Narrative Review Article

The Potential Role of GLP-1 Receptor Agonists for the Treatment of Alzheimer's Disease

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ABSTRACT

Alzheimer's Disease (AD) is currently one of the leading causes of mortality worldwide and is characterized by excessive accumulation of amyloid-β plaques, tau protein hyperphosphorylation, and chronic neuroinflammation. However, there are no effective cures or therapies for the treatment of AD. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), a class of medication commonly used to treat type 2 diabetes and obesity, have recently emerged as novel candidates for AD therapy. Preclinical studies demonstrate that GLP-1 RAs efficiently cross the blood-brain barrier, reduce amyloid burden, attenuate neuroinflammation, and improve neuronal survival. Furthermore, early clinical studies show their potential for cognitive benefits in patients with AD. This review paper examines the molecular mechanism of GLP-1R signaling in the central nervous system and its therapeutic effects in the treatment of AD. Additionally, emerging therapeutic strategies, such as dual agonist treatments and organoids, offer potential increases in research and development speed, paving the way for promising future development of GLP-1 RAs and their translational progress into AD. Together, these findings suggest that GLP-1RAs are promising therapies for the treatment of AD in humans.

Keywords: Alzheimer's disease, T2DM, GLP-1 Receptor Agonists, Aβ

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting over 7 million people in the United States and 47 million people worldwide (1). This disease leads as the primary cause of disability and death (2). Importantly, over 50 million people currently live with dementia, and this number is predicted to reach 152 million globally by 2050 (3). The most common symptoms observed in AD patients include the deterioration of basic cognitive functions, such as problem-solving and planning, as well as difficulty completing daily tasks and memory loss (4). This disease has a significant impact on the quality of life for patients and society, making it a critical global public health concern (1). Unfortunately, there are no effective therapies to treat this disease (5); thus, there is an urgent need to develop effective and safe therapies for the treatment of this disease.

Targeting the Glucagon-like peptide-1 (GLP-1) receptor provides novel therapeutic strategies for the treatment of AD. GLP-1 receptor agonists (GLP-1 RAs) are primarily used for the treatment of type 2 diabetes mellitus (T2DM) and obesity. Functionally, this class of drugs mimics the action of GLP-1 receptors to stimulate insulin secretion, which helps to control blood sugar levels, while regulating appetite (6). In

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addition, recent studies have shown that GLP-1 RAs are a potential candidate for the treatment of AD. In cellular and animal models of AD, GLP-1RAs exhibit anti-inflammatory effects in the central nervous system (CNS), reducing AD disease markers such as Aβ accumulation and tau hyperphosphorylation (1). These findings suggest repurposing of GLP-1RAs can be a promising alternative therapy to treat AD patients. This review paper examines the molecular mechanism of GLP-1R signaling in the context of AD and explores its therapeutic effects in the treatment of AD.

THE PHYSIOLOGY OF GLUCAGON-LIKE PEPTIDE 1 (GLP-1)

GLP-1 and GLP-1 Receptor

GLP-1 is an incretin hormone that is produced in enteroendocrine L-cells of the distal small bowel and colon. Additionally, GLP-1 can be made by neurons in the CNS (1). Some of the metabolic effects of GLP-1 include stimulating insulin secretion, decreasing gastric emptying, and inhibiting food intake (7). In addition to its metabolic functions, GLP-1 also exhibits neuroprotective effects, including the reduction of inflammation and apoptosis, as well as increased implications for learning and memory (7). Pharmacologically, GLP-1 binds to GLP-1 receptors (GLP-1R) to produce biological responses.

GLP-1Rs are widely expressed in several tissues such as the pancreas, gastrointestinal tract, adipose tissue, and CNS (Figure 1). It is highly expressed in pancreatic beta cells, and its activation enhances glucose-stimulated insulin secretion, glucagon secretion, and promotes beta cell proliferation. Additionally, its activation regulates gastric emptying and acid secretion in the gastrointestinal tract (1-6). In adipose tissue, it controls lipolysis and glucose uptake, thereby contributing to improved glucose homeostasis. In contrast, its activation in the CNS increases satiety (2). Moreover, GLP-1Rs are also expressed in various brain cell types, including neurons, oligodendrocytes, astrocytes, microglia, and endothelial cells, underscoring their potential roles in

