Narrative Review Article

The Neuroprotective Nexus: GLP-1 Receptor Agonists, Sleep, and the Glymphatic System in Alzheimer's Disease Prevention

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the deposition of extracellular amyloid-beta (Aβ) plaques and intracellular tau protein neurofibrillary tangles (NFTs), accompanied by prominent neuroinflammatory responses. Treating AD is extremely challenging because of its complex etiopathogenesis. AD and type 2 diabetes mellitus (T2D), a chronic metabolic disorder, share common pathophysiological features, such as insulin resistance and sleep and circadian rhythm disruptions, all of which are well-recognized risk factors for AD. Recently, glucagon-like peptide-1 receptor agonists (GLP-1RAs), approved medications for T2D and obesity, have been investigated as candidate disease-modifying agents for AD because of their neuroprotective, anti-inflammatory, improved insulin signaling, and anti-amyloidogenic properties. However, the mechanisms by which GLP-1 signaling affects sleep-wake regulation remain poorly defined. Thus, this review synthesizes the evidence linking GLP-1RAs to sleep architecture, specifically to sleep spindles and non-rapid eye movement (NREM) of the sleep-wake cycle, and to aquaporin 4 (AQP4)-dependent glymphatic clearance pathways, focusing on how these mechanisms could be leveraged to address sleep dysfunction and impaired clearance in AD. GLP-1RAs-driven mechanisms restoring the function of the glymphatic system, as well as the similar treatment benefits of melatonin, the key hormone regulating the sleep-wake cycle and circadian rhythm, are discussed. In addition, the rationale for combination strategies (GLP-1RAs plus melatonin) to target complementary sleep and glymphatic clearance is highlighted, while emphasizing the need for prospective clinical testing.

Keywords: Alzheimer's disease; GLP-1; GLP-1RA; sleep; NREM, sleep spindles; glymphatic system; melatonin

INTRODUCTION

Alzheimer's disease (AD) is a major global health concern and the most prevalent type of dementia, affecting approximately 58 million people worldwide as of 2019. This number is predicted to increase to 152 million by 2050, with the rising global aging population (1). The pathological hallmarks of AD include the formation of amyloid-beta (Aβ) plaques (2) and neurofibrillary tangles (NFTs) (3). Aβ plaques are primarily 40- or 42-amino acid-long peptides that arise when amyloid precursor protein (APP), a transmembrane protein, is sequentially cleaved by β- and γ-secretase (4). The cleavage of APP may be influenced by mutations in APP and other genes, such as presenilin 1, presenilin 2, and apolipoprotein E (4). While mutations in these genes are the basis for familial AD, aberrant accumulation

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of Aβ plaques occurs in sporadic AD due to reduced clearance of these peptides by the glymphatic system, a perivascular clearance pathway that facilitates the movement of cerebrospinal fluid (CSF)-interstitial fluid (ISF) in the brain (5). Extracellular Aβ accumulation disrupts cellular functions and activates microglia and cytokine signaling, promoting chronic inflammation and neurodegeneration (2, 4). NFTs are abnormal intracellular accumulations of tau protein, a microtubule-associated protein that normally stimulates tubulin and stabilizes the neuronal cytoskeleton of the axon (3, 6). Tau protein becomes hyperphosphorylated due to abnormal tau kinase and phosphatase activity, dissociates from the microtubule, forms paired helical filaments, and loses its ability to interact with tubulin, resulting in decreased axonal transport function and neurodegeneration (6, 7). AD affects various brain regions, including the cerebral cortex, hippocampus, amygdala, substantia nigra, basal ganglia, midbrain, and cerebellum, thereby impacting the respective brain functions (4). AD progression leads to dementia, characterized by the loss of coordination, communication abilities, spatial perception, memory, and cognition (8).

