved in other regulatory processes beyond glycemic control, such as energy balance [5], cardiovascular health [6,7], and

neuronal function [8]. Given its many functions, the GLP-1R has become an attractive target for therapeutic interventions in metabolic disorders and other diseases [9].

GLP-1 receptor agonists (GLP-1RAs) are synthetic analogs of the endogenous GLP-1 hormone [10]. They are engineered to avoid breakdown by degradation by dipeptidyl peptidase-4 (DPP-4) and exhibit longer half-lives, enabling sustained receptor activation [10]. GLP-1RAs have become an effective treatment for type 2 diabetes mellitus (T2DM) due to their capacity to improve glycemic control through several mechanisms, including the stimulation of the slowing of gastric emptying, reductions in glucagon release, and increased insulin secretion [11].

T2DM is a growing public health concern that has reached epidemic proportions globally [12]. The increasing prevalence of T2DM is largely attributed to lifestyle factors, including poor dietary habits, obesity, and physical inactivity [13]. The disease significantly impacts the quality of life of affected individuals and is associated with a heightened risk of various complications, such as cardiovascular disease, kidney disease, and neurological conditions, including AD [14,15].

Managing T2DM is therefore critical, not only for glycemic control but also for mitigating its associated comorbidities, including neurodegeneration [16,17]. The current standard of care for T2DM involves lifestyle modifications and pharmacotherapy [18]. Among the pharmacological treatments, metformin is considered the first-line therapy due to its efficacy in reducing blood glucose levels, its safety profile, and additional benefits, including modest weight loss and cardiovascular protection [18]. However, in patients who do not achieve adequate glycemic control with metformin or who have specific needs such as weight reduction or cardiovascular risk management, GLP-1RAs have emerged as an effective therapeutic option [19]. It is important to highlight that, unlike other diabetes therapies, GLP-1RAs do not induce hypoglycemia due to their glucose-dependent mechanism of action [20].

GLP-1RAs have also demonstrated significant benefits for weight loss, establishing them as effective treatments for obesity [21]. These drugs act on GLP-1 receptors in the hypothalamus by reducing appetite and food intake, which supports sustained weight loss in patients [22,23]. Given these effects, GLP-1RAs, including dulaglutide, liraglutide, semaglutide, and exenatide, have become important pharmacological options for T2DM, particularly for those individuals with comorbid obesity, thereby providing a therapeutic strategy for addressing these two prevalent metabolic disorders [11].

The effective use of GLP-1RAs for metabolic conditions has sparked interest in exploring their potential applications in other fields, especially in neurodegenerative diseases [24]. GLP-1RAs are also present in brain regions involved in cognitive functions, particularly the hippocampus, which is crucial for memory and learning [25]. Studies indicate that GLP-1RAs can cross the blood–brain barrier [25], where they exhibit anti-inflammatory, antioxidant, and neurotrophic effects [24]. These properties are believed to help maintain neuronal survival and protect against degenerative processes [24]. As a result, there is increasing interest in the potential of GLP-1RAs to provide therapeutic benefits for Parkinson's disease [26], Huntington's disease [27], and Alzheimer's disease (AD) [28], with considerable focus on AD mainly due to the urgent need for innovative treatment strategies [29].

AD is a progressive neurodegenerative disorder that represents 60 to 70% of the 55 million dementia cases worldwide, making it the most prevalent form of dementia [30]. The main pathophysiological mechanisms include the accumulation of amyloid-beta plaques and neurofibrillary tangles in the brain, which lead to neuroinflammation, synaptic dysfunction, neuronal loss, and cognitive decline [31]. Despite decades of research, the exact pathophysiology of AD remains unclear [32], and the current therapeutic options focus on

reducing symptoms and the development of the disease [33]. The failure of recent clinical trials targeting amyloid and tau pathology has shifted the focus to alternative mechanisms that could be explored to slow the disease progression [34]. In this context, the neuroprotective actions of GLP-1RAs seem to be a promising new therapeutic intervention [35].

This review examines the current literature on preclinical and clinical studies investigating GLP-1RAs as potential therapeutic agents for AD. Preclinical evidence showed the neuroprotective effects of GLP-1RAs, including reduced amyloid and tau pathology, improved synaptic function, and enhanced neuronal survival. The clinical studies provide insights into the optimal dosing strategies and patient selection criteria. Future research, including ongoing clinical trials, will be critical to clarify the therapeutic potential of these drugs in AD.

2. The GLP-1R and Its Agonists

GLP-1 is a peptide composed of 36 amino acids, mainly produced in the enteroendocrine L-cells of the distal small intestine and colon [36], although neurons in the central nervous system (CNS) can also synthesize this hormone [36,37]. Importantly, GLP-1 enhances insulin secretion from pancreatic beta cells and suppresses glucagon release from alpha cells only in hyperglycemic conditions, making it suitable for safe use in both diabetic and non-diabetic individuals [3,38]. Native GLP-1 has a very short half-life of approximately 1–2 min due to its rapid degradation by dipeptidyl peptidase-4 and renal clearance [39].

Given the rapid degradation and short half-life of native GLP-1, peptide analogs have been developed to enhance its stability and prolong its biological activity [10]. These analogs, known as GLP-1RAs, are commonly used to manage T2DM and, in some cases, obesity [11]. These drugs are categorized into two main groups based on their structures: human GLP-1-based agonists and exendin-4 derivatives [19]. Examples of human GLP-1-based agonists include dulaglutide, liraglutide, and semaglutide, whereas exenatide belongs to the exendin-4 category [19]. Each of these drugs has received U.S. Food and Drug Administration (FDA) approval and comes with specific guidelines for administration [10]. For glycemic control, dulaglutide (Trulicity®) is typically initiated at 0.75 mg once weekly, which can be increased to 1.5 mg per week if necessary [10,40]. Liraglutide (Victoza®) starts at 0.6 mg daily for the first week and may be increased to 1.2 mg, with a possible maximum dose of 1.8 mg daily [10,40]. Semaglutide (Ozempic®) is initiated at 0.25 mg once weekly for four weeks and is then increased to 0.5 mg weekly, with a maximum of 1 mg weekly [10,40]. Exenatide (Byetta®) is usually started at 5 mcg twice daily for the first month, followed by an increase to 10 mcg twice daily [10,40]. For weight management, both liraglutide (Saxenda®) [41] and semaglutide (Wegovy®) [42] are FDA-approved. Liraglutide (Saxenda®) is initiated at 0.6 mg daily, with weekly increments of 0.6 mg until reaching a maximum of 3 mg daily, while semaglutide for weight loss starts at 0.25 mg weekly, gradually increasing to a maximum of 2.4 mg per week [10].