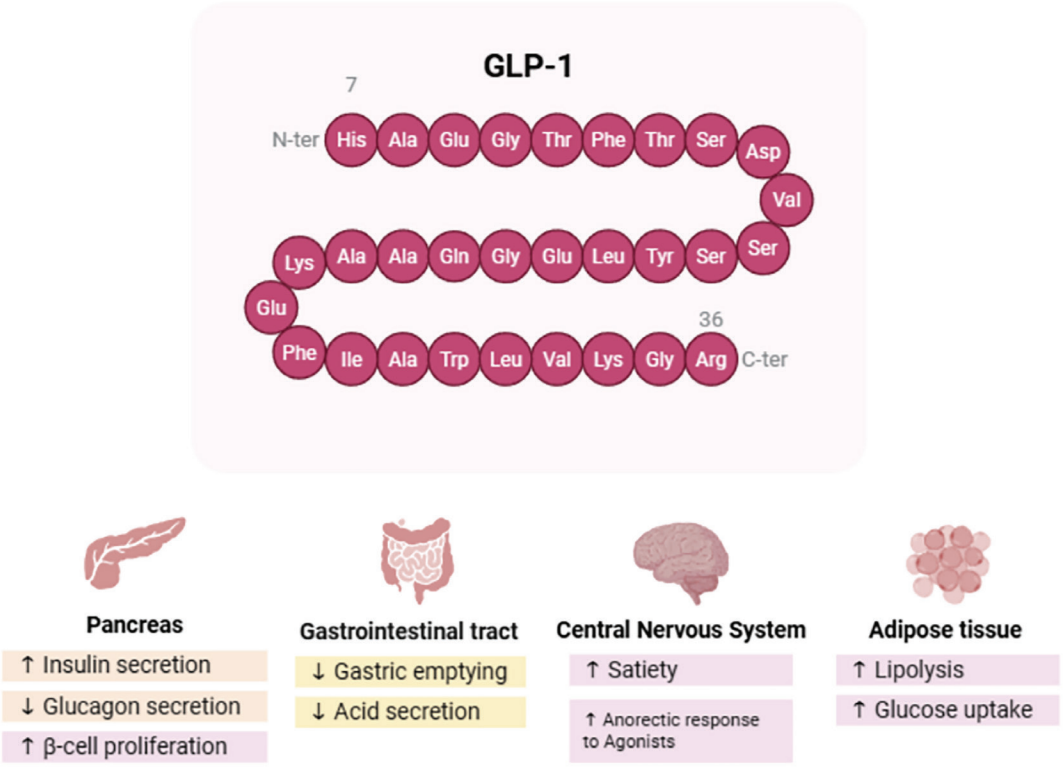

Figure 1. Structure of GLP-1 and its functional role in various metabolic tissues. This illustration depicts the GLP-1 peptide structure and its receptor expression in multiple tissues, regulating metabolic homeostasis. This figure was created in BioRender.com.

enhancing brain health (8). Specifically, its activation in the CNS increases satiety (2), thereby resulting in calorie deficiency and negatively affecting whole-energy balance. Therefore, it is a critical druggable target to treat metabolic disorders such as obesity and type 2 diabetes.

GLP-1 Receptor Agonists (GLP-1RAs)

Due to the metabolic benefits of GLP-1R activation, GLP-1R agonists (GLP-1RAs) are designed to mimic the natural GLP-1 peptide. In addition, to overcome the issue of rapid degradation of natural GLP-1 and keep its efficacy for the long term, these GLP-1RAs are structurally modified to delay the protease DPP-4-mediated degradation of GLP-1 (1). GLP-1RAs are effective pharmacological therapies for managing T2DM and obesity in patients; thus, numerous FDA-approved drugs are currently available for prescription in clinical cases for treating T2DM and obesity. These commonly used GLP-1RAs include exenatide, lixisenatide, dulaglutide, liraglutide, and semaglutide (1). For example, liraglutide facilitates an anorectic response as a long-acting GLP-1RA, while its chronic use stimulates the anorectic and weight loss effects (6). Additionally, a new class of medications has been developed to target both the GLP-1R and the glucose-dependent insulinotropic polypeptide receptor (GIPR), known as dual agonists (e.g., tirzepatide), to enhance metabolic benefits, including weight loss and the management of T2DM (5). In addition to their metabolic benefits, these drugs have also been repurposed for the treatment of other neurodegenerative diseases such as AD.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE (AD)

Traditionally, AD is characterized by two hallmark features: amyloid plaques and tau proteins, which result in the formation of amyloid plaques and neurofibrillary tangles (NFTs), respectively (Figure 2). Amyloid plaques are formed by the extracellular accumulation of Aβ40 and Aβ42 peptides, which result from the abnormal processing of the amyloid precursor protein

