INTERNATIONAL JOURNAL OF MEDICAL SCIENCE AND DENTAL HEALTH
(ISSN: 2454-4191)
www.ijmsdh.org (2026)

Received: 4 November 2025
Revised: 21 December 2025
Accepted: 14 January 2026
Published: 29 January 2026

Page No - 87-96
DOI - 10.55640/ijmsdh-12-01-12

Article Citation: Tula, S. L. (2026). A Review on The Glymphatic System and Meningeal Lymphatics. International Journal of Medical Science and Dental Health, 12(01), 87-96. https://doi.org/10.55640/ijmsdh-12-01-12

A Review on The Glymphatic System and Meningeal Lymphatics

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Abstract

The maintenance of neuronal homeostasis within the central nervous system (CNS) requires the efficient removal of metabolic waste products and neurotoxic proteins. Historically, the CNS was considered devoid of a conventional lymphatic system, relying solely on passive diffusion for solute clearance. This paradigm shifted with the identification of the glymphatic system, a macro-scale waste clearance pathway dependent on glial cells, and the subsequent rediscovery of meningeal lymphatic vessels lining the dural sinuses. Cerebrospinal fluid (CSF) enters the brain parenchyma via peri-arterial spaces, exchanging with interstitial fluid (ISF) mediated by aquaporin-4 (AQP4) water channels localized on astrocytic endfeet. This convective flux facilitates the washout of soluble proteins, including amyloid-beta and tau, directing them toward the meningeal lymphatic network for drainage into deep cervical lymph nodes. Physiological factors, primarily sleep and arterial pulsation, critically regulate this fluid transport, while aging and traumatic injury impair its efficacy. Disruption of this dual-component clearance axis contributes significantly to the pathophysiology of neurodegenerative proteinopathies. Delineating the molecular and anatomical architecture of these systems offers novel therapeutic targets for conditions characterized by accumulation of misfolded proteins and metabolic stagnation.

Keywords: Glymphatic system, meningeal lymphatics, cerebrospinal fluid, aquaporin-4, neurodegeneration.

Introduction

For decades, the central nervous system (CNS) was regarded as an immune-privileged organ, metabolically isolated from the systemic lymphatic circulation. While peripheral tissues rely on the lymphatic system to return interstitial fluid (ISF) and proteins to the general circulation and to traffic immune cells, the brain lacks conventional lymphatic vessels within its

parenchyma. This raised a fundamental physiological paradox: the brain has a high metabolic rate, consuming approximately 20% of total body energy [1], yet it appeared to lack a dedicated mechanism for clearing the substantial metabolic byproducts generated by this activity.

The traditional understanding of neurofluid dynamics was limited to the circulation of cerebrospinal fluid (CSF) within the ventricles and the subarachnoid space. It was widely believed that the blood-brain barrier (BBB) served as the primary gatekeeper, restricting entry of solutes, while waste removal was attributed to passive processes.

The Lymphatic Paradox and Diffusion Hypothesis

Early hypotheses suggested that the CSF served as a passive "sink" for waste. According to this view, solutes moved from the brain parenchyma into the CSF solely through diffusion a process governed by thermal motion and concentration gradients [2]. While diffusion is effective for small molecules and ions over microscopic distances, it is kinetically insufficient for the rapid clearance of large macromolecules, such as amyloid-beta (Aβ) and tau proteins, across the comparatively vast distances of the human brain parenchyma. This "lymphatic paradox" persisted for over a century, leaving a significant gap in our understanding of how the brain maintains its interstitial environment free of toxic accumulation.

Glymphatic and Meningeal Discovery

The resolution to this paradox arrived with the application of in vivo two-photon microscopy, which allowed for the direct visualization of CSF flow dynamics in living tissue. This technological advancement facilitated the characterization of a highly organized, brain-wide clearance pathway.