GLP-1 exerts its biological effects primarily through its receptor, the GLP-1R, a G-protein-coupled receptor that activates adenylate cyclase, leading to an increase in cAMP levels [43]. This elevation in cAMP triggers protein kinase A (PKA) activation, which plays a crucial role in glucose-dependent insulin secretion by beta cells in the pancreas [44]. The signaling cascades initiated by the GLP-1R extend beyond insulin regulation, involving pathways such as the epidermal growth factor receptor (EGFR), which activates phosphoinositide 3-kinase (PI3K), and extracellular signal-regulated kinases (ERK1/2), promoting beta-cell proliferation and differentiation [1,45]. In addition to its peripheral effects, the GLP-1R is expressed in key regions of the CNS, where it regulates appetite suppression and delays gastric emptying [22,23]. Furthermore, GLP-1 exerts both neuroprotective and

neurotrophic effects by binding to the GLP-1R [46], positioning it as a promising therapeutic target for neurodegenerative diseases, particularly AD, the most common form of dementia [30].

3. Pathophysiology of Alzheimer's Disease (AD)

AD is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and behavioral changes [47]. It is the most common cause of dementia in the elderly [30] and its pathophysiology is complex and multifactorial [48]. While the exact mechanisms remain elusive, several physiological pathways have been implicated in the development and progression of AD, including the accumulation of amyloid-beta (Aβ) plaques, tau protein hyperphosphorylation, oxidative stress, mitochondrial dysfunction, neuroinflammation, synaptic dysfunction, and neuronal apoptosis [33].

A key pathological feature of AD is the excessive formation and aggregation of Aβ peptides in the brain, which are derived from Amyloid Precursor Protein (APP) [49]. The cleavage of APP is mediated by alpha-, beta-, and gamma-secretase enzymes, and this process can follow two distinct pathways. In the non-amyloidogenic pathway, α-secretase and γ-secretase act on APP, resulting in the formation of a small hydrophobic fragment (p3), which plays a role in synaptic signaling [47,50]. Alternatively, in the amyloidogenic pathway, β-secretase and γ-secretase cleave APP, producing Aβ peptides of varying lengths [51]. The two primary forms, Aβ40 and Aβ42, consisting of 40 and 42 amino acids, respectively, are the major contributors to amyloid plaque formation [52]. In AD, there is a dysregulation in the balance between Aβ production and clearance, leading to the overproduction and insufficient removal of these peptides, which results in their accumulation as oligomers [49,50]. These oligomers eventually form fibrils, which aggregate into Aβ plaques [49,50]. The accumulation of oligomers is highly toxic to neurons, setting off a cascade of damaging processes, such as ion channel obstruction, disruptions in calcium homeostasis, enhanced mitochondrial oxidative stress, reduced energy metabolism, impaired glucose regulation, and eventually, neuronal death [47,50].

AD is also marked by the presence of neurofibrillary tangles in the brain, primarily composed of hyperphosphorylated tau protein [53]. Tau, a microtubule-associated protein (MAPT), is essential for the formation and stabilization of microtubules within axons [54]. The biological activity of tau is regulated through phosphorylation, a process controlled by several kinases, including glycogen synthase kinase-3β (GSK3β) and cyclin-dependent kinase 5 (CDK5) [54]. In AD, the abnormal activation of these kinases leads to the excessive phosphorylation of tau [55]. Hyperphosphorylated tau tends to oligomerize, causing structural changes that lead to the formation of insoluble paired helical filaments, which eventually aggregate into large neurofibrillary tangles (NFTs) [56]. These tangles interfere with axonal transport and disrupt communication between neurons, ultimately resulting in neuronal dysfunction [50,56,57].

Mitochondrial dysfunction is another pathophysiological mechanism of AD, which is characterized by changes in the morphology, distribution, and movement of mitochondria, as well as impaired biogenesis and elevated oxidative stress [58]. Given its high consumption of oxygen and glucose for cognitive activities, the brain becomes more susceptible to the action of free radicals generated during the cellular respiration process in the mitochondria [59]. Brain oxidative stress is inherent to the natural aging process [59]. However, individuals diagnosed with AD exhibit a marked increase in oxidative stress compared to age-matched elderly individuals without AD [60]. The increased production of reactive oxygen species (ROS) in AD is associated with the loss of mitochondrial function, an imbalance in metal homeostasis, and a reduction in antioxidant defense, and it directly affects synaptic activity and neurotransmission in neurons, resulting in cognitive dysfunction [61].

In AD, neuroinflammation is characterized by the activation of glial cells, such as microglia and astrocytes, in response to CNS damage [62]. Microglia serve as the first line of defense, responding to pathogens and tissue injury [63]. Astrocytes are essential for the health and stability of the CNS, as they regulate blood flow, balance neurotransmitters, promote synapse formation, and remove neurotoxic waste [64]. In the early stages of AD, these glial cells protect neurons by removing Aβ peptides [65]. However, glial cells become dysregulated with the advance of AD, leading to Aβ accumulation and releasing pro-inflammatory cytokines, which contribute to oxidative stress and neuronal damage [62,66].

The mechanisms described above, including tau hyperphosphorylation, the accumulation of extracellular amyloid plaques, mitochondrial dysfunction, and increased ROS production, contribute to synaptic dysfunction and neuronal apoptosis [67]. These processes lead to a progressive reduction in the number of synapses, culminating in significant neuronal loss during the later stages of the disease [68].

