Targeting the glymphatic system to promote α-synuclein clearance: a novel therapeutic strategy for Parkinson's disease

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From the Contents

Abstract

The excessive buildup of neurotoxic α-synuclein plays a pivotal role in the pathogenesis of Parkinson's disease, highlighting the urgent need for innovative therapeutic strategies to promote α-synuclein clearance, particularly given the current lack of disease-modifying treatments. The glymphatic system, a recently identified perivascular fluid transport network, is crucial for clearing neurotoxic proteins. This review aims to synthesize current knowledge on the role of the glymphatic system in α-synuclein clearance and its implications for the pathology of Parkinson's disease while emphasizing potential therapeutic strategies and areas for future research. The review begins with an overview of the glymphatic system and details its anatomical structure and physiological functions that facilitate cerebrospinal fluid circulation and waste clearance. It summarizes emerging evidence from neuroimaging and experimental studies that highlight the close correlation between the glymphatic system and clinical symptom severity in patients with Parkinson's disease, as well as the effect of glymphatic dysfunction on α-synuclein accumulation in Parkinson's disease models. Subsequently, the review summarizes the mechanisms of glymphatic system impairment in Parkinson's disease, including sleep disturbances, aquaporin-4 impairment, and mitochondrial dysfunction, all of which diminish glymphatic system efficiency. This creates a vicious cycle that exacerbates α-synuclein accumulation and worsens Parkinson's disease. The therapeutic perspectives section outlines strategies for enhancing glymphatic activity, such as improving sleep quality and pharmacologically targeting aquaporin-4 or its subcellular localization. Promising interventions include deep brain stimulation, melatonin supplementation, γ-aminobutyric acid modulation, and non-invasive methods (such as exercise and bright-light therapy), multisensory γ stimulation, and ultrasound therapy. Moreover, identifying neuroimaging biomarkers to assess glymphatic flow as an indicator of α-synuclein burden could refine Parkinson's disease diagnosis and track disease progression. In conclusion, the review highlights the critical role of the glymphatic system in α-synuclein clearance and its potential as a therapeutic target in Parkinson's disease. It advocates for further research to elucidate the specific mechanisms by which the glymphatic system clears misfolded α-synuclein and the development of imaging biomarkers to monitor glymphatic activity in patients with Parkinson's disease. Findings from this review suggest that enhancing glymphatic clearance is a promising strategy for reducing α-synuclein deposits and mitigating the progression of Parkinson's disease.

Key Words: aquaporin-4; astrocytes; cerebrospinal fluid; glymphatic system; interstitial fluid; neurotoxic protein clearance; Parkinson's disease; perivascular spaces; sleep disturbance; α-synuclein

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting approximately 3% of individuals over 75 years of age (Ascherio and Schwarzschild, 2016). This condition poses a significant socio-economic burden and is characterized by the excessive accumulation of neurotoxic α-synuclein deposits and progressive dopaminergic neurodegeneration in the substantia nigra pars compacta (SNc) (Dong et al., 2024; Park et al., 2024; Kerdiles et al., 2025). Currently, therapeutic options that effectively modify the progression of PD remain limited (Poewe et al., 2017; Foltynie et al., 2024; Kong et al., 2024).

"Proteinopathies" share the common feature of abnormal accumulation of misfolded proteins, including amyloid-β (Aβ), tau, and α-synuclein, either intracellularly or extracellularly (Wang et al., 2025; Zhao et al., 2025). These proteins lose their physiological functions, aggregate, and develop new neurotoxic properties that contribute to neuronal degeneration (Boland et al., 2018; Mondal et al., 2023). The glymphatic system, a newly discovered perivascular fluid transport network (Iliff et al., 2012), plays a crucial role in clearing neurotoxic proteins, including α-synuclein. It facilitates the removal of waste products from the brain through a unique arrangement of perivascular pathways. The effectiveness of the glymphatic system is especially significant in the context of PD, as emerging neuroimaging studies and experimental models reveal a strong correlation between glymphatic function and both the severity of clinical symptoms and the underlying pathology of PD (Shen et al., 2022;

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He et al., 2023; Wang et al., 2023; Mays et al., 2024; Meng et al., 2024). However, there remains a significant gap in the literature regarding the specific mechanisms by which the glymphatic system influences α-synuclein clearance and how various factors may compromise the glymphatic activity in PD. Moreover, intervention strategies to enhance the glymphatic function have not been fully explored. This review aims to synthesize current knowledge regarding the involvement of the glymphatic system in PD, highlight promising intervention strategies, and outline critical areas for future research to enhance our understanding of its role in this debilitating condition. Various factors—such as sleep disturbances, impairments in aquaporin-4 (AQP4), and mitochondrial dysfunction—may compromise glymphatic activity, creating a vicious cycle that exacerbates α-synuclein accumulation and worsens PD pathology. As the search for new treatment targets continues, elucidating the specific mechanisms by which the glymphatic system clears misfolded α-synuclein may pave the way for effective interventions that reduce α-synuclein deposits and mitigate the progression of PD.

Literature Retrieval Strategy

The articles cited in this review were sourced from the PubMed database, covering the period from 1970 to 2024. The initial search utilized the keywords "perivascular spaces" and "glymphatic system" in the Title/Abstract fields to extract data that provide an overview of the glymphatic system and its functions in various neurological disorders. The results were subsequently refined to include literature specifically related to "α-synuclein" and "Parkinson's disease." Studies focusing on other synucleinopathies, such as dementia with Lewy bodies (DLB) and multiple system atrophy (MSA), which are also associated with abnormal α-synuclein deposition, were excluded. To enhance search specificity, additional relevant keywords were incorporated, including "AQP4," "astrocytes," "sleep," "cerebrospinal fluid," "mitochondria," "neurotoxic protein clearance," and "diffusion tensor imaging along the perivascular space." We included studies that investigated the clearance pathways of α-synuclein, with a particular emphasis on the glymphatic system, while excluding intracellular clearance pathways and the clearance of other neurotoxic proteins such as Aβ. Our focus was on the interactions between glymphatic dysfunction and the progression of PD, the mechanisms underlying glymphatic system impairment in PD, and therapeutic strategies aimed at promoting α-synuclein clearance through the glymphatic system.

Glymphatic System

A brief history

The glymphatic system is a highly organized fluid transport network that surrounds blood vessels in the brain. Anatomically, it consists of periarterial and perivenous spaces, along with the intervening brain parenchyma, that serve a pseudo-lymphatic function for the central nervous system (CNS) (Plog and Nedergaard, 2018). In this system, cerebrospinal fluid (CSF) follows a specific circulation pathway. It first enters the brain through the periarterial spaces, then flows into the interstitium via the perivascular astrocytic AQP4 channels, and finally drains out the interstitial fluid (ISF) through the perivenous spaces (Plog and Nedergaard, 2018).

The perivascular system was first described by Durand-Fardel in 1842 and Pestalozzi in 1849 (Woollam and Millen, 1955; **Figure 1**). However, the anatomists Rudolf Virchow and Charles Robin are commonly credited with its discovery in the 1850s, as they identified spaces surrounding brain-perforating vessels (Woollam and Millen, 1955; Wardlaw et al., 2020). These spaces are now known as Virchow–Robin spaces (**Figure 1**). In 1869, Gustav Schwalbe provided experimental evidence by injecting dyes into the cranial subarachnoid space of animals, unexpectedly finding traces of the dye in the lymphatic system of the head and neck (Breslin et al., 2019). This discovery directly linked Virchow and Robin's initial observations to the potential existence of a lymphatic drainage-like mechanism in the CNS (**Figure 1**). Further research in the early 1900s revealed that dye injected into the CSF or subarachnoid space could enter the perivascular space (PVS), indicating an exchange of solutes between the CSF and ISF (Weed, 1914a, b; Wardlaw et al., 2020; **Figure 1**). The advent of MRI in the 1980s allowed for the *in vivo* detection of the PVSs (Braffman et al., 1988). However, visibility varied due to limitations in the imaging techniques, and these structures were largely overlooked until the early 2000s (**Figure 1**). It was not until 2012 that the concept of the glymphatic system was systematically described for the first time (**Figure 1**). Iliff et al. (2012) used two-photon imaging to capture the real-time dynamics of CSF circulation within the brain and proposed that the glymphatic system is highly dependent on astrocytes and the AQP4 proteins expressed on them. This system primarily involves the influx and efflux of CSF through the PVS, the exchange of substances with the ISF, and the clearance of metabolic waste. These groundbreaking findings established a brain-wide fluid transport pathway analogous to the structure of the lymphatic system. The research demonstrated that CSF enters the brain parenchyma from the PVSs, exchanges substances with ISF, clears metabolic waste, and ultimately drains out to the peripheral lymphatic system via the perivenous pathways (Iliff et al., 2012). This discovery challenged the long-held belief that the brain lacks a lymphatic system, and due to its functional similarities with the peripheral lymphatic system, it was aptly named the "glymphatic system" (Iliff et al., 2012; Jessen et al., 2015; Louveau et al., 2015). The role of the glymphatic system in regulating CSF circulation within the brain parenchyma and its involvement in the clearance of waste and pathological proteins have made it a focal point of emerging research on neurological diseases (Iliff et al., 2012; MacAulay, 2021).

Glymphatic system components and pathways

Since the discovery of the glymphatic system, its role in generating, transporting, and removing waste within the brain has been the subject of ongoing investigation. The glymphatic system is an evolving concept that comprises five main functional steps. The first step involves the production of CSF by epithelial cells in the choroid plexus of the cerebral ventricles. This is followed by the flow of CSF in the subarachnoid space. CSF is subsequently transported to the PVSs in the brain parenchyma, facilitated by arterial pulsations, inspiratory-respiratory pressure changes, and the pressure gradient of the CSF (Mestre et al., 2018), creating a periarterial influx. The third step involves the exchange of substances between CSF and ISF, including peptides and metabolites, in the interstitial space via convective flow (Jessen et al., 2015). Astrocytes are believed to assist in the movement of fluid between periarterial spaces and the interstitium, utilizing specialized water channels such as AQP4. These channels are highly polarized and are expressed in the astrocytic end-feet that surround brain vessels (Iliff et al., 2012; Silva et al., 2021). The fourth step, termed "glymphatic efflux," involves the drainage of metabolic waste and soluble proteins into the perivenous spaces surrounding the deep venous system. Finally, the fluid flows through the perivenous space or crosses the dura mater via meningeal lymphatic vessels (MLV), completing the waste clearance process from the glymphatic system to the cervical lymphatics (Da Mesquita et al., 2018b). Recent studies have revealed that the CNS eliminates fluid and metabolites through MLVs located at the skull base and in the dura mater of the cerebral convexity, which differ structurally from peripheral lymphatic vessels (Da Mesquita et al., 2018a; Ahn et al., 2019; Silva et al., 2021; Jacob et al., 2022; Li et al., 2022). Additionally, emerging evidence suggests that glymphatic and meningeal lymphatic structures work together (Ding et al., 2021; Silva et al., 2021).