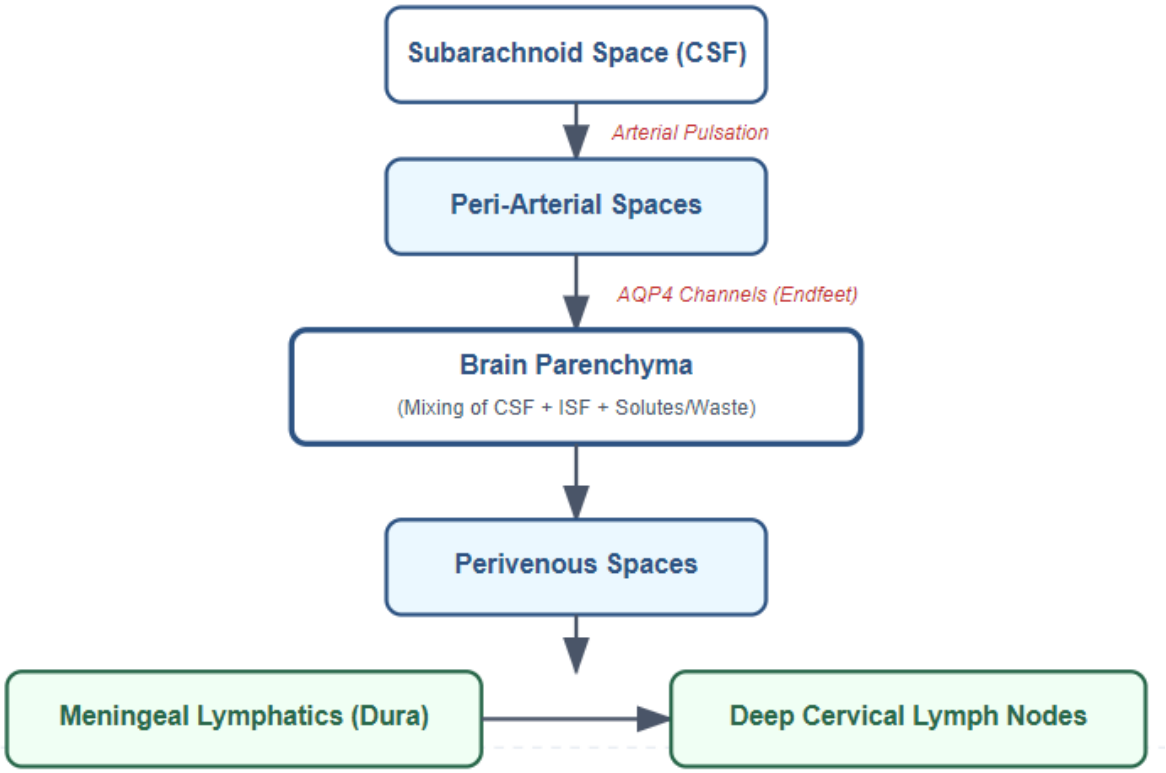

Figure 1. Glymphatic-meningeal clearance axis.

Cerebrospinal fluid (CSF) enters the brain parenchyma from the subarachnoid space via peri-arterial spaces, driven by arterial pulsation. It crosses the astrocytic glia limitans via aquaporin-4 (AQP4) channels to mix with interstitial fluid (ISF). This convective bulk flow washes metabolic waste (e.g., amyloid-β) towards perivenous spaces. Finally, fluid and solutes drain into the meningeal lymphatic vessels located in the dura mater, ultimately exiting the skull to reach the deep cervical lymph nodes

Emergence of the Glymphatic Concept

In 2012, Iliff and colleagues described the "glymphatic system," a portmanteau of "glial" and "lymphatic" [3]. This system utilizes a network of perivascular channels formed by astroglial cells to facilitate the convective flow of CSF through the brain parenchyma, effectively serving the functional role of a lymphatic system. This discovery was complemented shortly thereafter by the characterization of functional lymphatic vessels embedded within the dura mater, dismantling the long-held dogma of CNS lymphatic absence [4]. These meningeal vessels serve as the downstream drainage pathway, collecting fluid and immune cells from the CNS and transporting them to the cervical lymph nodes. Together, these systems form a complete fluid transport axis essential for maintaining protein homeostasis and immune surveillance.