In addition to aging, poor sleep habits, type 2 diabetes mellitus (T2D), and associated insulin resistance are risk factors for AD and related dementias (9, 10). Sleep and AD have a bidirectional relationship (11, 12). Sleep is essential for the clearance of Aβ plaques and NFTs by the glymphatic system (13), and sleep abnormalities are associated with increased Aβ and tau accumulation in the brain and can precede the development of cognitive disabilities by decades (14, 15). Conversely, the deposition of Aβ and tau in the cortex and thalamus, the two brain regions that regulate sleep, leads to sleep disturbances and consequently to cognitive decline (16, 17). Similar to T2D, a chronic metabolic disorder characterized by beta cell dysfunction and decreased insulin production, AD is also associated with low levels of insulin, as well as reduced insulin growth factor 1 (IGF1) and insulin growth factor 2 (IGF2) (18). Low insulin, IGF1, and IGF2 levels can directly cause AD abnormalities, such as APP cleavage, hyperphosphorylation of tau protein, oxidative stress, and neurodegeneration (18). Consistent with these overlaps, AD has been described by some as a brain-specific form of diabetes mellitus or type 3 diabetes, although this framing remains debated and should be interpreted as a heuristic highlighting insulin signaling deficits rather than a formal diagnosis (19, 20).

Currently, there is no effective cure for AD. Although medications such as cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists are available to help alleviate the symptoms of AD, none have been effective in curing the disease (21, 22). Recently, glucagon-like peptide-1 receptor agonists (GLP-1RAs), which were approved for the treatment of obesity and type 2 diabetes (T2D), have gained momentum in the treatment of neurodegenerative diseases considering their neurotrophic, neuroprotective, and anti-inflammatory effects (23-27). GLP-1 is a naturally occurring incretin hormone secreted in the intestinal L-cells, as well as in the neurons and glial cells of the hypothalamus (28). It decreases blood sugar levels by stimulating insulin activity and inhibiting glucagon production (29). GLP-1 also regulates food intake and appetite. It is secreted during food ingestion and reduces food intake (29, 30). While GLP-1 is a key player in regulating glucose homeostasis, emerging evidence also indicates that GLP-1RAs can decrease Aβ plaques, neuroinflammation, and oxidative stress, presenting a possible treatment for AD (31-40). However, little is known about the direct effects of GLP-1 or its analogs on sleep. Thus, this review examines the role of GLP-1RAs in modulating the sleep-wake cycle and glymphatic clearance, highlighting their unrecognized potential to deliver positive outcomes relevant to AD treatment.

SLEEP DYSFUNCTION IN AD AND GLP-1RA MODULATION

Sleep Architecture

Humans spend approximately one-third of their lives sleeping. Sleep is a behavioral state that is indispensable for many important bodily functions, such as learning, memory consolidation, neurodevelopment, synaptic plasticity, circadian rhythm setting, and glucose metabolism (41, 42). The sleep–wake cycle comprises different sleep stages, each lasting approximately 90–120 min and consisting of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep (Figure 1) (42). NREM sleep is further divided into N1, N2, and N3 sleep, and 75% of sleep is spent during these three NREM stages. N1 and N2 are light NREM stages, whereas N3, also known as slow-wave sleep (SWS), represents deep NREM sleep (Figure 1) (42). REM is the last sleep stage, in which dreaming, rapid eye movement, and irregular breathing occur (42).

Electroencephalogram (EEG) recordings during sleep depict brain waves that reflect the transfer and consolidation of neuronal information primarily between the two brain regions regulating the sleep cycle: the

neocortex and thalamus (43-45). During sleep, the thalamocortical sensory neural network of the brain is shut down, and the rapid mixed-frequency waves that occur during wakefulness transform into slow (0.5–1.5 Hz) and high-amplitude waves mixed with high-frequency (10–15 Hz) oscillations called sleep spindles (Figure 1) (46). A detailed discussion on the electrophysiology and functional significance of sleep spindles is beyond the scope of this review and has been well described by Schonauer *et al.* (2018) (46). Sleep spindles, generated through GABAergic thalamic reticular nucleus–thalamocortical interactions, occur during NREM sleep and are implicated in sleep onset and memory consolidation (46, 47). The synchronized thalamocortical spindle network enables memory consolidation in the neocortex and promotes synaptic plasticity by strengthening synaptic connections through associated rhythmic neuronal discharges (46, 47). Thus, spindles serve as measures of general learning and intellectual ability.