4. Preclinical Studies on GLP-1 Receptor Agonists in Alzheimer's Disease

4.1. Dulaglutide

Dulaglutide-treated mice showed improved learning and memory performances in the Morris water maze, reduced hyperphosphorylation of tau and neurofilament proteins by enhancing the PI3K/AKT/GSK3β signaling pathway, and increased GLP-1 and GLP-1 receptor expression levels, suggesting neuroprotective effects in an intracerebroventricular injection of streptozotocin (icv-STZ) in vivo AD model [69]. Moreover, pharmacokinetic studies have shown that dulaglutide efficiently crosses the blood–brain barrier within a short timeframe, supporting its potential for direct action in the brain [70].

4.2. Semaglutide

Semaglutide treatment has also been investigated in AD models. In SH-SY5Y cells damaged by $A\beta_{25–35}$, semaglutide enhanced autophagy by increasing LC3II, Atg7, Beclin-1, and P62 while inhibiting apoptosis through the modulation of the Bax and Bcl2 levels [71]. In 3xTg AD mice, semaglutide increased the SIRT1 and GLUT4 expression, reduced amyloid-β plaques and neurofibrillary tangles, and enhanced cognitive function [72]. In addition, semaglutide promoted glycolysis and alleviated glycolytic disorders, increasing GLUT4 translocation to the cell membrane in HT22 neurons [72]. These findings suggest that the SIRT1/GLUT4 signaling pathway may play a key role in the capacity of GLP-1RAs to improve glucose metabolism in the brain, highlighting it as a potential approach for AD treatment [72]. Conversely, despite improvements in glucose tolerance and weight reduction in models like 5XFAD and APP/PS1 mice, semaglutide did not show a significantly impact on Aβ accumulation, neuroinflammation, or neurobehavioral outcomes [73]. These discrepancies between the studies may be explained by differences in the AD mice models, treatment durations, administration routes, and dosages [72,73]. Also, pharmacokinetic studies indicated significantly higher concentrations of semaglutide in the hypothalamus compared to other brain regions, and plasma levels showing a multiexponential decline with an average half-life of 7.22 to 9.26 h in rats [74].

4.3. Exenatide/Exendin-4

Exenatide/exendin-4 has been evaluated in multiple AD models, demonstrating various neuroprotective effects [75]. In cellular studies, exendin-4 demonstrated protective effects [76]. In cultured hippocampal neurons, it protected against oxidative injury induced by Aβ [76]. In a PC12 neuronal cell model, exendin-4 attenuated Aβ1-42-induced apoptosis by increasing the anti-apoptotic protein Bcl-2 and reducing the caspase-3 levels, effects that

were linked to the upregulation of phosphorylated Akt and CREB, thereby enhancing the cell survival signaling pathways [77].

In 5xFAD transgenic mice, exenatide treatment improved the cognitive performance in the Morris water maze and reduced neuroinflammation and oxidative stress in astrocytes, potentially via the inhibition of the NLRP2 inflammasome [78]. Similarly, in another study involving 5xFAD mice, exenatide prevented cognitive decline, alleviated Aβ deposition and synapse damage, and improved the mitochondrial function by normalizing the mitochondrial dynamics and reducing oxidative damage [79]. In two transgenic AD mouse models (5xFAD and 3xTg-AD), exenatide blocked the microglia-mediated conversion of astrocytes to their reactive form, preserved neuronal viability, and improved spatial learning and memory [80]. In 3xTg-AD mice subjected to a high-fat diet, exenatide counteracted adverse changes in brain-derived neurotrophic factor (BDNF) signaling and neuroinflammation, although no significant effects on the systemic metabolism or cognitive function were observed [81].

In the Tg2576 AD mouse model, an 8-month intranasal treatment with exenatide combined with insulin was associated with improved learning and reduced cortical amyloid-beta levels, although the latter did not reach statistical significance [82]. Long-term exenatide treatment also enhanced the short- and long-term memory in PS1-KI mice, likely through increased lactate dehydrogenase activity and anaerobic glycolysis, while no significant effects were observed in 3xTg-AD mice [83]. Furthermore, exenatide treatment in 3xTg-AD mice with streptozotocin (STZ)-induced diabetes improved their glucose metabolism by elevating the plasma insulin and reducing the plasma glucose and HbA1c levels [84]. Exendin-4 also reduced the brain Aβ levels in this model, suggesting its potential benefit in managing AD associated with T2DM [84].

In various AD rat models, exendin-4 has shown multiple neuroprotective effects. In the icv-STZ rat model, exendin-4 prevented memory impairment and neuronal apoptosis in the hippocampus, increased cell proliferation, and enhanced synaptogenesis [85]. Similarly, in an icv-Aβ-injected AD rat model, exendin-4 improved the memory performance, decreased the Aβ levels, and restored the acetylcholine levels and mitochondrial function, possibly through the PI3K/Akt-mediated pathway [86]. Exendin-4 also reduced the brain TNF-α levels, preserved the choline acetyltransferase (ChAT) activity, improved the cognitive performance, and prevented the loss of hippocampal neurons in another icv-STZ rat model [87]. Moreover, exendin-4 mitigated neuronal injury caused by high glucose and oxidative stress in vitro and improved learning and memory in an icv-STZ-induced rat model by downregulating GSK-3β activity, thereby reversing tau hyperphosphorylation and protecting hippocampal neurons from degeneration [88].

Exendin-4 has also exhibited significant effects on synaptic plasticity, calcium homeostasis, and survival pathways. In icv-Aβ mice, exendin-4 increased the phosphorylation of cAMP response element-binding protein (CREB) and elevated the BDNF levels, which enhanced the synaptic plasticity through increased membrane GluR1 subunit and postsynaptic density protein-95 (PSD-95) levels [89]. These effects were mediated by increased α-secretase activity via ADAM10 membrane trafficking [89]. In a rat hippocampal CA1 model, exendin-4 counteracted Aβ1-42-induced deficits in long-term potentiation (LTP) and rescued the cAMP and phosphorylated CREB levels [90]. Moreover, exendin-4 regulated calcium homeostasis in the rat hippocampal CA1 region by reducing the Aβ-induced suppression of LTP by modulating the intracellular calcium concentration, thereby supporting its role in calcium regulation for neuroprotection [91].