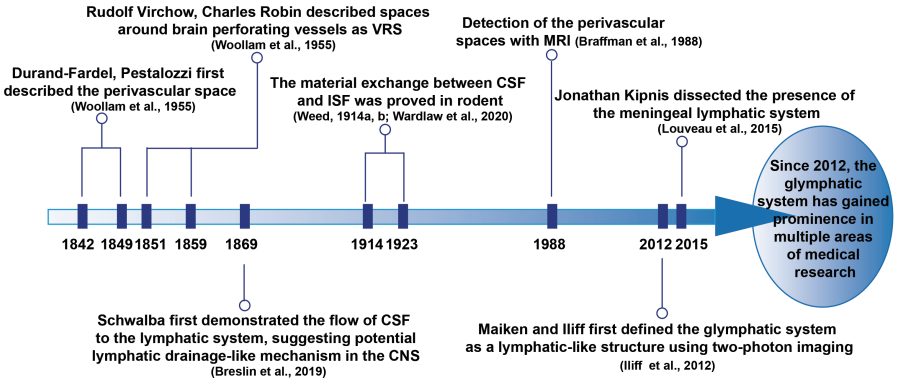

Figure 1 | **Timeline of the identification of the glymphatic system.**
CNS: Central nervous system; CSF: cerebrospinal fluid; ISF: interstitial fluid; MRI: magnetic resonance imaging; VRS: Virchow-Robin spaces.

Physiological functions and dysfunction in various neurological disorders

The glymphatic system serves several vital physiological functions, including facilitating the continuous exchange of CSF and ISF, draining ISF from the brain's parenchyma to nearby lymph nodes, and maintaining interstitial fluid balance (Iliff et al., 2012; Plog and Nedergaard, 2018). Beyond waste clearance, this system plays a crucial role in distributing nutrients—such as glucose and other essential substances necessary for the survival of neurons and astrocytes—and delivering therapeutic drugs (Lundgaard et al., 2015). Additionally, the glymphatic system promotes bulk flow that supports volume transmission and paracrine signaling, which are essential for rapid lipid diffusion and normal astrocytic Ca^{2+} signaling (Rangroo Thrane et al., 2013). Furthermore, the glymphatic system transports essential apolipoprotein E (apoE) from the choroid plexus and ventricles of the CSF to the deep brain parenchyma via the periarterial space. This transport is necessary for cholesterol transport and synaptic plasticity (Achariyar et al., 2016). The system also interacts with the immune system to regulate immune responses and surveillance (Chen et al., 2021).

A recent study found that fluid shear stress, similar to that produced by perivascular CSF or ISF dynamics, mechanically opens N-methyl-D-aspartate (NMDA) receptors on astrocytes and induces Ca^{2+} influx. This suggests a potential role for glymphatic flow in mechanotransduction (Maneshi et al., 2017).

Pathologically, studies have identified glymphatic system dysfunction in aging, various neurodegenerative diseases, cerebrovascular diseases, and neuroinflammation (Iliff et al., 2012, 2014; Gaberel et al., 2014; Kress et al., 2014; Xu et al., 2015; Peng et al., 2016; Harrison et al., 2020; Jiang et al., 2023a; **Table 1**). Research indicates that aging mice experience a significant decline in the efficiency of glymphatic CSF and ISF exchange, with a 40% reduction in Aβ protein clearance rates. This decline is likely due to diminished arteriole vessel-wall pulsatility and extensive depolarization of AQP4 (Kress et al., 2014). In the context of Alzheimer's disease (AD), Iliff et al. (2012) confirmed the ability of the glymphatic system to clear pathogenic proteins from the brain. They found that pretreatment of wild-type mice with Aβ significantly reduced CSF influx, indicating that AD leads to decreased glymphatic clearance of Aβ. In APP/PS1 AD mice, glymphatic transport was diminished by toxic Aβ oligomer deposits, and this dysfunction occurred prior to the formation of Aβ deposits. The impaired glymphatic function further exacerbated Aβ aggregation, creating a vicious cycle (Peng et al., 2016). Additionally, the deletion of AQP4 resulted in a 25%–50% increase in Aβ levels in the brain and worsened cognitive impairments in 12-month-old APP/PS1 mice. These mice exhibited increased Aβ aggregation, cerebral amyloid angiopathy, and decreased levels of synaptic proteins and brain-derived neurotrophic factor in the cortex and hippocampus (Xu et al., 2015). Iliff and colleagues further verified the ability of the glymphatic system to clear both Aβ and tau, leading to a growing body of evidence establishing a causal link between AD and glymphatic system dysfunction (Iliff et al., 2012, 2014; Harrison et al., 2020). Moreover, abnormalities in the glymphatic system have been observed in behavioral variant frontotemporal dementia (bvFTD) and are associated with the overall cognitive function and disease severity. Notably, this functional impairment primarily occurs in the anterior and middle regions of the brain in bvFTD and is negatively correlated with the expression of bvFTD-associated metabolic patterns (Jiang et al., 2023a). Therefore, regional glymphatic dysfunction may contribute to the pathogenesis of bvFTD. Additionally, traumatic brain injury (TBI) significantly impeded the perivascular influx of CSF tracers, and deletion of the AQP4 gene exacerbated glymphatic pathway dysfunction

Table 1 | **Glymphatic system impairment in PD**

Subjects/animals	References	Main findings
PD patients, iRBD patients, HCs	Si et al., 2020	Patients with iRBD exhibited a high burden of EPVS, and the burden of EPVS correlated with clinical symptom severity in iRBD and cognitive impairment in PD.
PD patients, HCs	Han et al., 2021	gBOLD-CSF coupling showed a significant reduction in patients with PD with cognitive impairment. The decoupling is associated with lower cognitive scores and structural changes.
PD patients	Chung et al., 2021	Baseline enlargement of BG-PVS may serve as a marker for the progression of motor disability in PD.
PD patients, piRBD patients, HCs	Si et al., 2022	Compared with HCs, patients with PD had a significantly lower ALPS index, and there were negative correlations between the ALPS index and disease severity.
PD patients, HCs	Shen et al., 2022	Compared with HCs, patients with PD exhibited significantly lower DTI-ALPS and higher PVS burden, which correlated with longer disease duration, higher motor and total UPDRS scores, and increased use of levodopa.
PD patients	He et al., 2023	Cross-sectional analysis demonstrated a negative correlation between the DTI-ALPS index and age, disease severity, and dyskinesia. Longitudinal analysis revealed that individuals with a low ALPS index experienced greater deterioration in motor and cognitive functions over 5 years.
PD patients	Jeong et al., 2023	CPV negatively correlates with dopamine transporter availability and UPDRS-III scores. Larger CPV volumes predict the future onset of freezing of gait and a more rapid increase in the need for dopaminergic medication.
PD patients, HCs	Wang et al., 2023	Drug-naïve patients with PD exhibited significantly weaker gBOLD-CSF coupling compared with HCs. Baseline gBOLD-CSF coupling negatively correlated with the rate of change in PD symptoms over time, while positively correlating with changes in motor function scores (UPDRS-III).
IPD patients, HCs	Cai et al., 2023	Compared with HCs, patients with PD had a lower ALPS index, which showed significant negative correlations with age, disease onset, sleep disturbances, history of diabetes, and motor symptom severity.
PD patients, HCs	Meng et al., 2024	Patients with PD exhibited significantly lower DTI-ALPS indices and higher EPVS counts, particularly in the basal ganglia and among those in the medium-to-late stages of the disease compared with HCs. The DTI-ALPS index showed negative correlations with age and UPDRS scores, while EPVS counts correlated positively with both age and UPDRS scores.
PD patients	Kim et al., 2024	Higher burdens of EPVS in the basal ganglia and temporal lobe were associated with worsening cognitive performance, increased neuropsychiatric symptoms, greater small vessel disease burden, and cortical atrophy.
PD patients, HCs	Pang et al., 2024	Patients with PD who progressed from mild cognitive impairment to dementia exhibited significantly lower DTI-ALPS indices compared with HCs. Additionally, higher volumes of perivascular spaces in the basal ganglia correlated with poorer cognitive performance.
PD patients, HCs	Pierobon Mays et al., 2024	Patients with PD exhibited significantly lower CSF signal decay rates, suggesting impaired CSF movement that correlates with decreased choroid plexus activity.
Mice	Zou et al., 2019	Blocking meningeal lymphatic drainage worsened glymphatic dysfunction, leading to increased α-synuclein accumulation, glial activation, inflammation, loss of dopaminergic neurons, and motor deficits.
Mice	Morawska et al., 2021	Enhancing slow-wave sleep reduced pathological α-synuclein accumulation and increased the recruitment of AQP4 at perivascular sites, implying improved glymphatic clearance.
Mice	Zhang et al., 2023	AQP4 deletion or acetazolamide treatment hindered α-synuclein clearance. Overexpression of A53T-α-synuclein reduced AQP4 expression and polarization, while AQP4 deficiency led to increased accumulation of α-synuclein, loss of dopaminergic neurons, and exacerbation of PD-like symptoms.
Mice	Si et al., 2024	PD models demonstrated reduced glymphatic function associated with impaired AQP4 polarization, leading to increased reactive astrogliosis and loss of dopaminergic neurons. Upregulation of MMP-9 and cleaved β-DG disrupted the localization of AQP4. Inhibiting MMP-9 restored the integrity of these structures, alleviating metabolic dysfunction and neuronal loss.

ALPS: Analysis along the perivascular space; AQP4: aquaporin-4; BG-PVS: basal ganglia perivascular spaces; β-DG: β-dystroglycan; CPV: choroid plexus volume; CSF: cerebrospinal fluid; DTI-ALPS: diffusion tensor image analysis along the perivascular space; EPVS: enlarged perivascular space; FPD: familial Parkinson disease; gBOLD-CSF: global blood oxygen-level-dependent signal-cerebrospinal fluid; HCs: healthy controls; IPD: idiopathic Parkinson's disease; iRBD: idiopathic rapid eye movement sleep behavior disorder; MMP-9: matrix metallopeptidase-9; MRI: magnetic resonance imaging; PD: Parkinson's disease; piRBDs: patients with possible iRBD; PVS: perivascular space; SNP: single-nucleotide polymorphism; UPDRS: Unified Parkinson's Disease Rating Scale.

following injury, leading to tau aggregation in the brain (Iliff et al., 2014; Xiong et al., 2021). These studies indicate the critical importance of the glymphatic system in the removal of extracellular pathological protein aggregates.