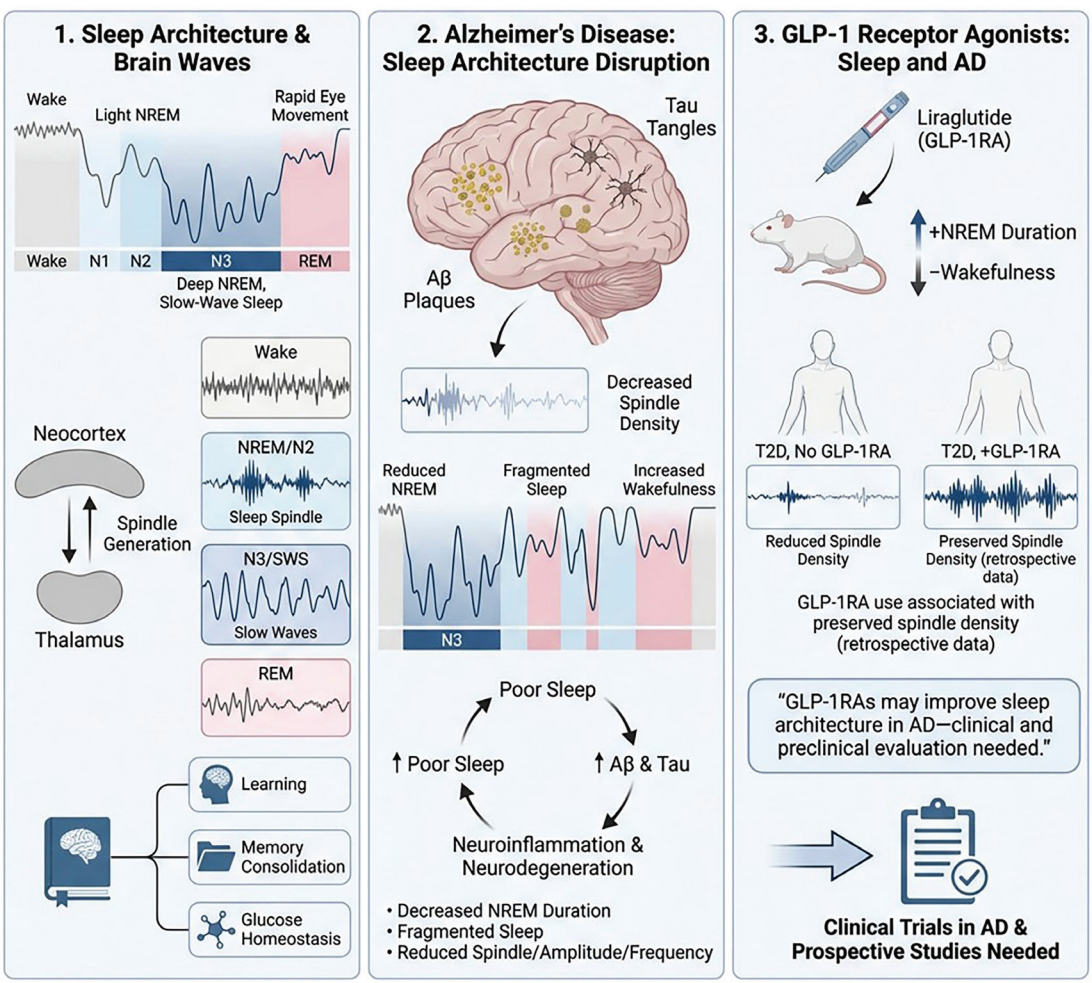

Figure 1. *Connections between the sleep–wake cycle, AD, and GLP-1RAs. Sleep includes NREM (N1–N3) and REM stages, with slow-wave sleep (N3) and sleep spindles (N2) supporting memory, metabolism, and thalamocortical regulation. In AD, sleep architecture is disrupted, with reduced NREM and spindle activity, contributing to impaired amyloid-β (Aβ) and tau clearance and promoting neurodegeneration. This relationship is bidirectional, as sleep disturbances can both precede and exacerbate AD pathology. Preclinical studies show that GLP-1RAs (e.g., liraglutide) increase NREM sleep and reduce wakefulness, while clinical data in T2D suggests preservation of spindle density. These findings indicate a potential role for GLP-1RAs in modulating sleep and AD pathology, though further clinical studies are needed. The figure was generated by the author using FigureLabs (Nano Banana Pro); https://chat.figurelabs.ai/chat.*

Disruption of Sleep Architecture in AD

Patients with AD exhibit decreased spindle density, as well as duration, frequency, and amplitude of spindles (Figure 1) (48, 49). Spindle density is inversely correlated with Aβ and tau pathologies (49). There is a bidirectional relationship between sleep and AD and related dementias (11, 12). Sleep is essential for Aβ and tau clearance, and sleep disturbances result in increased Aβ and tau accumulation, thereby increasing neuroinflammation and neurodegeneration in the brain, which are predisposing events for AD (Figure 1). Inadequate sleep patterns occur prior to the diagnosis of AD in approximately 50–60% of patients, indicating sleep disruptions as early biomarkers for AD (50). Decreased NREM sleep has been reported in both patients and animal models of AD prior to the loss of cognition (51, 52). Therefore, early intervention targeting sleep dysfunction has been proposed as an effective treatment strategy for patients with AD.