4.4. Liraglutide

In multiple studies utilizing SH-SY5Y human neuroblastoma cells, liraglutide has shown significant neuroprotective properties. In cells exposed to chronic endoplasmic reticulum (ER) stress induced by thapsigargin, liraglutide restored ER homeostasis, enhanced autophagy, improved the cell viability and proliferation, and promoted cellular survival by activating the Akt and STAT3 signaling pathways, thereby protecting against neurodegeneration [92]. In the APPswe/SH-SY5Y cellular model of AD, liraglutide was found to reduce Aβ42 production by enhancing autophagy through the activation of the JNK pathway, while inhibiting the beclin-1/bcl-2 complex [93].

In SH-SY5Y cells exposed to methylglyoxal-induced stress, liraglutide demonstrated neuroprotective effects by improving the cell viability, reducing apoptosis, and activating survival signaling kinases such as Akt and MEK1/2 and the transcription factor p90RSK [94]. In SH-SY5Y cells exposed to $A\beta_{25\text{-}35}$, liraglutide prevented neurotoxicity by inhibiting neuronal apoptosis and promoted neuroprotective actions through the activation of the PI3K/Akt signaling pathway [95]. Moreover, in cells treated with H_2O_2 to simulate oxidative stress, liraglutide enhanced the cell viability, reduced apoptosis, decreased lipid peroxidation, and ameliorated tau hyperphosphorylation through the modulation of the Akt/GSK-3β pathway [96]. Finally, liraglutide effectively alleviated neuronal insulin resistance in SH-SY5Y cells, reduced beta-amyloid formation, and decreased tau hyperphosphorylation and the activity of the BACE-1 enzyme [97].

In vivo models have shown that liraglutide demonstrates both preventive and restorative effects against AD pathology. In an icv-Aβ mouse model, liraglutide was shown to reduce the hyperphosphorylation of tau via the glycogen synthase kinase-3β pathway, improving the synaptic structure and cognitive impairment in AD [98]. In a mixed murine model of AD and T2DM (APP/PS1xdb/db), liraglutide treatment for 20 weeks led to improved cognitive function, reduced brain atrophy, a rescued neuronal density, a decreased amyloid plaque burden, tau hyperphosphorylation, spontaneous bleeding, and microglial activation [99]. These effects resulted in a better performance in memory tests, namely, the Morris water maze and new object discrimination tests [99]. In an icv-STZ AD model, liraglutide decreased the hyperphosphorylation of tau and neurofilament proteins, increased protein O-glycosylation, and reduced neurodegeneration, resulting in improved learning and memory [100]. Moreover, liraglutide showed anti-inflammatory and anti-amyloid properties in 5xFAD and STZ-induced sporadic AD models [101]. Furthermore, liraglutide treatment reduced neuroinflammatory responses and Aβ plaque deposition, prevented disruption of the insulin signaling pathway, and mitigated early neuropathological markers of AD, suggesting potential benefits before significant cognitive changes emerge [101].

In APP/PS1 mice, liraglutide treatment prevented synapse loss and the deterioration of synaptic plasticity, reduced the Aβ plaque burden, neuroinflammation, and aberrant insulin receptor localization and signaling, and increased neurogenesis in the dentate gyrus, indicating enhanced synaptic integrity in AD [102–107]. Additionally, liraglutide treatment restored the cerebral, splenic, and renal microvascular architecture, thereby reducing pathological features like microaneurysms and improving the vessel structure, which may enhance amyloid clearance [108]. In APP/PS1/Tau triple-transgenic mice, liraglutide reduced the hyperphosphorylation of tau and neurofilaments, as well as the amyloid plaque load, attenuated oxidative/nitrosative stress and inflammation, and improved the learning and memory performance in the Morris water maze test [109,110]. Conversely, in two APP/PS1 transgenic mouse models carrying different mutations, long-term liraglutide treatment exhibited no significant effect on the Aβ plaque load, indicating variability in its efficacy depending on the specific pathological characteristics of the model [111].

In rat models, liraglutide treatment effectively protected against Aβ-induced spatial memory deficits and improved long-term potentiation in the hippocampal CA1 region [112]. Finally, in non-human primates infused with Aβ oligomers, liraglutide treatment demonstrated neuroprotective effects by preventing synaptic loss and restoring the insulin receptor levels, supporting its potential effects on early pathological changes in AD [113]. Table 1 summaries preclinical studies on disease models.

Table 1. Overview of preclinical studies on GLP-1 receptor agonists in Alzheimer's disease models.

GLP1-RA	Reference	AD Model	Key Findings
Dulaglutide	[69]	icv-STZ mice	↑ GLP-1 and GLP-1R expression; ↓ tau hyperphosphorylation (via PI3K/AKT/GSK3β pathway); ↑ learning and memory (MWM test).
Semaglutide	[71]	SH-SY5Y cells damaged by Aβ25-35	↑ Autophagy (↑ LC3II, Atg7, Beclin-1, and P62 expression); ↓ apoptosis (↓ Bax and ↑Bcl2).
	[72]	3xTg AD mice	↑ SIRT1 and GLUT4 expression; ↓ amyloid-β plaques; ↓ neurofibrillary tangles; ↑ learning and memory.
		HT22 neurons	↑ Glycolysis and GLUT4 translocation.
	[73]	5XFAD and APP/PS1 mice	↑ Glucose tolerance; ↓ weight; no significant impact on Aβ accumulation, neuroinflammation, behavior, or cognitive function.
Exenatide/Exendin-4	[76]	Cultured hippocampal neurons	↓ Death induced by Aβ and iron.
	[77]	PC12 neuronal cells	↓ Apoptosis (↓ Caspase-3 and ↑ Bcl2); ↑ phosphorylation of Akt and CREB.
	[78]	5×FAD mice	↓ Neuroinflammation and oxidative stress; ↑ cognitive function (MWM test).
	[79]	5×FAD mice	↓ Aβ deposition and synapse damage; ↑ mitochondrial function; ↓ cognitive decline.
	[80]	5xFAD and 3xTg-AD mice	↓ Aβ-induced activation of microglia and astrocyte reactivity; ↑ learning and memory.
	[81]	3xTg-AD mice subjected to a high-fat diet	↓ Adverse changes in BDNF signaling; ↓ neuroinflammation; no significant effects on systemic metabolism or cognitive function.
	[82]	Tg2576 mice	In combination with insulin: ↓ IRSP genes; ↑ learning.
	[83]	PS1-KI mice	↑ Short- and long-term memory; ↑ brain lactate dehydrogenase activity; ↑ brain anaerobic glycolysis.
		3xTg-AD mice	No effects.