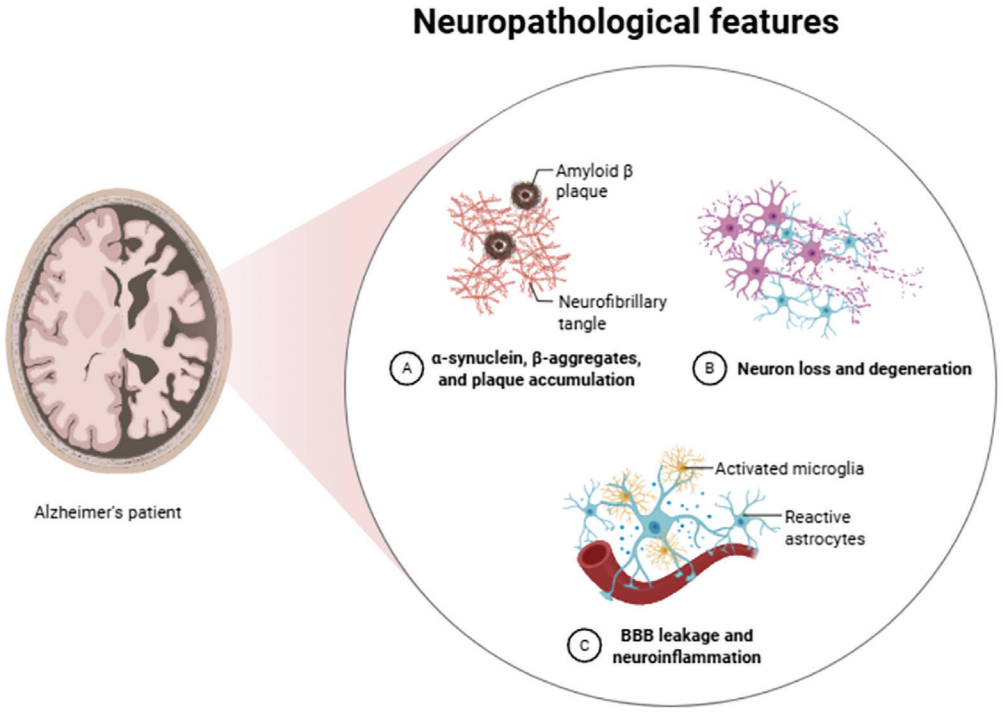

Figure 2. Neuropathological features of Alzheimer's disease. This figure shows key pathological alterations in Alzheimer's disease. (A) Formation of amyloid β plaques and neurofibrillary tangles, along with α-synuclein and β-aggregate accumulation. (B) Progressive neuronal loss and degeneration. (C) Activation of microglia and reactive astrocytes, as well as blood–brain barrier (BBB) leakage, leads to neuroinflammation. Together, these processes contribute to the structural and functional decline of the brain in Alzheimer's disease.

and an imbalance in the production and clearance pathways (4). Though nearly a dozen types of non-vascular Aβ amyloid plaques have been described, two types have been most observed in AD patients. Diffuse plaques, which are suspected to be benign and can be observed in cognitively normal individuals, and dense core plaques, also known as cored plaques, which are often identical to neuritic plaques, are associated with cognitive decline (9). Cored neuritic plaques, or senile plaques, which contain tau-positive neurites, usually have a central zone of dense amyloid, forming a compact core. The thick core can produce radiating Aβ fibrils, where dystrophic neurites and activated microglia are concentrated (4).

NFTs, the second significant pathological finding in AD, are formed by aggregates of the protein tau. As AD progresses in a patient, NFTs begin to affect the entorhinal cortex and the hippocampal pyramidal cell layer, spreading forward into the adjacent inferior temporal cortex, as well as the superior temporal cortex and frontal cortex (9). These later stages are commonly associated with clinically observed dementia, revealing its correlation with clinical symptoms of AD.

GLP-1 RAS IN AD

In the case of AD, recent studies have revealed several physiological properties of GLP-1 RAs, including neuroprotective, neurotrophic, and anti-inflammatory effects, which may be beneficial in slowing the progression of the disease (10). Activation of GLP-1 exhibits anti-neuroinflammatory and anti-neurodegenerative effects in preclinical animal models. Some studies have also reported that GLP-1 can reduce the accumulation of Aβ plaques and tau protein hyperphosphorylation, thereby contributing to the reversal of AD progression (1).