Sleep Parameters as Targets for GLP-1RAs in AD

Spindle activity and SWS oscillations during sleep have been found to predict the following day's insulin-dependent glucose regulation (46). Additionally, insulin sensitivity is reduced upon suppression of SWS in healthy volunteers (53). Collectively, these data imply the role of brain waves during sleep and circadian rhythm in peripheral glucose regulation, highlighting them as potential therapeutic targets for metabolic diseases, such as type 2 diabetes (T2D), as well as memory, cognitive, and learning disabilities, including Alzheimer's disease and related dementias (47, 53-55). With the known effects of approved metabolic therapeutics like GLP-1RAs on insulin and glucose regulation and given these mechanisms are tightly interconnected with sleep and circadian rhythm, it raises the question of whether the anti-amyloid and anti-neuroinflammatory effects of GLP-1RAs (23-27) are linked to improved sleep architecture.

In a recent study, Fang *et al*. (2023) reported that subcutaneous liraglutide, a GLP-1RA, increased NREM sleep duration and reduced wakefulness in rats in a dose-dependent manner compared to controls (Figure 1) (56). This key finding provides the first evidence of the impact of GLP-1RAs on the sleep-wake cycle and their potential applications in treating sleep abnormalities associated with metabolic and/or neurodegenerative diseases.

A retrospective analysis conducted by Yeung *et al.* (2025) reported that T2D patients had nearly half the spindle density (the number of spindles per NREM sleep in minutes) as healthy participants (57). They also compared the differences in sleep spindle density between T2D patients and those treated with GLP-1RAs. Based on a cohort analysis of 260 T2D patients taking GLP-1RAs and 692 T2D patients not taking GLP-1RAs, they found that the spindle density deficit relative to healthy controls was smaller among GLP-1RA users (Figure 1). Such trends or differences in spindle densities were not observed in a comparative analysis of patients treated with or without other diabetic medications, such as metformin and/or insulin. Together, these findings illustrate an association between GLP-1RA use and relatively preserved spindle density in T2D. While these correlations between GLP-1RA treatment and sleep spindle densities were inferred from retrospective T2D data (57), prospective studies are needed to further test this hypothesis (Figure 1). Given the overlapping pathophysiological features between T2D and AD, a similar association between treatment with GLP-1RAs and sleep spindles could possibly occur in patients with AD. However, to confirm such a correlation in patients with AD, it is essential to evaluate data from AD clinical trials with GLP-1RAs (Figure 1). Subsequently, well-designed studies in AD animal models would further define any potential direct GLP-1RA treatment-related effects on sleep parameters. Results from such preclinical evaluations could serve as a proof-of-concept, unraveling the previously unknown effects of GLP-1RAs on sleep architecture, including but not limited to increasing NREM duration and sleep spindle density, thereby improving memory consolidation and decreasing the severity of AD pathologies.

GLYMPHATIC CLEARANCE IN AD AND GLP-1RA MODULATION

The Sleep-Dependent Glymphatic Clearance and Dysfunction in AD

Primarily during sleep, neurotoxic waste is removed from the brain via the glymphatic system. The glymphatic system, or the glial-dependent lymphatic transport system, uses perivascular tunnels formed by astrocytes to remove soluble waste and replenish important substances within the central nervous system, such as glucose and neuromodulators (5, 13). CSF enters along the periarterial spaces, exchanges with ISF, and the solute-laden fluid exits along the perivenous routes, ultimately clearing toward the meningeal and cervical lymphatic outflow (Figure 2). Aquaporin 4 (AQP4)

protein channels located on the end-feet of astrocytes play a critical role by allowing the bulk transport of water molecules into ISF, thereby enabling the movement of solutes in the CSF and the removal of waste products (Figure 2) (5, 13).