Table 1. *Cont.*

GLP1-RA	Reference	AD Model	Key Findings
Exenatide/Exendin-4	[84]	Neuronal cultures and human SH-SY5Y	↓ Toxicity of Aβ and oxidative challenge.
		3xTg-AD mice with STZ-induced diabetes	↑ Plasma insulin; ↓ plasma glucose and HbA1c; ↓ Aβ levels.
	[85]	icv-STZ rats	↓ Memory impairment, apoptosis, and neuronal death; ↑ cell proliferation and synaptogenesis.
	[86]	icv-Aβ rats	↓ Aβ levels; ↑ memory (MWM test); ↑ acetylcholine levels and the activity of cholineacetyl transferase; ↑ mitochondrial function.
	[87]	icv-STZ rats	↓ Brain TNF-α levels; preserved choline acetyltransferase activity; ↑ cognitive performance; prevented the loss of hippocampal neurons.
	[88]	PC12 cells	↑ Cell viability; ↓ oxidative stress.
		icv-STZ rats	↑ Learning and memory; ↓ tau hyperphosphorylation and neurodegeneration.
	[89]	icv-Aβ mice	↑ Phosphorylation of CREB and BDNF levels; ↑ AMPA receptor GluR1 subunit and PSD-95; ↑ α-CTF of APP and ADAM10.
	[90]	Rat hippocampal CA1	↑ Learning and memory (MWM test); ↑ LTP and CREB levels.
	[91]	Rat hippocampal CA1	Regulated calcium homeostasis; ↓ Aβ-induced suppression of LTP.
Liraglutide	[92]	SH-SY5Y cells exposed to ER stress induced by thapsigargin	Restored ER homeostasis; enhanced autophagy; improved cell viability and proliferation.
	[93]	APPswe/SH-SY5Y cells	↓ Aβ42 generation; ↑ autophagy (activating the JNK pathway); ↓ Beclin-1/bcl-2 complex [93].
	[94]	SH-SY5Y cells exposed to methylglyoxal-induced stress	↑ Cell viability; ↓ cytotoxicity and apoptosis; ↑ influx of calcium into the cell; ↑ Mcl1, Akt, MEK1/2, and p90RSK; ↓ Bax and Bik.
	[95]	SH-SY5Y cells exposed to Aβ25-35	↓ Cytotoxicity, LDH, cytochrome-c, and apoptosis; ↑ P-Akt and Bcl-2/Bax.
	[96]	SH-SY5Y cells exposed to H_2O_2	Enhanced cell viability (↓ cytotoxicity, lipid peroxidation, tau hyperphosphorylation, and apoptosis); ↑ Bcl-2 and ↓Bax; ↓ tau hyperphosphorylation.

Table 1. *Cont.*

GLP1-RA	Reference	AD Model	Key Findings
Liraglutide	[97]	SH-SY5Y cells	↓ Neuronal insulin resistance, Aβ formation, tau hyperphosphorylation, and activity of BACE-1 enzyme.
	[98]	icv-Aβ mice	↓ Tau hyperphosphorylation (via the glycogen synthase kinase-3β pathway); improved synaptic structure and cognitive impairment.
	[99]	APP/PS1xdb/db mice	↑ Cognitive function and neuronal density; ↓ brain atrophy, amyloid plaque burden, tau hyperphosphorylation, spontaneous bleeding, and microglial activation.
	[100]	icv-STZ mice	↓ Tau hyperphosphorylation and neurofilament proteins; ↑ protein O-glycosylation; ↓ neurodegeneration; ↑ learning and memory.
	[101]	icv-STZ-5xFAD mice	↓ Neuroinflammatory and Aβ plaque deposition preventing disruption of the insulin signaling pathway.
	[102–107]	APP/PS1 mice	Prevented synapse loss and deterioration of synaptic plasticity; ↓ Aβ plaque burden, neuroinflammation, and aberrant insulin receptor localization and signaling; ↑ neurogenesis in the dentate gyrus.
	[108]	APP/PS1 mice	Restored cerebral, splenic, and renal microvascular architecture; ↓ incidence of cerebral microaneurysms and leakage.
	[109,110]	APP/PS1/Tau triple-transgenic mice	↓ Tau hyperphosphorylation, neurofilaments, amyloid plaque load, oxidative/nitrosative stress, and inflammation; ↑ learning and memory (MWM test).
	[111]	APP/PS1 mice	No significant effect on Aβ plaque load.
	[112]	icv-Aβ (25–35) rats	↑ Learning and memory (MWM test) and L-LTP.
	[113]	Non-human primates infused with Aβ oligomers	↓ Synaptic loss and tau pathology; restored insulin receptor levels.

5. Clinical Trials of GLP-1 Receptor Agonists in Alzheimer's Disease

A study published in 2022, although focused on dementia in general rather than specifically on AD, integrated data from three randomized, double-blind, placebo-controlled cardiovascular outcome trials, including a total of 15,820 participants, and analyzed the use of GLP-1RAs and subsequent dementia diagnoses in T2DM [114]. The results showed a significantly lower incidence of dementia among patients treated with GLP-1RAs compared to those using the placebo (hazard ratio [HR]: 0.47; 95% confidence interval [CI]: 0.25–0.86). This association was consistent across national cohorts (HR: 0.89; 95% CI: 0.86), indicating that GLP-1RA therapy may help reduce the risk of dementia in individuals with T2DM [114]. Additionally, an analysis of 66,085 patients aged 65 and older, who voluntarily reported their use of antidiabetic drugs to the FDA Adverse Event Reporting System, revealed

that GLP-1RAs, including exenatide, liraglutide, and dulaglutide, were associated with a significantly lower risk of AD compared to metformin [115]. Specifically, exenatide showed a reporting odds ratio (OR) of 0.22 (95% CI: 0.11–0.37), while liraglutide and dulaglutide had ORs of 0.36 (95% CI: 0.19–0.62) and 0.39 (95% CI: 0.17–0.77), respectively [115]. Below, we show the specific clinical studies conducted on each GLP-1 receptor agonist, including dulaglutide, semaglutide, exenatide, and liraglutide, regarding their potential effects on AD.