Another key component observed in AD patients is insulin resistance (IR) in the brain. Several studies using animal models provide strong evidence that IR and neuroinflammation feed AD neuropathology. IR can increase levels of neuroinflammation by producing chronically elevated blood sugar levels and an unhealthy lipid imbalance in the blood (2). Conversely, specific neurobiological characteristics of AD can aggravate IR and neuroinflammation, such as solubilized amyloid-β triggering pro-inflammatory signaling that amplifies vascular inflammation and vasoconstriction (2). These findings highlight the essential role of GLP-1RAs as an insulin-sensitizing agent to prevent or treat AD.

GLP-1 RAs in Preclinical AD Models

A study using cultured rat primary hippocampal neurons treated with GLP-1 showed that they were protected against amyloid-β-induced neurotoxicity (2). Furthermore, GLP-1-RA treatment reversed inflammation-induced synaptic impairments in the hippocampus. This treatment also reduced amyloid-β deposition, suppressed inflammatory glial activation, and the expression of proinflammatory molecules, including COX-2, TNF-α, IL-1β, and TLR4, in mice exposed to lipopolysaccharide (LPS) to mimic AD-like neuroinflammation (2). Furthermore, mice treated with dulaglutide, a GLP-1 RA, further improved learning and memory in the Morris water maze and reduced hyperphosphorylation of tau and neurofilament proteins, providing its potential role to reverse AD-related pathology (2). Importantly, pharmacokinetic studies indicate that dulaglutide efficiently crosses the blood–brain barrier (BBB) within a short timeframe, enabling direct effects in target brain regions (5). Similarly, liraglutide has demonstrated both preventive and restorative effects against AD pathology in vivo. Specifically, liraglutide reduced tau hyperphosphorylation via inhibition of glycogen synthase kinase-3β pathway, which contributes to improved synaptic structure and cognitive function in a mouse model of AD (5). Other GLP-1RAs, including exendin-4 and lixisenatide, reduced amyloid-β-induced oxidative stress, cytotoxicity, and neuroinflammation in cultured primary rat astrocytes and neurons. Moreover, three ongoing registered clinical trials (NCT05891496, NCT04777396, NCT04777409) are currently investigating semaglutide versus placebos in patients with AD and could provide benefits for individuals in the early stages of AD (2-5). These studies confirm the beneficial effects of GLP-1RAs in ameliorating AD and its symptoms.

GLP-1 RAs in Clinical Studies

The therapeutic potential of GLP-1 RAs in CNS diseases is further supported by meta-analyses (11), which reveal that patients with T2DM prescribed GLP-1R-stimulating medications may experience neuroprotective benefits and promote CNS health. A phase II clinical trial demonstrated that liraglutide administration in patients with AD significantly enhanced glucose transport across the BBB, thereby elevating the cerebral metabolic rate for glucose and reversing impairments in brain glucose metabolism commonly associated with AD pathology (2).

Additionally, a placebo-controlled double-blind phase II clinical trial testing liraglutide in 200 patients with AD was conducted, revealing that liraglutide significantly slowed down the deterioration in cognitive impairments, as well as a decrease in shrinkage within the brain temporal lobe, parietal lobe, and the total grey matter cortical volume (7). Furthermore, there are multiple ongoing trials aiming to explore similar hypotheses. Specifically, two large-scale EVOKE (NCT04777396) and EVOKE+ (NCT04777409) clinical, randomized, double-blind, placebo-controlled Phase 3 trials are investigating the efficacy, safety, and tolerability of once-daily oral semaglutide versus placebo in early-stage symptomatic AD (7).

COMPARATIVE ANALYSIS OF GLP-1 RECEPTOR AGONISTS

Although numerous GLP-1RAs have demonstrated beneficial effects in AD models, their pharmacokinetic profiles and CNS penetration display variability, influencing therapeutic potential. Exenatide and lixisenatide, both shorter-acting peptides, exhibit rapid absorption and clearance, allowing transient receptor engagement but limited CNS exposure. In contrast, liraglutide and dulaglutide possess longer half-lives and improved plasma stability, permitting sustained GLP-1R activation. Importantly, liraglutide and semaglutide have been shown to cross the blood–brain barrier (BBB) more efficiently than exenatide, suggesting greater direct neuroprotective effects.

Preclinical studies mentioned above also reveal that liraglutide and semaglutide more effectively reduce amyloid-β deposition and tau phosphorylation than shorter-acting agonists. However, while dulaglutide also crosses the BBB and shows robust neuroprotection in murine models, its larger molecular size may limit CNS diffusion compared to semaglutide. Together, these distinctions emphasize the need for more head-to-head clinical trials to determine which GLP-1RA offers the optimal balance of CNS penetration, metabolic benefit, and safety for AD therapy.