Glymphatic flux is enhanced during sleep, particularly during slow-wave N3 sleep, relative to wakefulness (5). The slow oscillatory brain waves during this stage increase the amount of CSF within interstitial cavities, thereby activating the glymphatic system. Reduced levels of norepinephrine during sleep lead to the expansion of extracellular space and, therefore, an increase in CSF influx and activity of the glymphatic system (5, 13). Glymphatic impairment may be a consequence of sleep dysfunction. Glymphatic clearance is significantly impaired in AD (Figure 2) (13). Patients with AD have abnormally large perivascular spaces that signal the build-up of Aβ and abnormal tau proteins (13). AD mouse models are also characterized by abnormal localization and overall reduced number of AQP4 channels on astrocytic end-feet, significantly compromising glymphatic clearance (Figure 2) (13). Furthermore, sleep and circadian disruptions caused by AD may further enhance glymphatic impairment, leading to a vicious cycle that progressively increases AD pathology (Figure 2) (5, 13).

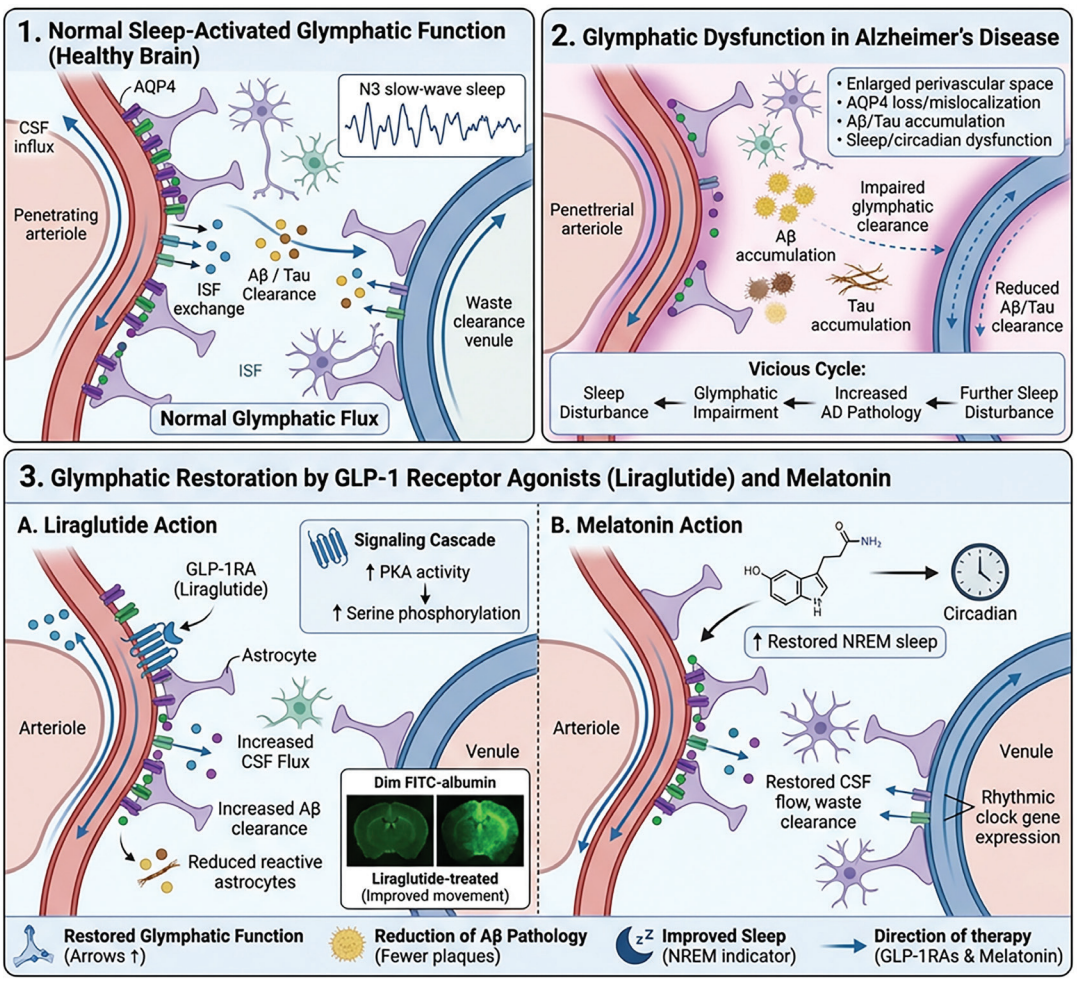

Figure 2. *Glymphatic dysfunction in AD and its modulation by GLP-1RAs and melatonin. The glymphatic system, active during slow-wave (N3) sleep, clears brain waste via CSF–ISF exchange through astrocyte-lined perivascular pathways, mediated by AQP4 channels. In AD and sleep disruption, AQP4 mislocalization and reduced expression impair clearance, leading to Aβ and tau accumulation and a worsening pathological cycle. Preclinical studies show that GLP-1RAs (e.g., liraglutide) enhance AQP4 activation and glymphatic flux, reducing Aβ burden. Similarly, melatonin restores sleep architecture, AQP4 polarization, and circadian regulation, improving glymphatic clearance. The figure was generated by the author using FigureLabs (Nano Banana Pro); https://chat.figurelabs.ai/chat.*

Restoration of Glymphatic Function by GLP-1RAs in AD

Sasaki *et al*. (2024) tested liraglutide, a GLP-1RA, for its ability to restore AQP4 localization and its impact on Aβ clearance in a mouse model of AD (58). In liraglutide-treated mice, the accumulation of Aβ plaques and the number of reactive astrocytes were significantly reduced compared to age-matched controls (Figure 2). Immunofluorescence analysis revealed that liraglutide-treated mice had significantly increased AQP4 positivity in astrocytes, increased serine phosphorylation (important for activation and membrane localization of AQP4), and increased protein kinase A activity compared to controls (Figure 2) (58). Following perfusion with fluorescein isothiocyanate-albumin (FITC-albumin) as a tracer, liraglutide-treated mice showed greater tracer flux from the perivascular to interstitial compartments (Figure 2) (58). These data indicate that GLP-1RAs can facilitate AQP4 membrane localization, activation, and increased Aβ clearance, thereby restoring glymphatic function. Similarly, melatonin produced overlapping effects in a mouse model of chronic unpredictable mild stress (CUMS) (59). Melatonin treatment of CUMS mice restored normal sleep architecture by rescuing NREM sleep duration, restoring AQP4 polarization in astrocytes, glymphatic clearance, and rhythmic expression of clock genes (Per2, Bmal1, Clock, and Per1) (Figure 2) (59). Overall, these data reflect that GLP-1RAs and melatonin elicit similar therapeutic effects that would help resolve AD pathologies through enhanced glymphatic function and by attenuating sleep disturbances.

CONCLUSION

This review summarizes the potential targeting of two key modifiable risk factors for AD by GLP-1RAs: low NREM sleep duration and reduced sleep spindle density (Figure 3). It further highlights the role of GLP-1RAs in modulating the glymphatic system via activation of AQP4 channels, thus improving the clearance of toxic AD biomarkers, including Aβ plaques and NFTs (Figure 3). These connections are largely based on preclinical studies in AD mouse models, which require further validation and assessment of their potential clinical translation and subsequent testing in well-designed clinical trials with highly efficacious and safe GLP-1RA candidates.

Exploratory and early phase clinical trials (ELAD study, REWIND LEADER, SUSTAIN 6, and PIONEER 6) conducted with GLP-1RAs, such as liraglutide and dulaglutide, resulted in greater preservation of cognitive function versus placebo (60). Subsequently, large-scale phase 3 trials (Evoke and Evoke+) were conducted with semaglutide, a more potent GLP-1RA, in AD patients with mild dementia (60). These consisted of two randomized, double-blinded trials in a total of 3808 patients enrolled between May 2021 and September 2023 to test the efficacy of orally administered semaglutide compared to a placebo. Semaglutide reduced AD biomarkers in both trials; however, unlike in the early phase trials, it failed to achieve clinical efficacy on the primary functional/cognitive endpoints. This raises several questions: how does peripherally administered semaglutide gain access to and elicit its function in the brain, whether semaglutide crosses the blood–brain barrier (BBB), is there adequate brain exposure of the active drug substance, and how broadly does it engage with its targets (GLP-1 receptors) in the brain.