Severely impaired glymphatic perfusion has been observed in conditions such as subarachnoid hemorrhage, acute ischemic stroke, and multiple microinfarctions, and it has been shown to reduce the brain's solute clearance rate, potentially contributing to neurodegeneration (Gaberel et al., 2014; Wang et al., 2017; Lin et al., 2020). In a model of TBI, the function of the glymphatic system was reduced by 60%, and this impairment lasted for 1 month following the injury. AQP4 knockout further exacerbated glymphatic pathway dysfunction and promoted tau pathology and neurodegeneration in the post-traumatic brain, leading to significant impairments in motor function, object memory, and spatial memory (Iliff et al., 2014). Moreover, although previous research has investigated the role of adrenergic receptors in TBI, none have conclusively demonstrated how an adrenergic storm affects CSF flow after brain injury. Recently, Hussain et al. (2023) reported that post-TBI adrenergic storm suppressed glymphatic and lymphatic fluid flow, decreasing solute clearance and causing acute post-traumatic edema. Damage to the glymphatic system following TBI may be due to the adrenergic storm or increased intracranial pressure, both of which worsen edema, cause the retention of neural debris, and intensify glymphatic obstruction in a vicious cycle. Pan-adrenergic receptor inhibition enhances the lymphatic export of cellular debris and reduces inflammation and phosphorylated tau deposits, minimizing cerebral edema and improving or normalizing sensorimotor and cognitive functions in mice (Hussain et al., 2023). These findings suggest that targeting the adrenergic system may be a potential therapeutic strategy to mitigate glymphatic dysfunction in TBI and neurodegenerative diseases.

Furthermore, dysfunction of the glymphatic pathway has also been implicated in diabetes (Jiang et al., 2017), depression (Xia et al., 2017), migraine with aura (Schain et al., 2017), multiple sclerosis (Fournier et al., 2019), and chronic alcohol use (Lundgaard et al., 2018). These studies indicate the crucial role of the glymphatic system in a wide range of diseases (Jiang et al., 2017; Schain et al., 2017; Xia et al., 2017; Lundgaard et al., 2018; Fournier et al., 2019), highlighting a significant emerging therapeutic target. Research on the clearance of α-synuclein by the glymphatic system holds immense potential, though research in this field is still in its infancy.

Glymphatic System in Parkinson's Disease

α-Synuclein overview

α-Synuclein is a cytosolic neuronal protein encoded by the SNCA gene, and it constitutes 1% of cytosolic proteins and forms the pathological Lewy bodies (LBs) and Lewy neurites (LNs) (Lashuel et al., 2013). It primarily resides at the presynaptic terminals of neurons, where it regulates synaptic neurotransmitter vesicle trafficking and membrane stability (Stefanis, 2012). Additionally, α-synuclein is found in various organelles, such as the mitochondria, Golgi apparatus, endoplasmic reticulum, endolysosomal system, and nucleus (Burré et al., 2018). Its widespread presence and interactions with different organelles highlight its importance to normal neuronal function.

Structure, toxicity, and transmission of α-synuclein

α-Synuclein is a natively unfolded protein that exists primarily in a disordered monomeric form in solution, making it inherently unstable and prone to aggregation (Bartels et al., 2011). It is known for its strong preference for binding to lipid membranes, particularly those of smaller vesicles such as synaptic vesicles, which corresponds to its critical role in the release of neurotransmitters (Burré et al., 2018). Research has shown that when α-synuclein associates with membranes, it can adopt structured conformations, including either a continuous lengthened α-helix or a broken α-helix, particularly within its characteristic 11-mer repeat regions (Sung and Eliezer, 2018; Loureiro et al., 2021; Palazzi et al., 2021; Martins and Galamba, 2024). Under pathological conditions, α-synuclein undergoes a conformational change to a neurotoxic β-sheet amyloid form, which facilitates its aggregation (Yonetani et al., 2009). This process is exacerbated by the ability of membrane-bound α-synuclein to oligomerize, forming active species that are involved in synaptic vesicle release (Burré et al., 2014; Wang et al., 2014; Tosatto et al., 2015; Braun et al., 2021; Wagner and Gross, 2024). These oligomers can further assemble into protofibrils, which can ultimately aggregate into insoluble fibrils and ribbons, leading to the formation of LBs (Choi et al., 2022). While fibrils are often regarded as the toxic entities in neurodegenerative diseases, evidence suggests that smaller oligomeric forms of α-synuclein are particularly detrimental, disrupting axonal transport and inducing cellular toxicity through various mechanisms, including mitochondrial dysfunction, lysosomal leakage, and microtubule disruption (González-Sanmiguel et al., 2020). Several factors have been identified that influence the misfolding and aggregation of α-synuclein. These include acidic pH (Hu et al., 2022), elevated temperatures (Zheng et al., 2021), exposure to divalent and trivalent metal ions (Rokad et al., 2017), certain pesticides (Rokad et al., 2017), spermidine (De Risi et al., 2020; Vrijsen et al., 2023), nitric oxide (Stykel and Ryan, 2022), lipids (Kiechle et al., 2020), and even the gut microbiome (González-Sanmiguel et al., 2020). The intercellular propagation of α-synuclein misfolding is thought to follow a prion-like mechanism, where misfolded α-synuclein recruits endogenous proteins into a pathological state, thereby amplifying its neurotoxic effects and aggravating the pathology of PD (Tarutani et al., 2022).

Extracellular α-synuclein clearance pathways

The glymphatic system

The recent discovery of the glymphatic system has garnered attention for its potential role in promoting the clearance of neurotoxic proteins in neurodegenerative disorders. Traditionally, the intracranial space was believed to lack lymphatic drainage; however, evidence for the existence of an intracranial lymphatic system, including the glymphatic system and MLVs, has been confirmed within the past decade (Iliff et al., 2012). The glymphatic system facilitates dynamic fluid exchange between the CSF and ISF, a process supported by astrocytes and extracellular spaces (Jessen et al., 2015). This system is capable of conducting solute exchange and clearing metabolic waste, potentially opening new avenues for research into the diagnosis and treatment of neurodegenerative diseases.

Given the critical role of the glymphatic system in clearing extracellular pathological protein aggregates, research on the clearance of α-synuclein holds considerable promise. However, studies in this area remain limited. In recent years, novel techniques have been used to investigate glymphatic dysfunction in patients with PD (**Table 1**). Several studies utilizing a non-invasive imaging method known as diffusion tensor imaging along the perivascular space (DTI-ALPS) have demonstrated malfunctions within the glymphatic system in patients with PD (Shen et al., 2022; Si et al., 2022; Bae et al., 2023; Cai et al., 2023; Wood et al., 2024; **Table 1**). These studies have identified significant perivascular diffusion abnormalities, as indicated by a lower DTI-ALPS index, which correlates with factors such as age, disease duration, disease severity, progression, the severity of white matter lesions, and higher doses of levodopa (Han et al., 2021; Ma et al., 2021; McKnight et al., 2021; Ruan et al., 2022; Shen et al., 2022; Si et al., 2022; Cai et al., 2023). The ALPS index serves as a precursor and clinical indicator of PD, showing a decrease as the disease progresses from the prodromal to the clinical stages (Si et al., 2022). Additionally, diffusion tensor imaging to assess PVS burden contributes to our understanding of the relationship between the glymphatic system and PD pathology. Studies have shown that patients with PD exhibit a significantly higher number and volume of PVSs than healthy controls (Chung et al., 2021; Donahue et al., 2021; Shen et al., 2021, 2022; Ramirez et al., 202; **Table 1**). The decline in the DTI-ALPS index in patients with PD begins in the left hemisphere and gradually involves the right hemisphere as the disease progresses. This decline is associated with an increased PVS burden, suggesting that both measures could provide supporting evidence for impaired glymphatic function in patients with PD (Shen et al., 2022). These findings indicate that MRI assessment of the PVS load and diffusion within the PVS may serve as valuable imaging biomarkers for tracking PD progression (**Table 1**).

Functionally, the deterioration of the glymphatic system in patients with PD is associated with motor dysfunction (Chung et al., 2021; Han et al., 2021; Ruan et al., 2022; Shen et al., 2022; Jeong et al., 2023), cognitive decline (Wang et al., 2023; Kim et al., 2024; Pang et al., 2024), and rapid eye movement sleep behavior disorder (RBD) (Morawska et al., 2021; Si et al., 2022; **Table 1**). Recent studies on late-stage motor impairments in PD have compared the activity of the glymphatic system in patients with and without freezing of gait (FOG) (Gao et al., 2020; Chung et al., 2021; Ruan et al., 2022; Jeong et al., 2023). Patients with PD, regardless of FOG status, showed a significant reduction in the DTI-ALPS index compared to healthy controls. This result shows a relationship between glymphatic system dysfunction and PD. However, the difference in DTI-ALPS index

between patients with PD with and without FOG is not significant, suggesting that the DTI-ALPS index may lack sensitivity in discriminating between the two with regards to vascular diffusion differences (Ruan et al., 2022). Moreover, as a component of the glymphatic system, the volume of the choroid plexus has been analyzed in patients with early PD. Findings suggest that larger choroid plexus volume is associated with the future development of gait freezing and faster increases in dopaminergic medication, indicating that choroid plexus volume can also function as a biomarker for motor disabilities in PD (Jeong et al., 2023; **Table 1**). In addition, unlike the DTI-ALPS, which cannot dynamically assess glymphatic system function, global blood oxygen-level-dependent signal (gBOLD)-CSF coupling serves as additional evidence supporting a link between overall brain activity and glymphatic function (Han et al., 2021; Wang et al., 2023). Compared to patients with PD without mild cognitive impairment and control groups, gBOLD-CSF coupling is significantly reduced in patients with PD who exhibit cognitive impairment (Han et al., 2021). The reduced coupling of gBOLD-CSF inflow dynamics may be indicative of decreased glymphatic function, providing another potential biomarker of glymphatic dysfunction in PD (**Table 1**).

AQP4 is a key player in the glymphatic system (**Figure 2**), and polymorphisms in the AQP4 gene have been associated with alterations in glymphatic efficacy, which in turn have been linked to the rates of cognitive decline in patients with PD. One possible explanation is that genetic variations in AQP4 may influence the clearance of α-synuclein within the brain's glymphatic system (Fang et al., 2022). Furthermore, immunohistochemical analysis of brain tissue from patients with PD revealed an inverse correlation between α-synuclein aggregation and astrocytic AQP4 levels. Furthermore, patients with PD exhibited a higher number of AQP4-positive astrocytes in the neocortical regions than controls. However, these astrocytes were less prevalent in areas that are rich in α-syn. Semi-quantitative analysis demonstrated a significant negative correlation between AQP4 levels in layers V–VI and α-synuclein levels, as well as between AQP1 levels in layers II-III and α-synuclein levels. These findings suggest that the glymphatic system plays a critical role in the pathophysiology of PD (Hoshi et al., 2017).