CHALLENGES AND FUTURE DIRECTIONS

Technical Challenges

While GLP-1 RAs are currently being explored in the field of AD treatment, several technical challenges exist regarding the effective and efficient progress and development of these therapies. First is the use of animal models and cell culture in relation to translational studies. Specifically, translational research necessitates a renewed perspective in the light of various hurdles, including limited resources, higher dropout rates, and the lengthy time required for novel drug development (12). Due to these challenges, the potential applications of findings from preclinical studies are limited when translating them to clinical studies. Another challenge is the relative difficulty of examining AD and its biomarkers within a patient. A current method of evaluation involves examining cerebrospinal fluid (CSF) for Aβ42 and hyperphosphorylated tau peptide (p-tau). This method achieves a diagnostic accuracy of 85–90% and carries the risks and inconveniences associated with a lumbar puncture procedure. It often takes weeks to obtain results due to the scarcity of laboratory facilities that perform fluid analysis. This process is also quite invasive to the patient (13).

Safety and Side Effects

Along with technical challenges, safety concerns, and possible side effects of a GLP-1 RA treatment for AD are raised. One primary concern of side effects regarding GLP-1 RA treatment is the risk of pancreatic inflammation and pancreatitis. In a clinical study including 1,269 hospitalized cases with acute pancreatitis and 1,269 control subjects matched for age, sex, enrollment pattern, and T2DM complications, it was shown that the use of incretin-mimetic therapies within 30 days, or their use over a period ranging from 30 days to 2 years was linked to increased risk of acute pancreatitis compared with non-users (9). Another concern of GLP-1 RAs is the increased risk of thyroid cancer. Although this field is not explored deeply, and consensus around its validity is still conflicting, a recent study using immunocytochemistry to detect GLP-1 receptors described such receptors not only on human C cells but also in some, but not all, follicular cells and in some papillary thyroid carcinomas, indicating a potential of GLP-1 receptor stimulation to influence the growth rate of other thyroid cancer types (3).

Emerging Trends and Future Innovation

GLP-1 RAs are still in development and are becoming more advanced as treatments for T2DM and obesity. They will continue to grow in capabilities, usage, and versatility as further research and trials are conducted. This is significant for the treatment of AD, as current uses for GLP-1 RAs as AD treatment are still being explored and discovered. GLP-1 RAs

may become more efficient and versatile in treating neurodegenerative diseases as improvements are made to both their primary effects and their potential anti-inflammatory effects in the brain. Along with significant innovations to come within GLP-1 RAs and their main effects, other, less significant innovations within GLP-1 RA treatment should also not be overlooked. Precision medicine approaches and the exploration of combination therapies such as dual agonists are promising in improving treatment outcomes.

Furthermore, improving drug delivery across the BBB could be another critical direction. Alternative forms of administration, such as oral forms, also have room for further innovation (14). Additionally, a primary technical challenge faced during preclinical studies was the translation of results from cell culture to animal models. One possible prospect for innovation in this field is the use of brain organoids. Organoids are small, self-organized three-dimensional tissue cultures grown from stem cells and crafted to replicate much of the complexity of an organ. The specific advantages of organoids grown from human induced pluripotent stem cells, rather than animal models, can help scientists conduct disease modeling with much greater accuracy and potentially increase trial efficiency within preclinical studies (15).

CONCLUSION

AD remains one of the most urgent public health challenges of our time, with its growing prevalence and lack of effective therapies, along with a lack of treatment strategies. Recent studies have highlighted GLP-1 receptor agonists, initially developed for T2DM and obesity, as potential treatments due to their neuroprotective, anti-inflammatory, and metabolic benefits. Mechanically, GLP-1R activation enhances neuronal insulin sensitivity, suppresses microglial-mediated inflammation, reduces amyloid-β accumulation, and mitigates tau hyperphosphorylation. Evidence from preclinical models and early clinical trials suggests these drugs can reduce amyloid-β accumulation, tau hyperphosphorylation, and improve brain glucose metabolism. When viewed alongside their well-characterized metabolic effects, these molecular actions are observed to improve synaptic integrity and neuronal survival, ultimately translating into measurable cognitive benefits in early clinical trials. Additionally, comparative pharmacokinetic analyses suggest that long-acting agents such as liraglutide, semaglutide, and dulaglutide may provide the strongest neuroprotective outcomes. However, challenges such as translational and diagnostic limitations, along with potential safety concerns, remain significant barriers to widespread clinical use. Overall, GLP-1 receptor agonists represent a possible new avenue for future AD therapies, but further large-scale clinical investigation is still required.

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CONFLICT OF INTEREST

The author declares that there are no conflict of interests related to this work

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