GLP-1 exerts incretin hormone functions, such as postprandial increased insulin and reduced glucagon secretion, as well as delayed gastric emptying, upon binding to its respective GLP-1 receptors on pancreatic β islets, stomach, and intestine (23). In addition, it suppresses appetite by signaling to the hindbrain through gastrointestinal vagal afferent fibers (23-24). However, to elicit broader neuroprotective effects in the brain, peripheral GLP-1 secretion is insufficient and requires administered GLP-1RAs to cross the BBB. Recent labeling studies indicate that central exposure of peripherally administered GLP-1RAs, including semaglutide, is limited and does not occur through either the BBB or the blood–CSF barrier but occurs via specialized uptake by regions with reduced barrier function. This includes circumventricular organs (CVOs), such as the area postrema and median eminence of the hypothalamus (61). A specialized cell type in the CVO, called tanycytes, expresses GLP-1 receptors and acts as a gatekeeper, linking GLP-1 signaling with the intricate control of sleep and circadian rhythm balance in the hypothalamus and brainstem regions (61). It is worth noting that semaglutide distribution was localized mainly to the CVO and brainstem, despite the presence of GLP-1 receptors in many other brain regions (61). This observation could be attributed to the limitations of labeling methods in demonstrating the distribution of GLP-1RAs, which are internalized upon binding to the receptors and translocated to other regions, thus confounding biodistribution data (61). Certainly, there is more to learn about the pharmacokinetics and pharmacodynamics of GLP-1RAs in brain. However,

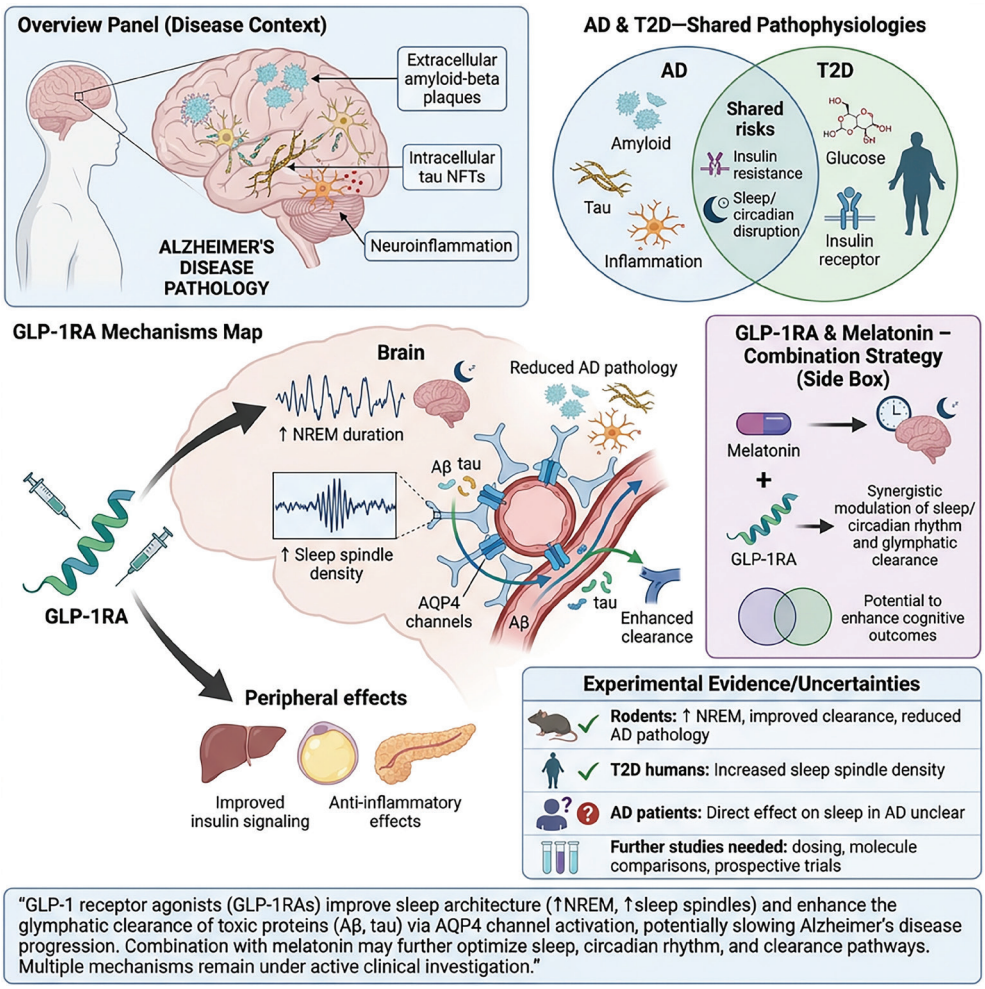

Figure 3. *Schematic overview of the proposed framework. AD involves amyloid-β (Aβ) plaques, tau tangles, and neuroinflammation, and shares features with T2D, including insulin resistance and sleep disruption. GLP-1RAs improve metabolic signaling and show neuroprotective effects. They may also enhance sleep architecture and glymphatic clearance of Aβ and tau via AQP4, potentially slowing disease progression. Combination approaches and further studies are needed to optimize therapeutic use. The figure was generated by the author using FigureLabs (Nano Banana Pro); https://chat.figurelabs.ai/chat.*