In an experimental 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD model, AQP4 polarization and the perivascular influx and efflux of CSF were impaired (Si et al., 2024; **Table 1**). Furthermore, AQP4 deficiency or inhibition further aggravated reactive astrogliosis, reduced transforming growth factor beta 1 production by astrocytes, and exacerbated glymphatic drainage impairments, which may lead to significantly stronger microglial inflammatory responses and severe dopaminergic neuronal loss in the midbrain (Xue et al., 2019; **Table 1**). Knocking out AQP4 in the midbrains of mice led to higher levels of α-synuclein regardless of MPTP treatment, indicating that a compromised glymphatic system may have contributed to exacerbated α-synuclein-related pathology (Xue et al., 2019). Using fluorescent tracers to track the flow of CSF in A53T mice, a recent study demonstrated that glymphatic clearance was compromised in the early stages of PD-like pathology, as indicated by the impairment of CSF flow near blood vessels, increased perivascular aggregation of α-synuclein, impaired AQP4 polarization in the SNc, loss of dopaminergic neurons, and motor deficits when cervical lymphatic drainage was disrupted (Zou et al., 2019; **Table 1**). The overexpression of A53T-α-synuclein itself impaired AQP4 polarization and inhibited glymphatic function (Zhang et al., 2023; **Table 1**). Similarly, reduced expression of AQP4 or treatment with AQP4 antagonists has been shown to significantly accelerate the pathological deposition of α-synuclein and reduce the clearance of injected α-synuclein from the brain. This impairment contributes to the loss of dopaminergic neurons and motor dysfunction in PD models that receive injections of α-synuclein preformed fibrils into the striatum or SNc (Cui et al., 2021; Zhang et al., 2023; **Table 1**). These findings suggest that glymphatic system dysfunction is an aggravating factor in PD pathology, emphasizing the significance of a glymphatic clearance pathway in removing α-synuclein from the brain.

Glia

Pathological α-synuclein is believed to primarily accumulate within neurons; however, this protein and its aggregates can also be secreted from neuronal cells. Once in the extracellular space, α-synuclein becomes more susceptible to aggregation. Research has shown that all major brain cell types—including neurons, microglia (Choi et al., 2020; Scheiblich et al., 2021), and astrocytes (Tsunemi et al., 2020; Streubel-Gallasch et al., 2021; Yang et al., 2022)—play a role in maintaining α-synuclein homeostasis in the brain by phagocytosing and degrading extracellular α-synuclein aggregates (**Figure 2**). The currently recognized most effective way of clearing α-synuclein is phagocytosis by microglia. When α-synuclein accumulates within neurons, it can lead to persistent microglial activation, and the efficiency of this clearance pathway is influenced by the activation state of microglia. Studies conducted *in vitro* and *in vivo* have demonstrated that microglia can engulf extracellular α-synuclein, forming autophagosomes for degradation through selective autophagy. Inhibition of autophagy in microglia within PD models has been shown to exacerbate α-synuclein aggregation (Choi et al., 2020).

Recently, a novel "on-demand" mechanism that enhances microglial clearance of α-synuclein has been identified. In this model, microglia establish a cellular network via F-actin-dependent connections, allowing the transport of α-synuclein from overloaded microglia to adjacent naïve microglia through tunneling nanotubes. This process enables the rapid and effective degradation of the α-synuclein cargo, resulting in a reduction of the inflammatory profiles of microglia and promoting their survival (Scheiblich et al., 2021).

Furthermore, recent findings indicate that astrocytes can swiftly internalize and degrade fibrillar α-synuclein through the endo-lysosomal pathway, demonstrating even higher degradation rates than neurons (Tsunemi et al., 2020). Disruption of this pathway leads to α-synuclein aggregation in human dopaminergic neurons. Transplantation of ventral midbrain-derived astrocytes has been shown to significantly reduce pathological α-synuclein accumulation and protect dopaminergic neurons from degeneration in PD models, primarily by capturing and scavenging extracellular α-synuclein (Yang et al., 2022). In addition to their clearance functions, astrocytes can also hinder the aggregation of extracellular α-synuclein by modulating the inflammatory environment and utilizing paracrine mechanisms to suppress α-synuclein deposition (Yang et al., 2022).

Immune system

Natural killer (NK) cells are innate immune lymphocytes that play a crucial role in regulating innate immune responses in both the central and peripheral nervous systems. While there is an increased presence of NK cells in the brains of patients with PD and in PD model mice, research on their role in α-synuclein clearance remains limited (Jiang et al., 2023b). Recent studies have demonstrated that NK cells can effectively internalize and clear extracellular α-synuclein (**Figure 2**). Depletion of NK cells has been found to exacerbate α-synuclein pathology through specific pathways mediated by Toll-like receptors 4 and 2 (TLR4 and TLR2; Earls and Lee, 2020; Earls et al., 2020; Guan et al., 2022; Matveyenka et al., 2024). Unlike glial cells, NK cells do not contribute to abnormal activation or pathological progression. Furthermore, NK cells can reduce the production of pro-inflammatory interferon-γ and exhibit lower cytotoxicity (Earls et al., 2020). Additionally, vaccination with α-synuclein has been shown to produce antibodies against α-synuclein in mice, effectively reducing its production or aiding in its clearance. This finding suggests that adaptive immunity may represent an extracellular pathway for α-synuclein clearance (Masliah et al., 2005).

Protease

Neurons and glial cells actively secrete diverse classes of extracellular proteases that promote the clearance of neurotoxic proteins, including α-synuclein (**Figure 2**). One of the most abundant serine proteases, kallikrein-6 (KLK6), is primarily secreted by oligodendrocytes, pyramidal cells, and astrocytes (Prassas et al., 2015). The relationship between KLK6 and α-synuclein was initially established when KLK6 was found to co-localize with pathological Lewy bodies in the brains of patients with PD (Ogawa et al., 2000). Furthermore, the levels of KLK6 were found to inversely correlate with α-synuclein levels in CSF (Pampalakis et al., 2017), suggesting that KLK6 may influence PD and other α-synuclein-related disorders. KLK6 directly degrades extracellular α-synuclein and its fibrils via a proteolytic cascade that involves matrix metalloproteinases (MMPs), thereby inhibiting cell-to-cell propagation of α-synuclein (Pampalakis et al., 2017; Mella et al., 2020). Additionally, KLK6 inhibits α-synuclein polymerization by reducing the levels of α-synuclein monomers and producing fragmented α-synuclein, which further impedes polymerization. Another α-synuclein-degrading fibrinolytic protease, plasmin, cleaves and

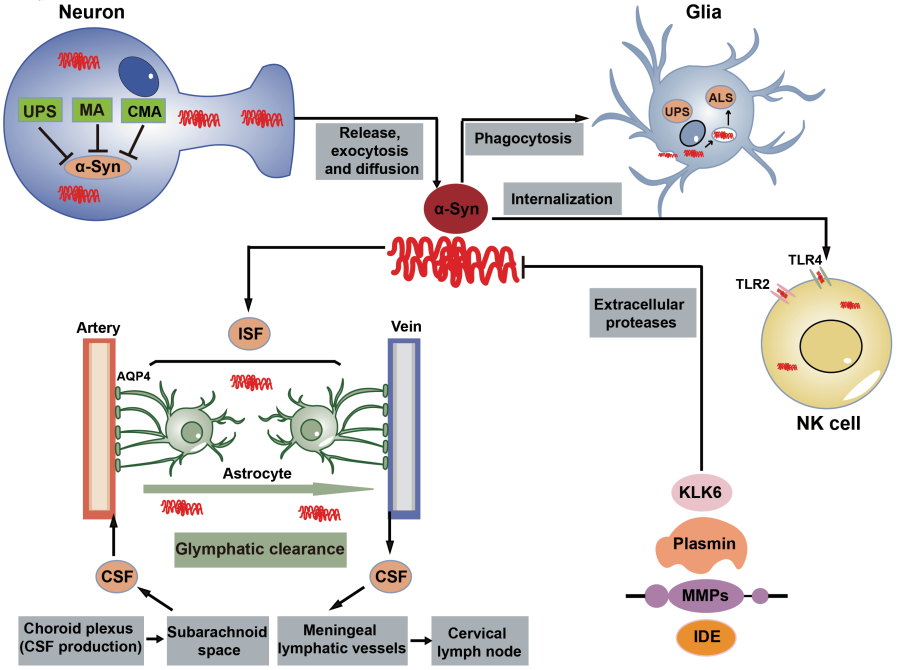

Figure 2 | Overview of intracellular and extracellular mechanisms for α-synuclein clearance in the brain.
α-Synuclein is cleared from the brain by various cell types, including neurons, glial cells, and immune cells. Intracellular clearance occurs in both neurons and glial cells, primarily through two pathways: the ALS and the UPS. The ALS plays a significant role in pathological conditions, with MA and CMA identified as the main routes for α-synuclein degradation. Extracellular α-synuclein is produced through several mechanisms, including passive diffusion, active release from neuronal terminals, exocytosis, and dispersion following cell death. The recently discovered glymphatic system facilitates the clearance of extracellular α-synuclein by eliminating metabolic waste and pathological proteins via the exchange of CSF and ISF within the brain parenchyma. CSF, produced in the choroid plexus, flows through the peri-arterial space and passes through AQP4-bearing vascular astrocytes to access the ISF. Arterial pulsations drive convective flow, propelling α-synuclein through astrocytes and into the peri-venous space, where it ultimately returns to the CSF. α-Synuclein cleared by the glymphatic system enters the meningeal lymphatic vessels and eventually converges in the cervical lymph nodes. Moreover, glial cells actively participate in the extra-neuronal clearance and degradation of α-synuclein. Microglial cells utilize selective phagocytosis, which is the most efficient pathway for removing extracellular α-synuclein. Additionally, NK cells from the innate immune system can internalize and clear extracellular α-synuclein through specific pathways mediated by toll-like receptors TLR4 and TLR2. Furthermore, extracellular proteases, including KLK6, plasmin, MMPs, and IDE, are capable of cleaving and degrading extracellular α-synuclein. These combined intracellular and extracellular processes illustrate the intricate and multifaceted nature of α-synuclein clearance, which is crucial for maintaining brain homeostasis and preventing the accumulation of pathological α-synuclein. ALS: Autophagy-lysosomal system; AQP4: aquaporin-4; CMA: chaperone-mediated autophagy; CSF: cerebrospinal fluid; IDE: insulin-degrading enzyme; ISF: interstitial fluid; KLK6: kallikrein-6; MA: macroautophagy; MMPs: matrix metalloproteinases; NK: natural killer; TLR2: toll like receptor 2; TLR4: toll like receptor 4; UPS: ubiquitin-proteasome system.

degrades both aggregated and monomeric forms of extracellular α-synuclein in a dose- and time-dependent manner. Plasmin also hinders the translocation of extracellular α-synuclein into neighboring cells and reduces the activation of microglia and astrocytes induced by extracellular α-synuclein (Guo et al., 2024). In addition to KLK6 and plasmin, other human proteases such as MMPs (Behl et al., 2021) and insulin-degrading enzyme have also demonstrated the ability to degrade extracellular α-synuclein (Sharma et al., 2015).