5.1. Dulaglutide

Only one clinical study examined the effects of dulaglutide on cognitive function. The REWIND trial was a randomized, double-blind, placebo-controlled study designed to explore the potential cognitive benefits of dulaglutide in individuals with T2DM [116]. The study was conducted across 371 sites in 24 countries and included 8828 participants aged 50 years and older, with either established or recently diagnosed diabetes, along with additional cardiovascular risk factors [116]. Participants were assigned to receive either a weekly subcutaneous dose of dulaglutide (1.5 mg) or the placebo [116]. Cognitive assessments were carried out using the Montreal Cognitive Assessment (MoCA) and the Digit Symbol Substitution Test (DSST), both at baseline and during the follow-up period [116]. The findings indicated that dulaglutide reduced the risk of significant cognitive decline by 14%, suggesting a potential neuroprotective effect in people with T2DM [116].

5.2. Semaglutide

There are three registered and ongoing studies on ClinicalTrials.gov, which aim to compare treatment with semaglutide versus placebos in patients with AD. The first study (NCT05891496), entitled "A Research Study Looking at the Effect of Semaglutide on the Immune System and Other Biological Processes in People With Alzheimer's Disease", aims to determine how semaglutide affects the immune system and various biological processes in individuals with AD [117]. The study is expected to last a total of 77 weeks. During the initial 12 weeks, participants will be randomly assigned to either the semaglutide group or a placebo group. After this phase, all participants will receive semaglutide for a period of 52 weeks [117].

The EVOKE (NCT04777396) [118] and EVOKE Plus (NCT04777409) [119] trials are currently underway to determine whether semaglutide could provide benefits for individuals in the early stages of AD. In both trials, participants are assigned randomly to either the semaglutide group or a placebo group, with an equal likelihood of receiving either treatment [118,119]. The trials are designed to last up to 173 weeks, during which participants will attend 17 clinic visits and have one phone call with the study doctor. Various assessments, including tests and scans, will be conducted, and blood samples will be collected 10 times during the clinic visits. Both studies require participants to have a study partner who will be involved throughout the trial [118,119]. Women who are pregnant, breastfeeding, or planning to become pregnant are excluded from participation [118,119]. Additionally, a cerebrospinal fluid (CSF) sub-study will be conducted at selected sites based on their experience and willingness to perform CSF sampling, with the endpoints of this sub-study being exploratory in nature. These trials will help determine whether semaglutide is effective at slowing or improving the course of early AD [118,119].

Finally, a protocol published in 2024 outlines the ISAP trial, a double-blind, placebo-controlled, randomized study that aims to evaluate the effects of oral semaglutide on the amyloid positivity, cortical tau accumulation, and neuroinflammation in adults with preclinical or prodromal AD [120]. The trial also aims to evaluate whether semaglutide can delay or prevent neurotoxic processes associated with AD [120]. Up to 88 individuals

aged 55 years or older with confirmed brain amyloid positivity, as determined by positron emission tomography (PET) or cerebrospinal fluid analysis, will be enrolled and randomly assigned to receive either semaglutide or a placebo in a 1:1 ratio [120]. Treatment will begin with a daily oral dose of 3 mg of semaglutide, which will be gradually increased to 14 mg over 8 weeks [120]. Participants will attend several safety visits throughout the 52-week trial, providing blood samples for AD biomarkers and undergoing repeat PET and magnetic resonance imaging (MRI) scans to assess the tau and neuroinflammation [120]. Cognitive assessments will also be repeated at week 26 and at the final study visit in week 52. The primary endpoint of the study is the change in the tau PET signal over one year [120]. The trial has received ethical approval, and it aims to provide insights into whether semaglutide may serve as a viable intervention to delay or prevent the progression of AD-related neurotoxicity [120].

5.3. Exenatide/Exendin-4

In an 18-month double-blind, placebo-controlled phase II trial, exenatide was assessed for its safety, tolerability, and impact on clinical, cognitive, and biomarker outcomes in early AD [121]. This trial included 18 participants who completed the entire study before its early termination. While exenatide was generally safe and well tolerated, with some expected side effects, such as nausea and decreased appetite, no significant improvements were observed in the clinical or cognitive outcomes, MRI cortical metrics, or most biomarkers compared to the placebo [121]. The only notable finding was a reduction in the Aβ42 levels in plasma neuronal extracellular vesicles (EVs), suggesting potential biomarker utility, though its clinical relevance remains unclear. The early termination of the trial resulted in insufficient power to draw definitive conclusions regarding the disease-modifying potential of exenatide in AD [121].

Another study aimed to assess whether slow-release exenatide could improve the cognitive performance in individuals with mild cognitive impairment (MCI), considered a prodromal stage of AD [122]. This proof-of-concept trial randomized 32 participants to receive either weekly exenatide injections or no treatment for 32 weeks [122]. The primary endpoint was the change in cognitive performance as measured by the ADAS-Cog11 score. Results showed no significant cognitive benefit of exenatide compared to the control group [122]. Interestingly, a gender-specific interaction was observed, with female participants treated with exenatide experiencing a worsening of cognitive scores [122]. Despite reductions in the fasting plasma glucose levels and body weights in those treated with exenatide, there was no evidence of a beneficial effect on cognitive outcomes over the 32-week period [122].

5.4. Liraglutide

One double-blinded, placebo-controlled study examined the effects of 12-week liraglutide treatment on the neural connectivity in cognitively normal, late-middle-aged individuals with subjective cognitive complaints [123]. The results showed significant improvements in the intrinsic connectivity within the default mode network (DMN) in the liraglutide group compared to that in the placebo group [123]. However, no cognitive differences were observed between the groups after the treatment period, suggesting that longer and larger studies are needed to determine its neuroprotective effects in AD [123].