GLP-1RA molecules with well differentiated structural modifications (eg: agonists that have more broader receptor engagement), and those resistant to the GLP-1 hydrolyzing enzyme Dipeptidyl peptidase-4 (DPP4) and have more favorable hydrophobic and hydrophilic properties are required to prolong the half-life and enhance brain penetrance thereby leading to the desired functional outcomes including clinical biomarkers and improved cognition.

The lack of clinical benefits with semaglutide underscores disease complexity and the need to target multiple signaling pathways. A potentially viable option would be to consider combining GLP-1RAs with melatonin. As a naturally occurring hormone, melatonin is known for its chronobiotic (modifying the amplitude of circadian rhythm and sleep) and cytoprotective (anti-inflammatory, antioxidant, anti-tau, and anti-amyloidogenic) properties (62, 63). When administered alone, melatonin showed promising therapeutic effects in animal models and preclinical studies. However, these benefits have not been consistently translated to humans in the clinic, thereby suggesting gaps in our understanding of melatonin's potential in mitigating AD. Recent studies in animal models demonstrated that melatonin results in efficacious responses, similar to those of GLP-1RAs (59). These include restoration of AQP4 functional expression

in astrocytes and stabilizing glymphatic function, restoring NREM sleep duration as well as the abnormal expression of circadian clock genes (Per2, Bmal1, Clock, and Perl) (59). Perhaps, the co-administration of GLP-1RAs and melatonin in patients with AD following a precision medicine approach with careful consideration of dosage, timing, drug-drug interaction assessment, and clinical supervision would yield synergistic effects and better treatment outcomes. As discussed above, GLP-1RA- and melatonin-driven mechanisms of restoration of glymphatic function have been demonstrated in rodent models (58, 59). However, translating these observations to humans is largely hampered by the limitations of glymphatic measurement methods (64). In addition to the tracer-based method that was used in a liraglutide-treated AD mouse model (58), several invasive and non-invasive methods are available to measure glymphatic flux in humans. These include two-photon microscopy, contrast-enhanced magnetic resonance imaging, diffusion tensor imaging, and multimodal wearable device-based continuous measurement (64, 65). However, the results are inconsistent between rodents and humans because of differences in anatomical and physiological features (brain size and complexity, cortical folds, astrocyte morphology, sleep architecture, and cardiovascular parameters) (66). Therefore, it remains unclear to what extent glymphatic transport mechanisms are conserved across species.

In summary, in addition to the well-recognized clinical benefits of GLP-1RAs on glycemic and metabolic control of T2D and obesity, preclinical studies in animal models of neurodegenerative diseases have indicated their emerging neuroprotective and disease-modifying effects. In AD mouse models, GLP-1RAs reduced amyloid-associated pathology and neuroinflammation, supporting a potentially translatable clinical efficacy. GLP-1RAs have been shown to shift sleep architecture, including increasing NREM sleep duration in rodents and sleep spindle density in patients with T2D (Figure 3). It remains unclear whether GLP-1RAs directly improve sleep spindles and NREM in AD patients, and whether such effects are a cause or effect of improved cardiovascular and metabolic profiles observed in patients treated with GLP-1RAs. More studies are required to better understand the impact of GLP-1RAs on sleep parameters as well as glymphatic clearance. These could include, but are not limited to, optimizing the treatment regimen (dose, timing, and duration), testing with a range of GLP-1RAs to rule out if the effects are generalized across different GLP-1RA molecules, and confirming the anticipated synergism with melatonin in modulating sleep and circadian rhythm and restoring glymphatic function, leading to better cognitive outcomes (Figure 3).

In conclusion, learnings from additional investigations evaluating the role of GLP-1RAs in improving sleep parameters and glymphatic clearance could provide novel insights into their neuroprotective mechanism and/or act as the link between their metabolic benefits and anti-neuroinflammatory effects.

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CONFLICT OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this article.

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