Intracellular α-synuclein clearance pathways

In addition to various extracellular clearance pathways, the intracellular elimination of pathological proteins is also vital (**Figure 2**). Multiple intracellular clearance pathways for α-synuclein exist not only in neurons but also in astrocytes and microglia, ranging from the ubiquitin-proteasome system (UPS) to two pathways within the autophagy-lysosome system (ALS) (Xilouri et al., 2016; **Figure 2**). The UPS is essential for maintaining protein homeostasis within cells; it involves tagging target proteins with ubiquitin, which are then recognized and specifically degraded by proteasome complexes (Swatek and Komander, 2016). Immunoblot analysis of brain samples from patients with PD has revealed the co-localization of α-synuclein aggregates and 20S proteasome components, which occurs prominently within Lewy bodies. Studies have demonstrated that maintaining normal UPS function can reduce phosphorylated serine 129 α-synuclein (pSer129-α-syn) levels, while proteasome inhibition leads to the accumulation of α-synuclein, highlighting the significance of UPS in α-synuclein clearance (Li et al., 2018; Behl et al., 2022; Suresh et al., 2023). Initially, studies suggested that the UPS was the primary proteolytic system responsible for degrading α-synuclein (Tofaris et al., 2001; Behl et al., 2022; Suresh et al., 2023). However, more recent research indicates that the ALS may play a more prominent role in α-synuclein clearance (Webb et al., 2003; Cuervo et al., 2004). Under physiological conditions, a previous *in vivo* study suggests that the degradation of α-synuclein primarily relies on both the UPS and ALS (Webb et al., 2003). In contrast, in pathological settings, the ALS assumes greater significance, particularly as α-synuclein levels increase (Cuervo et al., 2004).

Compared to proteasomes, the ALS has been extensively studied and is responsible for the degradation of long-lived proteins, large portions of the cytoplasm, and even cellular organelles (Xilouri et al., 2016). Two primary autophagic pathways—macroautophagy (MA) and chaperone-mediated autophagy (CMA)—play major roles in degrading α-synuclein (**Figure 2**). To date, no data linking microautophagy to α-synuclein degradation have been reported. Treatment with the mammalian target of rapamycin complex 1 (mTORC1) inhibitor and MA stimulant rapamycin effectively cleared both wild-type and mutant α-synuclein. In contrast, the inhibition of MA using 3-methyladenine led to a significant increase in α-synuclein levels in cell culture models (Webb et al., 2003; Vogiatzi et al., 2008), and it also promoted the production of A53T α-synuclein oligomers in transgenic mice that overexpressed this mutant form (Yu et al., 2009). Conditional deletion of the autophagy-related 7 (Atg7) gene in dopaminergic neurons resulted in impaired autophagy, accumulation of α-synuclein, and the formation of ubiquitinated protein aggregates, ultimately leading to the loss of dopaminergic neurons (Ahmed et al., 2012). The PD-causing D620N substitution in vacuolar protein sorting 35 (VPS35) disrupted autophagy by interfering with the trafficking of the autophagy-related 9 (ATG9) protein, inhibiting autophagosome formation and α-synuclein clearance (Zavodszky et al., 2014). Additionally, mutations or knockdowns of the lysosomal gene ATP13A2 have been linked to lysosomal dysfunction, α-synuclein deposition, and autosomal-recessive parkinsonism (Ramirez et al., 2006). Depending on the specific conformational state of α-synuclein, macroautophagy predominates in the clearance of α-synuclein under conditions of overexpression or mutation.

Wild-type α-synuclein contains a CMA-targeting motif (a KFERQ-like sequence) and serves as a substrate for the highly selective CMA process. In contrast, the A53T and A30P α-synuclein mutants have stronger interactions with lysosomal-associated membrane protein 2 (Lamp2a), but these interactions do not lead to the internalization or degradation of the mutant α-synuclein. CMA is a dominant pathway for α-synuclein degradation, and its inhibition results in the formation of detergent-insoluble or high molecular weight oligomeric α-synuclein (Vogiatzi et al., 2008). Mice exposed to mitochondrial toxins, as well as α-synuclein transgenic mice, exhibited increased levels of lysosomal Lamp2a and demonstrated more effective degradation of α-synuclein (Mak et al., 2010). However, CMA can also be adversely affected by aberrant α-synuclein; the A30P and A53T mutant forms of α-synuclein inhibit CMA (Cuervo et al., 2004). A significant decrease in heat shock cognate 71 kDa protein (Hsc70) or Lamp2a is correlated with increased levels of α-synuclein expression, as well as elevated levels of cytosolic CMA substrates such as myocyte enhancer factor 2 (Mef2d) and the nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IkBα). Accumulation of these proteins has been found in the substantia nigra, amygdala, and cingulate cortex in the postmortem brains of

patients with PD, suggesting that CMA dysfunction may precede and contribute to α-synuclein deposition in PD (Murphy et al., 2015).

Mechanisms of Glymphatic System Impairment in Parkinson's Disease

Sleep disturbance

The glymphatic system, which serves as a waste clearance mechanism for the brain, functions primarily during sleep and exhibits minimal activity during wakefulness. A study involving the injection of a fluorescent tracer into the subarachnoid space compared the dynamic flow of CSF into the cortex of awake, anesthetized, and sleeping mice using two-photon imaging. The results showed that glymphatic flow in the brains of awake mice decreased by approximately 95% compared to that in sleeping mice. This decrease was attributed to the contraction of interstitial spaces. Conversely, during natural sleep or anesthesia, interstitial spaces expanded by approximately 60%, facilitating better convective exchange of CSF with ISF. This increased fluid flow significantly enhances the clearance of amyloid-β (Xie et al., 2013). In a follow-up study, Hablitz et al. (2019) demonstrated that anesthetized animals exhibited increased perivascular spaces and enhanced glymphatic transport. They found that the influx speed varied according to specific anesthetic agents, indicating that the glymphatic system is most active during sleep-like states in mice. Electroencephalography recordings revealed a positive correlation between increased glymphatic inflow and enhanced cortical δ wave power, a characteristic feature of sleep and sleep-like states (such as anesthesia).

Consequently, disruptions in sleep patterns—including sleep deprivation, idiopathic REM sleep behavior disorder (iRBD), and circadian rhythm disorders—may impact the efficiency of the glymphatic system (**Figure 3**). Studies in humans have shown that individuals experiencing sleep deprivation exhibited elevated levels of residual tracers in their brain CSF compared to controls, potentially affecting glymphatic clearance pathways (Christensen et al., 2021; Liu et al., 2023a; Vinje et al., 2023; Voumvourakis et al., 2023). While extracellular diffusion alone cannot fully account for whole-brain tracer transport, it likely involves extracellular convection. Additionally, reduced advection can fully explain the decrease in tracer clearance observed following sleep deprivation (Vinje et al., 2023). These findings highlight the complex dynamics involved in metabolic waste clearance mechanisms during sleep deprivation. An MRI study revealed that patients with iRBD had significantly enlarged perivascular spaces relative to controls, which positively correlated with the severity of clinical symptoms, indicating impaired glymphatic system function (Si et al., 2020, 2022).

In early-stage PD, epidemiological studies have identified a high prevalence of sleep disorders such as insomnia, REM sleep behavior disorder (RBD), excessive daytime sleepiness, restless legs syndrome (RLS), and sleep-disordered breathing, often occurring in combination (Busková et al., 2011; Lysen et al., 2019; Dodet et al., 2024). A recent study involving 162 patients with PD and 58 healthy controls found that 71% of patients with PD experienced sleep disorders, with insomnia being the most common (41%), followed by RBD (25%), excessive daytime sleepiness (25%), and RLS (16%). The frequency of these disorders increased with disease duration and dysautonomia, while sleep-disordered breathing was less common and similar across both groups. Insomnia was linked to reduced sleep time and RLS, whereas RBD correlated with dysautonomia and age (Dodet et al., 2024). Sleep disturbances in PD may lead to impaired dilation of the perivascular space, contributing to disruptions in the glymphatic system and resulting in decreased clearance of extracellular α-synuclein (**Figure 3**). Recent clinical research has reported lower DTI-ALPS indices in patients with PD compared to normal controls, revealing a negative correlation with disease severity and providing neuroimaging evidence of glymphatic system dysfunction in these patients (Si et al., 2022). Consequently, improving sleep quality may be a promising approach to prevent neurodegenerative diseases characterized by abnormal protein deposition.

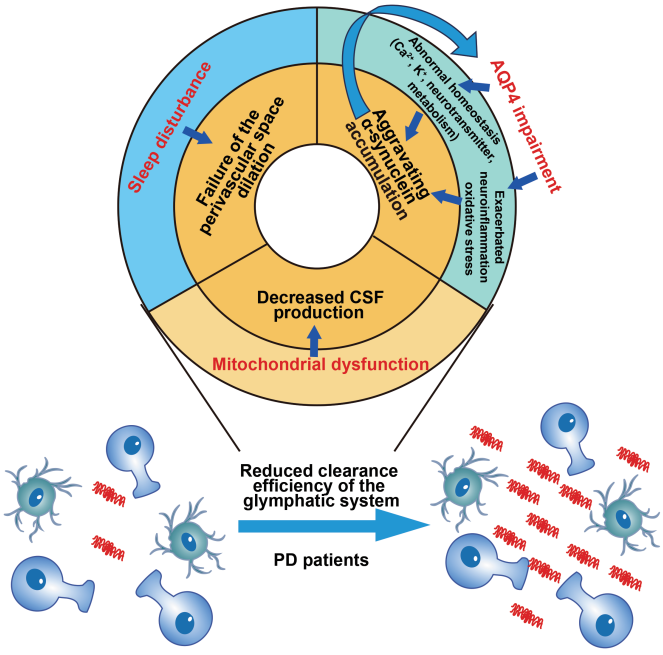

Figure 3 | **Potential mechanisms of glymphatic system dysfunction in PD.**
The mechanisms behind the reduced clearance efficiency of glymphatic flow in PD include sleep disturbances, impairment of AQP4, and mitochondrial dysfunction, all of which may contribute to the extracellular aggregation of α-synuclein. Sleep disturbances in PD can lead to a failure in the dilation of perivascular spaces, reducing the efficiency of glymphatic flow. AQP4 impairment disrupts homeostasis of ions (such as Ca^{2+} and K^+), neurotransmitters, and metabolic processes, exacerbating neuroinflammation and oxidative stress, which in turn promotes further accumulation of α-synuclein. This increased accumulation of α-synuclein further impairs AQP4-mediated glymphatic function, creating a vicious cycle that accelerates the pathological progression of PD. Additionally, mitochondrial dysfunction in PD leads to decreased CSF production and slows glymphatic flow. AQP4: Aquaporin-4; CSF: cerebrospinal fluid; PD: Parkinson's disease.