The ELAD trial was a 12-month, multi-center, double-blind, placebo-controlled phase IIb study designed to assess the effects of liraglutide on the cerebral glucose metabolism in individuals with mild Alzheimer's dementia [124]. Participants were randomly assigned to receive either liraglutide or a placebo, with the primary outcome being the change in the cerebral glucose metabolic rate (CMRglc) in cortical areas such as the hippocampus

and medial temporal lobe [124]. Patients treated with liraglutide showed significantly better outcomes compared to those of the placebo group in terms of the temporal lobe and overall cortical MRI volume, as well as in terms of cognitive function as measured by the ADAS-EXEC (ADAS-Cog including Executive domains of the Neuropsychological Test Battery) [125].

Another study involved 38 AD patients randomized to receive either liraglutide or a placebo for 26 weeks [126]. While the CMRglc declined significantly in the placebo group, the liraglutide treatment showed a numerical but statistically insignificant increase in CMRglc [126]. Cognitive measures did not significantly change, and regional or global differences in Aβ retention were not observed between the groups [126]. This suggests that liraglutide may prevent glucose metabolism decline, a hallmark of synaptic dysfunction and cognitive impairment in AD [126].

A subsequent study explored liraglutide's potential to enhance glucose transport across the blood–brain barrier, hypothesizing that it could prevent the decline in CMRglc by increasing glucose transporter numbers [127]. In a cohort of 38 AD patients and six healthy controls, liraglutide treatment significantly raised the Tmax estimates of cerebral cortex glucose transfer, bringing them to levels comparable to those of healthy volunteers [127]. This indicates that liraglutide may restore impaired glucose transport at the blood–brain barrier (BBB) in AD, offering potential neuroprotective effects [127].

Furthermore, findings from the Alzheimer's Association International Conference 2024 reported on a phase IIb trial with 204 participants with mild to moderate AD [128]. Participants received either liraglutide or a placebo for 12 months. MRI scans and cognitive assessments revealed a slower decline in the temporal lobe volume, total gray matter volume, and cortical volume in the liraglutide-treated group compared to the placebo group [128]. The study highlighted the potential of liraglutide in slowing both structural brain changes and cognitive decline in AD patients [128]. A summary of the studies is represented in Table 2.

Table 2. Overview of clinical studies evaluating the effects of GLP-1RAs on patients with Alzheimer's disease.

GLP-1RA	Reference	Study Type	Population Studied	Outcomes or Study Objectives
Dulaglutide	[116]	REWIND: randomized, double-blind, placebo-controlled trial.	Total of 8828 individuals aged >50 years, male or female, with T2DM and cardiovascular risk factors.	Reduced risk of significant cognitive decline by 14%, suggesting potential neuroprotective effects.
Semaglutide	[117]	Randomized, double-blind, placebo-controlled trial.	Individuals aged 55–75 years, male or female, with AD.	Investigating the effect of semaglutide on the immune system and other biological processes in AD patients.
	[118,119]	EVOKE and EVOKE Plus: randomized, double-blind, placebo-controlled trials.	Individuals aged 55–85 years, male or female, with early AD.	Determining whether semaglutide is effective at slowing or improving the course of early AD.
	[120]	ISAP: randomized, double-blind, placebo-controlled trial.	Total of 88 individuals aged ≥55 years with brain amyloid positivity.	Investigating whether semaglutide reduces accumulation in the brain of cortical tau protein and neuroinflammation.

Table 2. *Cont.*

GLP-1RA	Reference	Study Type	Population Studied	Outcomes or Study Objectives
Exenatide/Exendin-4	[121]	Randomized, double-blind, placebo-controlled, phase II trial.	Total of 18 individuals aged >60 years, male or female, with high-probability AD based on cerebrospinal fluid biomarkers.	Exenatide was safe and well tolerated. No significant changes in clinical, cognitive, MRI, or biomarker outcomes, except for reduced Aβ42 in plasma neuronal EVs.
	[122]	Proof-of-concept randomized trial.	Total of 32 individuals aged $\geq$50 and $\leq$ 80 years, male or female, with mild cognitive impairment (MCI).	No significant cognitive benefits. Observed gender-specific interactions, with cognitive worsening in treated females.
Liraglutide	[123]	Randomized, double-blind, placebo-controlled trial.	Total of 32 individuals aged 45–70 years, male or female, at risk for Alzheimer's disease (cognitively normal, late-middle-aged individuals with subjective cognitive complaints).	Liraglutide treatment improved intrinsic connectivity within default mode network (DMN) but did not result in cognitive differences between groups after 12 weeks.
	[124,125]	ELAD: multi-center, randomized, double-blind, placebo-controlled, phase IIb trial.	Total of 206 individuals aged >50 years, male or female, with mild AD dementia.	Liraglutide improved temporal lobe and whole cortical MRI volumes and cognitive function (ADAS-EXEC) compared to placebo.
	[126]	Randomized, double-blind, placebo-controlled trial.	Total of 38 individuals aged >50 years and <80 years, male or female, with Alzheimer's disease.	Liraglutide showed a numerical but insignificant increase in glucose metabolism compared to placebo, preventing its decline; no significant changes in cognitive measures or Aβ retention were observed.
	[127]	Randomized, double-blind, placebo-controlled trial.	Total of 38 individuals age-matched with Alzheimer's disease.	Liraglutide restored glucose transport across the BBB, increasing Tmax estimates to levels comparable to those of healthy controls.
	[128]	Multi-center, randomized, double-blind, placebo-controlled, phase IIb trial.	Total of 204 individuals with mild to moderate AD.	Liraglutide slowed the decline in temporal lobe, total grey matter, and whole cortical volumes, with associated slower cognitive decline compared to placebo.

6. Discussion

Evidence shows that individuals with diabetes have a higher risk of developing cognitive decline and dementia [129]. Patients with T2DM have over a 50% increased

risk of developing AD compared to non-diabetics [130], which has led to several studies examining the pathways linking glucose metabolism disorders and neurodegeneration [15]. Recent findings have prompted researchers to refer to AD as "Type 3 Diabetes", due to the shared cellular and molecular characteristics between AD and T2DM, including insulin resistance, which is associated with memory deficits and cognitive decline in older individuals [131].