Aquaporin-4 impairment

As a water-selective channel, AQP4 plays a critical role in maintaining brain water homeostasis and the proper functioning of the glymphatic system. Mice deficient in AQP4 (AQP4 KO) exhibit structural brain abnormalities, including increased interstitial spaces and increased overall brain volume, which leads to higher water content but decreased CSF space. Despite unchanged CSF production and vascular density, these mice show altered fluid transport, characterized by slower molecular diffusion and reduced glymphatic influx. This may result in fluid stagnation in the interstitial space due to impaired glymphatic clearance (Gomolka et al., 2023). Extensive evidence demonstrates the involvement of AQP4 dysfunction and glymphatic impairments in various neuropsychiatric diseases, including AD (Zeppenfeld et al., 2017; Simon et al., 2022; Mohaupt et al., 2023; Pedersen et al., 2023), amyotrophic lateral sclerosis (Dai et al., 2017; Eisen et al., 2024), and epilepsy (Binder et al., 2012; Hubbard et al., 2016; Szu and Binder, 2022).

Recent research has identified a link between abnormal AQP4 expression and location and PD pathology (**Figure 3**). A study examining aquaporin expression in the temporal neocortex of patients with PD revealed a significant negative correlation between AQP4 levels and α-synuclein levels in the deeper cortical layers. This suggests that specific populations of reactive astrocytes expressing AQP4 may play a role in modulating α-synuclein deposition in the neocortex of patients with PD (Hoshi et al., 2017). Immunofluorescence and Western blot analyses indicate that AQP4-deficient mice ($AQP4^{-/-}$) exhibit significantly higher residual α-synuclein levels in their SNcs 2 hours after an intrastriatal injection of soluble α-synuclein monomers compared to wild-type (WT) controls. Notably, the absence of AQP4 did not result in increased aggregation of insoluble α-synuclein oligomers following phosphate-buffered saline or α-synuclein injections, suggesting that AQP4 specifically facilitates the clearance of soluble macromolecules from the brain parenchyma (Zou et al., 2019). Cui et al. (2021) further explored the

interaction between α-synuclein levels and AQP4, discovering that reduced AQP4 expression in AQP4$^{+/-}$ mice exacerbated pathological α-synuclein deposition in the striatum and cortex, as well as increased its propagation rates and behavioral impairments. They observed significant increases in insoluble α-synuclein protein levels in both the cortices and the striatum of α-synuclein preformed fibril (PFF)-injected AQP4$^{+/-}$ mice, highlighting the potential role of AQP4-mediated glymphatic clearance of insoluble proteins (Cui et al., 2021). Decreased AQP4 expression not only affects pathological α-synuclein deposition but also impacts dopaminergic neurons. In AQP4$^{+/-}$ mice, the number of dopaminergic neurons in the SNc decreased significantly by 55.2% over time (Cui et al., 2021). In line with this, Zhang et al. (2023) found that the inhibition of glymphatic activity through AQP4 gene deletion or treatment with acetazolamide reduced the clearance rate of intracerebrally injected α-synuclein from the mouse brain and contributed to the loss of dopaminergic neurons. Furthermore, overexpression of A53T-α-synuclein led to the reduced expression and polarization of AQP4, which suppressed glymphatic activity and exacerbated α-synuclein deposition (Zhang et al., 2023). This indicates a close interaction between AQP4-mediated glymphatic function and parenchymal α-synuclein levels. Evaluation of glymphatic function via ex vivo imaging revealed that matrix metalloproteinase-9 (MMP-9)-mediated cleavage of β-dystroglycan impairs AQP4 polarization, exacerbating reactive astrogliosis, restricting glymphatic drainage, and increasing dopaminergic neuron loss, thereby worsening PD. Inhibition of MMP-9 restored the integrity of the basement membrane and astrocytic end feet AQP4, improving glymphatic flow and emphasizing the crucial role of MMP-9-mediated β-dystroglycan cleavage in regulating AQP4 polarization and maintaining glymphatic function (Si et al., 2024). Additionally, neonatal stress has been shown to interfere with brain development, as evidenced by reduced AQP4 polarization in mice subjected to 14 days of maternal deprivation. This impairment of the glymphatic system's function persists into adulthood. Modeling PD in juvenile mice demonstrated that neonatal stress accelerated α-synuclein accumulation and the emergence of PD-like symptoms in adulthood, indirectly highlighting the importance of AQP4 in α-synuclein accumulation and further highlighting how alterations in glymphatic flow can influence disease progression (Song et al., 2024). Thus, AQP4 potentially mediates the glymphatic system's regulation of extracellular α-synuclein in the progression of PD. However, there is still limited information on the interaction between AQP4 dysfunction and PD, particularly concerning α-synuclein pathology and its distribution. The mechanisms linking AQP4 dysfunction to α-synuclein accumulation remain largely unclear.

The role of AQP4 in the CNS is pivotal for maintaining water and ion homeostasis. Dysfunction of AQP4 can lead to a range of issues, including disturbed intracranial pressure, imbalances in water and ion levels, and alterations in fluid microcirculation. These disturbances are linked to various pathologies, such as edema, tumors, and hydrocephalus (Papadopoulos and Verkman, 2007; Maugeri et al., 2016; Zhao et al., 2022). Recent studies have elucidated the interaction between AQP4 and the transient receptor potential vanilloid member-4 (TRPV4), a thermosensitive calcium channel. This interaction plays a crucial role in regulating cell volume and calcium homeostasis (Jo et al., 2015; Mola et al., 2016), although the exact contribution of TRPV4 to volume regulation is still debated (Toft-Bertelsen et al., 2018). Activation of TRPV4 has been shown to facilitate calcium influx, which subsequently influences AQP4-mediated water influx, thereby affecting cellular swelling responses (Jo et al., 2015). Additionally, a recent study identified a gain-of-function mutation in the TRPV4 gene that leads to increased cytosolic Ca^{2+} levels and mitochondrial dysfunction via the AKT-α-synuclein pathway (Sun et al., 2023). This suggests that AQP4 may play a role in the pathogenesis of PD through the AQP4/TRPV4/Ca^{2+}/AKT/α-synuclein signaling pathway, which deserves further investigation. Furthermore, AQP4 interacts structurally and functionally with the inwardly rectifying K^+ channel Kir4.1 in glial cells. AQP4 deficiency has been shown to impair Kir4.1-mediated extracellular K^+ uptake, potentially leading to increased neuro-excitability (Amiry-Moghaddam et al., 2003; Connors et al., 2004; Nagelhus et al., 2004). Research has also highlighted a connection between AQP4 deficiency and alterations in neurotransmitter levels, including glutamate and serotonin levels (Fan et al., 2005). Because approximately 70% of extracellular α-synuclein is released via an activity-dependent pathway, changes in glutamatergic neurotransmission could influence extracellular α-synuclein levels (Yamada and Iwatsubo, 2018). Additionally, microglia activated by released α-synuclein have been found to produce glutamate, further exacerbating excitotoxicity (dos-Santos-Pereira et al., 2018). This interplay suggests that the attenuation of K^+ buffering and alterations in glutamate transmission linked to AQP4 deficiency may contribute to the increase in extracellular α-synuclein and the progression of PD. Moreover, AQP4 depolarization in PD models has been associated with significant metabolic changes, including the upregulation of lipids, lipid-like molecules, organic acids, and neurotoxic substances, all of which may exacerbate PD (Si et al., 2024). In conclusion, impaired AQP4 function can disrupt ionic homeostasis, neurotransmitter activity, and metabolic processes, potentially leading to α-synuclein accumulation and neurodegeneration in PD. This intricate network of interactions highlights the importance of AQP4 in maintaining CNS health and the potential consequences of its dysfunction. Further research is needed to explore these mechanisms in detail (**Figure 3**).

AQP4 is also involved in CNS inflammation and immune regulation in the brain, although research yields mixed results. AQP4 knockout mice exhibit reduced levels of inflammatory cytokines and lower microglial activation in PD models, suggesting a pro-inflammatory role for AQP4 (Li et al., 2011; Dai et al., 2018; Prydz et al., 2020). Conversely, some studies indicate that AQP4 deficiency increases pro-inflammatory cytokine levels and exacerbates neuronal loss. This deficiency is also associated with a decrease in $CD4^+CD25^+$regulatory T cells and reduced levels of transforming growth factor beta 1, which increases neuroinflammation (Fan et al., 2008; Chi et al., 2011; Xue et al., 2019). Overall, AQP4 appears to influence neuroinflammation, a major contributor to oxidative stress and pathological α-synuclein aggregation. However, its specific role and context warrant further investigation (**Figure 3**). Additionally, astrocytes remove extracellular α-synuclein through phagocytosis and impact the autophagic clearance of intracellular α-synuclein via paracrine signaling, which relies on AQP4 functionality (Yang et al., 2022). Dysfunctional AQP4 can impair astrocytic migration, as well as their ability to capture and degrade α-synuclein, potentially increasing toxicity and inflammation (Saadoun et al., 2005). Meanwhile, microglia utilize toll-like receptors to internalize and clear extracellular α-synuclein (Park et al., 2009; Domingues et al., 2022). Dysregulation of AQP4 may disrupt the collaboration between astrocytes and microglia, hindering the degradation of pathological α-synuclein aggregates and contributing to neuroinflammation (Sun et al., 2016; Yi et al., 2022).

Furthermore, the underlying mechanism by which α-synuclein accumulation affects the expression and polarized localization of AQP4 remains unclear. A postmortem histological analysis revealed that phosphorylated α-synuclein tends to accumulate at the end feet of astrocytes (Nakamura et al., 2016). This finding has also been demonstrated in exogenous α-synuclein-injected mice and A53T mice (Zhang et al., 2023). The accumulated α-synuclein in the astrocytic end feet may interact with proteins in the dystrophin-glycoprotein complex, including α-syntrophin, dystrophin, and dystroglycan, disrupting the anchoring of AQP4 to the membrane of the end feet and leading to AQP4 depolarization (Nicchia et al., 2008; Noell et al., 2011; Hoddevik et al., 2017; Zhang et al., 2023; **Figure 3**). Another possibility is that extracellular α-synuclein aggregation activates astrocytes and microglia, inducing the secretion of MMP-9 (Lee et al., 2010; He et al., 2017; Tamtaji et al., 2019). MMP-9 has been shown to mediate the cleavage of β-dystroglycan and modulate AQP4 polarization (Si et al., 2024).

Therefore, AQP4 deficiency leads to two main problems: first, it impairs the ability of the glymphatic system to clear α-synuclein in PD; second, it disrupts the homeostasis of ions (such as Ca^{2+} and K^+), neurotransmitters, and metabolism, which exacerbates neuroinflammation and oxidative stress, further promoting α-synuclein accumulation. This increased accumulation of α-synuclein, in turn, further impairs AQP4-mediated glymphatic function, creating a vicious cycle that accelerates the progression of PD (**Figure 3**).

Mitochondrial dysfunction

Mitochondrial dysfunction is recognized as a primary target of α-synuclein-induced toxicity, with cellular abnormalities in mitochondrial function evident in both α-synuclein-overexpressing cells and transgenic mice (Rocha et al., 2018; Luth and Stavrovskaya, 2019). Furthermore, patients with PD exhibit decreased mitochondrial membrane potential and morphological abnormalities in the brain (Angelova et al., 2018). The aggregation of

α-synuclein leads to mitochondrial membrane depolarization, deficiencies in mitochondrial complex I activity, disruption of mitochondrial quality control, and excessive production of reactive oxygen species. These changes contribute to oxidative stress and the degeneration of dopaminergic neurons (Choong et al., 2023; Kopeć et al., 2023).

Mitochondrial function is essential for the effective operation of the glymphatic system, which facilitates the flow of CSF and is crucial for maintaining brain homeostasis (**Figure 3**). CSF is primarily produced in the choroid plexus through an osmotic gradient, with Na^+/K^+-ATPase activity playing a critical role in this process (Jessen et al., 2015). Experimental data suggest that inhibiting Na^+/K^+-ATPase, such as through the local application of ouabain—which binds to the Na^+/K^+-ATPase α1-subunit—results in a significant decrease in the secretion rate of the choroid plexus and a 50%–60% reduction in CSF production (Damkier et al., 2013; Jessen et al., 2015). The activity of the Na^+/K^+-ATPase requires substantial amounts of ATP and accounts for nearly half of the total energy consumption in the brain. This activity heavily relies on mitochondrial oxidative phosphorylation and glycolysis (Shrivastava et al., 2020). Mitochondrial dysfunction plays a key role in the pathophysiology of neurodegenerative disorders. Proteins such as α-synuclein, Aβ, tau, and SOD1, whose aggregations are linked to these conditions, can directly bind to and impair Na^+/K^+-ATPase activity. Reduced Na^+/K^+-ATPase function has been observed in AD, PD, and aging, likely contributing to a significant decline in CSF production (May et al., 1990; Silverberg et al., 2003; Pierobon Mays et al., 2024). Therefore, the integrity of mitochondrial function could impact CSF production and circulation, subsequently affecting the ability of the glymphatic system to efficiently clear metabolic waste and toxic proteins (**Figure 3**).

Therapeutic Perspectives

Given the critical role of the glymphatic system in clearing pathological proteins from the brain, targeting this system or its key molecule, AQP4, could represent an attractive new therapeutic strategy for modifying the pathological processes involved in PD. Sleep disturbances are a significant factor that leads to impaired glymphatic function in patients with PD, making the improvement of sleep quality the most straightforward strategy to naturally regulate glymphatic activity. Subthalamic nucleus deep brain stimulation has been shown to enhance nocturnal sleep quality and prevent daytime drowsiness in patients with PD (Baumann-Vogel et al., 2017; Choi et al., 2019; Liu et al., 2020), potentially promoting the glymphatic clearance of neurotoxic proteins and mitigating PD pathology. The multifaceted drug melatonin has demonstrated the ability to restore the circadian rhythm of AQP4 polarization and improve glymphatic system function, as well as enhance sleep structure and correct the abnormal expression of circadian genes such as *Per2*, *Bmal1*, *Clock*, and *Per1* in a mouse model of depression (Yao et al., 2023). Mechanistically, Per2 interacts with the α-dystrobrevin subunit of the dystrophin-glycoprotein complex and modulates the localization of AQP4. It is proposed that melatonin regulates the expression of circadian proteins, thereby improving AQP4 polarity and glymphatic system activity, which may help alleviate depressive outcomes (Yao et al., 2023). Moreover, melatonin has been effective in regulating clock genes and improving sleep quality and non-motor symptoms in patients with PD, suggesting its potential as a candidate drug for modulating glymphatic system activity and α-synuclein pathology (Ahn et al., 2020; Delgado-Lara et al., 2020). Melatonin is commonly used at low doses for treating sleep disorders and jet lag, and it is increasingly utilized for a variety of conditions, including COVID-19 prevention and treatment. However, issues regarding its optimal dosage and potential dependency remain a concern (Yao et al., 2023). A meta-analysis investigating the safety of high-dose melatonin (≥ 10 mg) in adults suggests that high doses do not lead to a detectable increase in serious adverse events or withdrawals, based on current evidence (Menczel Schrire et al., 2022). Overall, melatonin demonstrates a favorable safety profile and is easily translatable for clinical use.

Researchers investigated the regulatory effect of gamma-aminobutyric acid (GABA) on the glymphatic pathway by administering GABA or its antagonist and utilizing an AQP4 knockout model to assess the effects of GABA on glymphatic drainage. The findings revealed that GABA enhances glymphatic clearance in an AQP4-dependent manner through $GABA_A$ receptor activation. Additionally, continuous theta burst stimulation was shown to modulate the glymphatic pathway via the GABA system, suggesting potential therapeutic avenues for enhancing the glymphatic clearance of α-synuclein in PD by targeting the GABA system (Wu et al., 2023).

Another proposed strategy for regulating glymphatic function to enhance α-synuclein clearance is the direct targeting of its key molecule, AQP4, with pharmacological modulators. Studies on several AQP4 inhibitors, including arylsulfonamide, acetazolamide, TGN-020, AER-270, and the facilitator TGN-073, have been reported (Huber et al., 2018; Salman et al., 2022a; Verghese et al., 2022). While AQP4 is recognized as a druggable target due to its crucial roles in various physiological functions, its modulation may be a double-edged sword (Salman et al., 2022a; Lapshina and Ekimova, 2024). Furthermore, it remains uncertain whether small molecules can effectively block or facilitate the AQP4 pore (Salman et al., 2022a). This highlights the potential for new therapies that could emerge from a deeper understanding of the dynamic roles and protein interactions of AQP4. Aquaporins are more commonly regulated by the dynamic control of their subcellular localization than by gating. Thus, an alternative strategy for drug development involves targeting the regulation of the subcellular localization of AQP4 (Kitchen et al., 2020; Salman et al., 2022a, b). One study determined that AQP4 translocation is mediated by a calmodulin (CaM)- and PKA-dependent mechanism during hypoxia-induced swelling (Kitchen et al., 2020). CaM binding to AQP4 induces a conformational change that enhances its localization at the blood–brain and blood–spinal cord barriers. The inhibition of CaM using trifluoperazine results in reduced AQP4 localization, leading to decreased CNS edema and improved recovery (Kitchen et al., 2020). These findings suggest that activating CaM-mediated AQP4 translocation could be a promising strategy for developing treatments for PD, in which the AQP4 polarity is often impaired. Moreover, the phosphorylation of AQP4 at the specific site Ser276 in astrocytes may enhance its localization to the plasma membrane (Kitchen et al., 2015, 2020). A recent study explored the connection between R1441G mutant leucine-rich repeat kinase 2 (LRRK2)-mediated AQP4 phosphorylation and neuroinflammation. It found that LRRK2 interacts with and phosphorylates AQP4, leading to disrupted glymphatic interferon-γ clearance and increased neuroinflammation (Huang et al., 2024). Inhibiting LRRK2 was shown to restore AQP4 polarity, improve glymphatic function, and mitigate neuroinflammation and dopaminergic neurodegeneration (Huang et al., 2024). This research offers insights into potential LRRK2-targeted therapies aimed at improving AQP4 polarity and glymphatic system activity in PD. Additionally, the study emphasizes the crucial role of MMP-9-mediated β-dystroglycan cleavage in modulating AQP4 polarization and maintaining glymphatic function, suggesting that MMP-9 inhibition could be an effective strategy for restoring AQP4 integrity and enhancing glymphatic flow in PD (Si et al., 2024).