AD and T2DM are connected through several mechanisms, such as insulin resistance, oxidative stress, mitochondrial dysfunction, advanced glycation end products (AGEs), and neuroinflammation [132]. Brain insulin resistance appears to be a key factor in AD pathogenesis [133]. Insulin and insulin-like growth factor 1 (IGF-1) enter the central nervous system by crossing the BBB through specific receptors on endothelial cells [134]. However, this process is affected by risk factors like diabetes, obesity, inflammation, and elevated blood triglycerides [132]. In the brain, insulin receptors are widely distributed but are more concentrated in areas critical for memory and cognition, such as the hippocampus, cerebral cortex, and hypothalamus [129]. Insulin and IGF-1 are essential for neuronal survival and central nervous system integrity, functioning as mediators of neuronal and glial growth, metabolism, survival, gene expression, protein synthesis, and the maintenance of synaptic function and neurotransmitter networks [133]. Insulin plays a protective role in AD by promoting the expression of ADAM-10, which reduces the expression of genes like BACE1, GSK3β, and APP, thereby decreasing Aβpeptide production [133]. Insulin deficiency has been linked to the accumulation of Aβ, increased tau phosphorylation, the formation of neurofibrillary tangles, and memory impairment, creating a vicious cycle that exacerbates neurodegeneration [133].

These pathological changes begin years before clinical symptoms manifest, making early intervention difficult and treatment more challenging [135]. The current treatment options for AD are limited to symptomatic relief and do not effectively halt or reverse the disease progression [136]. Therefore, there is an urgent need for novel therapeutic strategies that target the underlying pathophysiological mechanisms of AD, potentially at an earlier stage [137].

Given the overlapping mechanisms between T2DM and AD, GLP-1RAs have gained considerable interest as a potential treatment for AD [28]. Several preclinical studies, both in vitro and in vivo, have demonstrated the neuroprotective effects of GLP-1RAs in models of AD, as described above.

Challenges, Limitations, and Future Perspectives Regarding GLP-1RAs in AD Therapy

Despite these encouraging preclinical findings, translating the use of GLP-1RAs into effective clinical interventions for AD poses several challenges. One major obstacle is the BBB, which limits the central effects of peripherally administered drugs [138]. Although studies have shown that GLP-1RAs can cross the BBB [139], the efficiency of CNS delivery and the therapeutic dose required to achieve neuroprotective effects in humans remain uncertain. Furthermore, the variability in responses among different transgenic mouse models of AD, with some showing no effect on the Aβ plaque burden [111], highlights the complexity of AD pathology and the need for individualized therapeutic approaches [140]. Moreover, a recent systematic review examined randomized control trials and protocol studies and concluded that GLP-1RAs, such as liraglutide and exenatide, did not significantly alter core AD biomarkers (Aβ and tau) or improve cognitive outcomes in the short term [35]. However, some metabolic benefits were observed, including a reduced body mass index and improved glucose tolerance [35].

There are also safety considerations to be addressed. The long-term administration of GLP-1RAs is generally well tolerated in T2DM [140], but potential adverse effects must be

carefully monitored in patients with AD, who may have additional vulnerabilities due to age or comorbidities [140].

The most common adverse events of GLP-1RAs are gastrointestinal, including nausea, vomiting, diarrhea, and delayed gastric emptying, which are often dose-dependent and tend to diminish over time [141–143]. Long-acting agents tend to cause less nausea and vomiting but are linked to a higher incidence of diarrhea [142]. Rare but significant adverse events include cutaneous reactions and renal injury [141,144,145]. Other reported adverse events include hepatic, immunologic, endocrine/metabolic, hematologic, neurological, cardiovascular, and angioedema events [141]. Safety concerns have also emerged regarding potential associations with pancreatitis and neoplasms, although clinical evidence remains inconclusive and regulatory agencies like the FDA and European Medicines Agency (EMA) consider the risks manageable [146,147]. Injection site reactions and antibody formation are more frequent with exendin-4-based GLP-1RAs [147]. Considering that these potential adverse events are comorbidities commonly observed in the elderly, the use of these medications requires greater monitoring to avoid worsening complications.

Despite these risks, GLP-1RAs offer significant benefits for glycemic control, weight loss, and cardiovascular protection, making them valuable therapeutic options [146,148]. However, there are no studies that have specifically addressed the optimal timing for GLP-1RA intervention. Since AD pathology begins long before clinical symptoms appear [149], early intervention seems to be more effective, but its long-term use is not clear.

Despite these challenges, the use of GLP-1RAs in AD treatment holds significant promise [150]. The results from preclinical models provide a strong foundation for future research, and several clinical trials are currently underway to evaluate the efficacy of GLP-1RAs in patients with AD [151]. At this point, we need to wait for the completion of these clinical trials, which will help clarify the neuroprotective potential of GLP-1RAs in human populations and provide insights into the optimal dosing strategies and patient selection criteria [35].

In the future, GLP-1RAs could become part of a multi-faceted therapeutic approach to AD, possibly in combination with other agents targeting complementary pathways. For example, preclinical studies in AD mouse models have shown that combining a GLP-1RA with insulin results in improved memory function and normalizes insulin receptor signaling pathways, highlighting the synergistic potential of such therapies [82]. Advances in biomarker research could also enhance our ability to detect early pathological changes in at-risk individuals, enabling timely intervention with GLP-1RAs [152].

7. Conclusions

In conclusion, GLP-1RAs target multiple pathological pathways shared by T2DM and AD. Preclinical evidence has consistently shown the neuroprotective effects of GLP-1RAs, including reduced amyloid and tau pathology, improved synaptic function, and enhanced neuronal survival. However, several challenges need to be addressed before GLP-1RAs can be fully integrated into AD treatment strategies, including efficient CNS drug delivery, optimal intervention timing and dosing strategies, tolerance of adverse events, and patient selection, considering the AD clinical spectrum. Further studies, including ongoing clinical trials, will be critical in clarifying the therapeutic potential of GLP-1RAs in AD.

Author Contributions: Conceptualization, L.C.R.T., M.R.L., and K.B.G.; methodology, L.C.R.T.; writing—original draft, L.C.R.T.; writing—review and editing, L.C.R.T., M.R.L., and K.B.G. 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.

Data Availability Statement: Not applicable.

Acknowledgments: M.R.L. and K.B.G. thank Conselho Nacional de Desenvolvimento Científco e Tecnológico (CNPq) Brazil for the research grant.

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

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