A recent study has explored non-invasive neuromodulation methods to enhance glymphatic system function. High-intensity bright-light therapy has been shown to significantly improve insomnia and depression in patients with PD (Lin et al., 2021), potentially promoting glymphatic activity. Additionally, photobiomodulation (PBM) therapy increases blood-brain barrier permeability and induces the relaxation and dilation of MLVs through vasodilation, leading to the enhanced clearance of Aβ (Salehpour et al., 2022). PBM has also been found to enhance glymphatic fluid pumping by increasing perivascular permeability. The stimulation of both intracranial and extracranial drainage systems via PBM could serve as a potential approach to improve α-synuclein clearance (Salehpour et al., 2022). A recent study investigated the role of multisensory gamma (γ) stimulation at 40 Hz in enhancing glymphatic function in a mouse model of AD (Murdock et al., 2024). The results indicated that this stimulation promotes the influx of CSF and the efflux of ISF in the cortex, facilitated by increased polarization of AQP4 in astrocytes and dilated MLVs. Furthermore, vasoactive intestinal peptide interneurons were found to regulate arterial pulsatility, thereby aiding glymphatic clearance (Murdock et al., 2024). Another study utilizing fluorescence tracing, two-photon imaging, and MRI demonstrated that a 40 Hz light flicker significantly enhanced glymphatic influx and efflux, independent of sleep or anesthesia, through increased astrocytic AQP4 polarization and improved vasomotion (Sun et al., 2024). Adenosine-A2A receptor signaling has been identified as a mechanism behind this enhancement, further confirming the potential of 40 Hz light flickering as a non-invasive method to improve glymphatic flow (Sun et al., 2024). Liu et al. (2023b) showed that auditory and visual flickering stimulations at γ

frequency reduces α-synuclein accumulation and improves both motor and non-motor symptoms in a mouse model of PD. The multisensory γ stimulation may influence glymphatic function through neurovascular coupling mechanisms mediated by vasoactive intestinal peptide or adenosine (Holstein-Ronsbo et al., 2023; Williams et al., 2023; Murdock et al., 2024; Sun et al., 2024), thereby reducing α-synuclein aggregates. Moreover, physical exercise has been demonstrated to accelerate glymphatic clearance, improve astrocytic AQP4 expression and polarization, and consequently reduce amyloid plaque accumulation, offering protection against synaptic dysfunction and cognitive decline in the aging brain (Penn et al., 2011). Recently, a novel technique involving ultrasound combined with microbubbles has been proposed to mechanically enhance glymphatic flow within the brain. Focused ultrasound has been shown to induce the dilation and contraction of PVSs around small arteries, thereby enhancing the pumping of glymphatic fluid and improving flow efficiency (Ye et al., 2023). Non-invasive neuromodulation methods provide safer and more practical alternatives to invasive methods. While PBM shows promise in targeting abnormal protein aggregates, the underlying mechanisms remain unclear. A deeper understanding of these mechanisms is essential for advancing PBM and other non-invasive therapies. However, it is important to note that this method is currently limited to *in vitro* experiments and requires significant development before reaching clinical trials, although it presents exciting new potential therapeutic targets. Furthermore, pharmacological or hyperosmotic interventions can enhance periarterial CSF influx and facilitate brain drug delivery. Acute systemic hyperosmolality has been shown to improve the delivery of intrathecal therapeutic drugs to deep brain structures and the spinal cord (Blomqvist et al., 2022), providing a promising intervention to enhance glymphatic function and facilitate effective drug delivery to the brain.

For potential translation, clinically available methods aimed at improving sleep quality in patients with PD may speculatively enhance the function of their glymphatic systems. Small molecules that directly target AQP4 are a double-edged sword; while they hold promise, they also carry potential side effects, and uncertainties remain regarding the effective blocking or facilitation of AQP4 by these compounds. An alternative pharmacological approach that focuses on regulating the subcellular localization of AQP4 may be safer and more effective. Additionally, non-invasive interventions, such as exercise, ultrasound, light therapy, and multi-sensory gamma stimulation, offer relatively better safety and clinical applicability.

Limitations

While accumulating evidence suggests that impairments in AQP4-mediated glymphatic clearance could be crucial in the onset and progression of PD, our understanding of the mechanisms underlying glymphatic system disturbances in PD remains in its infancy, necessitating further basic and clinical research. The general molecular mechanisms through which the glymphatic system clears various pathological proteins, such as Aβ and α-synuclein, are not yet well understood. Additionally, there are significant gaps in our knowledge regarding the precise role of AQP4 in this process. How does AQP4 mediate the clearance of neurotoxic α-synuclein aggregates? What forms of α-synuclein aggregates can the glymphatic system clear? What molecular mechanisms govern the polarization of AQP4, and how does α-synuclein influence the localization and expression of AQP4? These questions highlight the urgent need for further investigation into the intricacies of glymphatic clearance and its implications for PD.

Experimental studies have demonstrated various therapeutic approaches to improve glymphatic function, thereby enhancing the clearance of extracellular α-synuclein by targeting sleep disturbances and AQP4 impairment in PD models (Delgado-Lara et al., 2020; Liu et al., 2020; Salman et al., 2022a; Verghese et al., 2022; Si et al., 2024). While these interventions show promise in research, they face limitations when applied to clinical settings. Both physical therapies, such as non-invasive multi-sensory stimulation and ultrasound, as well as pharmacological treatments, including melatonin and AQP4-targeting drugs, may offer benefits. However, the mechanisms underlying these interventions are not yet fully understood, highlighting the need for further research to refine and enhance their clinical applicability. Additionally, while intrathecal injection of gadolinium allows for the direct visualization of glymphatic flow in clinical research, this method poses risks. High doses of gadolinium can lead to severe brain retention, which is often accompanied by serious headaches, particularly in patients with neurodegenerative diseases (Aydin et al., 2008; Akbar et al., 2012). Currently, indirect imaging techniques are commonly used, highlighting the urgent need to develop methods for directly assessing glymphatic flow in patients.

Conclusions

Excessive neurotoxic α-synuclein is a key factor in the pathophysiology of PD. Insufficient clearance of α-synuclein significantly contributes to the development of PD, making the improvement of glymphatic system function a promising strategy for reducing CNS α-synuclein burden. This review highlights the role of the glymphatic system in α-synuclein clearance and suggests that toxic aggregates can disrupt this system, creating a vicious cycle that exacerbates PD. Improving glymphatic function could facilitate the removal of α-synuclein, presenting a promising avenue for new therapies. Furthermore, the glymphatic system plays a crucial role in removing waste from the brain and supporting the flow of important substances, such as nutrients. A healthy glymphatic system can enhance neural regeneration by providing a clean microenvironment and supporting the health of nerve cells. This relationship is vital for recovery following brain injuries or in cases of neurodegenerative diseases.

Multifaceted mechanisms for clearing α-synuclein were summarized in this article, highlighting the importance of extracellular routes, including immune responses, proteolytic pathways, and the glymphatic system. Glymphatic system dysfunction has been correlated with disease severity and cognitive impairments in patients with PD. Several mechanisms contribute to the reduced clearance efficiency of glymphatic flow in PD. Sleep disturbances commonly experienced by patients with PD can lead to inadequate dilation of the perivascular spaces, which in turn reduces the efficiency of glymphatic flow. Additionally, impairment of AQP4 channels disrupts ion homeostasis (such as Ca^{2+} and K^{+} homeostasis), neurotransmitter balance, and metabolic processes. This disruption exacerbates neuroinflammation and oxidative stress, leading to further accumulation of α-synuclein. The increased accumulation of α-synuclein further impairs AQP4-mediated glymphatic function, creating a vicious cycle that accelerates the progression of PD. Moreover, the mitochondrial dysfunction associated with PD results in decreased CSF production and slows glymphatic flow, compounding the challenges with α-synuclein clearance. Addressing these interconnected mechanisms may provide new therapeutic targets for enhancing glymphatic function and improving outcomes in patients with PD.

Therapeutic strategies aimed at enhancing sleep quality and targeting AQP4 through pharmacological interventions or neuromodulation show promise for improving glymphatic function and addressing PD pathology. Sleep disturbances significantly impair the glymphatic system in patients with PD; therefore, improving sleep quality could enhance its efficacy. For instance, deep brain stimulation of the subthalamic nucleus may promote better sleep and assist in the clearance of neurotoxic proteins. Melatonin has emerged as a potential agent for restoring AQP4 polarization and improving sleep, suggesting its role in enhancing glymphatic activity and alleviating PD symptoms. GABA also appears to promote glymphatic clearance in an AQP4-dependent manner, indicating new therapeutic avenues for intervention. Direct modulation of AQP4 via pharmacological inhibitors is complex due to its diverse roles in brain physiology. Recent research indicates the importance of targeting the subcellular localization of AQP4 in the context of PD and neuroinflammation. Mechanisms such as calmodulin and protein kinase A-dependent pathways can enhance AQP4 expression at the blood-brain barrier during hypoxic conditions. Additionally, inhibiting leucine-rich repeat kinase 2 can restore AQP4 polarity, thereby improving glymphatic function and reducing inflammation. Non-invasive approaches, including bright-light therapy and multisensory gamma stimulation, have also been shown to enhance glymphatic activity. Physical exercise not only aids in glymphatic clearance but also boosts AQP4 expression, further supporting brain health. Furthermore, innovative techniques such as ultrasound combined with microbubbles may improve fluid transport within the brain, facilitating a more effective clearance of waste products. Acute systemic hyperosmolality has the potential to enhance CSF flow and promote therapeutic drug delivery to deep brain structures, leveraging the capabilities of the glymphatic system. Collectively, these strategies highlight a multifaceted approach to enhancing glymphatic function and addressing the underlying mechanisms of PD.

Moreover, identifying biomarkers related to glymphatic activity could refine the diagnosis and treatment of PD. Research findings suggest that the DTI-ALPS index and PVS load serve as precursors and clinical indicators of PD, as well as potential imaging biomarkers for its progression. Additionally, a larger choroid plexus volume has been associated with the future onset of motor dysfunction and more rapid increases in dopaminergic medication, indicating its potential role as a biomarker for motor disabilities in PD. Furthermore, reduced coupling of gBOLD-CSF inflow dynamics may signify decreased glymphatic function, offering another possible biomarker for glymphatic dysfunction in PD. Given the close relationship between α-synuclein aggregates and glymphatic system function, it is highly worthwhile to explore the potential of using non-invasive imaging techniques to assess glymphatic function as an indicator of the pathological progression of α-synucleinopathies.

Although the specific roles of the glymphatic system in PD represent a relatively new area of research and challenges remain, targeting the glymphatic system offers a potentially effective strategy to prevent and slow the progression of PD. This evolving field suggests several avenues for future research:

1) Mechanistic research: to investigate the specific mechanisms by which the glymphatic system clears misfolded α-synuclein. This can provide insight into how impaired clearance might contribute to disease progression.

2) Intervention research: to explore therapeutic interventions aimed at enhancing glymphatic function, such as the effects of sleep, exercise, and pharmacological agents on glymphatic clearance in PD.

3) Imaging biomarkers: to develop and refine imaging technologies to visualize glymphatic function and dynamics *in vivo*, particularly in patients with PD. Research to identify biomarkers related to glymphatic function that could serve as early indicators of PD and aid in diagnosis and monitoring disease progression are also required.

4) Age-related changes: there is a need to examine how aging affects the glymphatic system and its efficiency in clearing neurotoxic substances and how this relates to the onset of symptoms of PD.

5) Inflammation: research to assess the mutual effect of neuroinflammation and the glymphatic system and determine whether modulating glymphatic system efficiency could affect inflammation in PD and vice versa are needed.

6) Comparative studies: to compare glymphatic function in PD with that in other neurodegenerative diseases (e.g., AD) and identify unique or shared pathways in the disease pathology are required.

7) Clinical studies: large scale longitudinal clinical studies should be conducted to evaluate the safety and effectiveness of targeting the glymphatic system to clear α-synuclein for the treatment of PD.

These suggestions represent a range of approaches that can deepen our understanding of the glymphatic system and its potential implications in PD and other neurological disorders.

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