The Glymphatic System

The glymphatic system represents a distinct, polarization-dependent transport pathway that runs parallel to the systemic vasculature. Its primary function involves the rapid exchange of CSF and ISF, driven by hydrostatic pressure gradients and facilitated by the molecular machinery of astrocytes.

Perivascular Spaces and Aquaporin-4 Channels

The anatomical basis of the glymphatic pathway lies in the perivascular spaces (PVS), also known as Virchow-Robin spaces, which serve as the highway for fluid entry into the brain.

Anatomy of the Virchow-Robin Spaces

These fluid-filled compartments surround penetrating arteries and veins, created by the invagination of the pia mater as vessels dive deep into the brain parenchyma [5]. Structurally, the PVS is bounded internally by the vascular smooth muscle cells and externally by the glia limitans a dense network of astrocytic endfeet that completely ensheathes the cerebral vasculature. This unique architecture creates a continuous channel allowing CSF to penetrate deep into the brain, effectively bypassing the high resistance of the neuropil.

Molecular Polarization of AQP4

Crucial to the function of this system is the polarized expression of the water channel protein aquaporin-4 (AQP4). In healthy neural tissue, AQP4 is highly concentrated at the perivascular endfeet of astrocytes, occupying up to 50% of the membrane surface area facing the vessel [6]. This polarization is maintained by the dystrophin-associated protein complex (DAPC), specifically via anchoring by alpha-syntrophin. This arrangement allows for low-resistance water movement between the peri-arterial space and the interstitium. CSF flows from the subarachnoid space into the peri-arterial PVS, moves across the astrocytic endfeet via AQP4 channels into the neuropil, and mixes with the ISF. Genetic deletion of AQP4 or mislocalization of the channel, as seen in reactive gliosis, results in a marked suppression of CSF influx and a failure to clear toxic solutes such as amyloid-beta (Aβ) [7, 8].

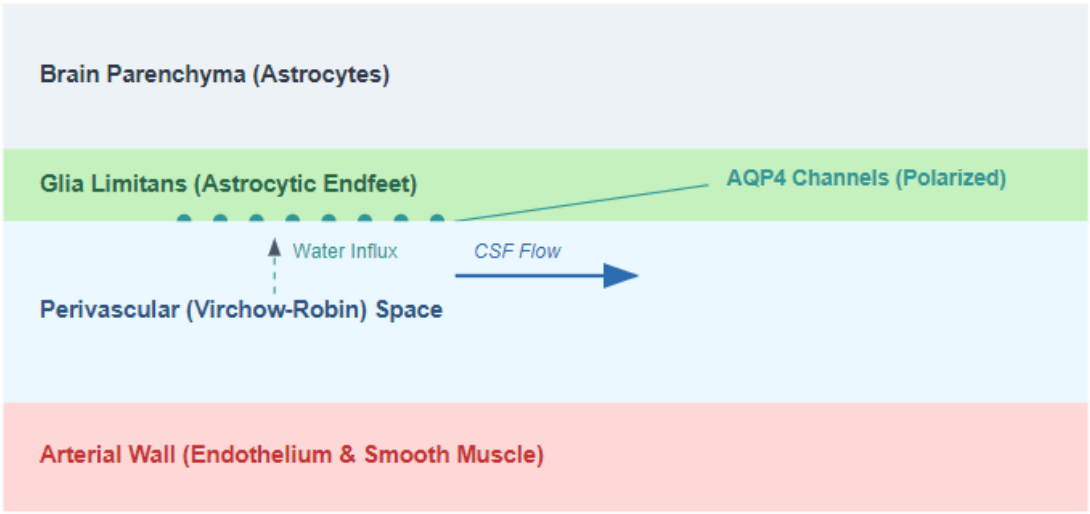

Figure 2. Cross-sectional view of the perivascular interface (Neurovascular Unit).

Cerebrospinal fluid (CSF) flows through the Perivascular (Virchow-Robin) Space, bounded internally by the arterial wall and externally by the glia limitans. Aquaporin-4 (AQP4) water channels are densely concentrated on the astrocytic endfeet (polarized expression), permitting the rapid influx of fluid from the PVS into the brain parenchyma

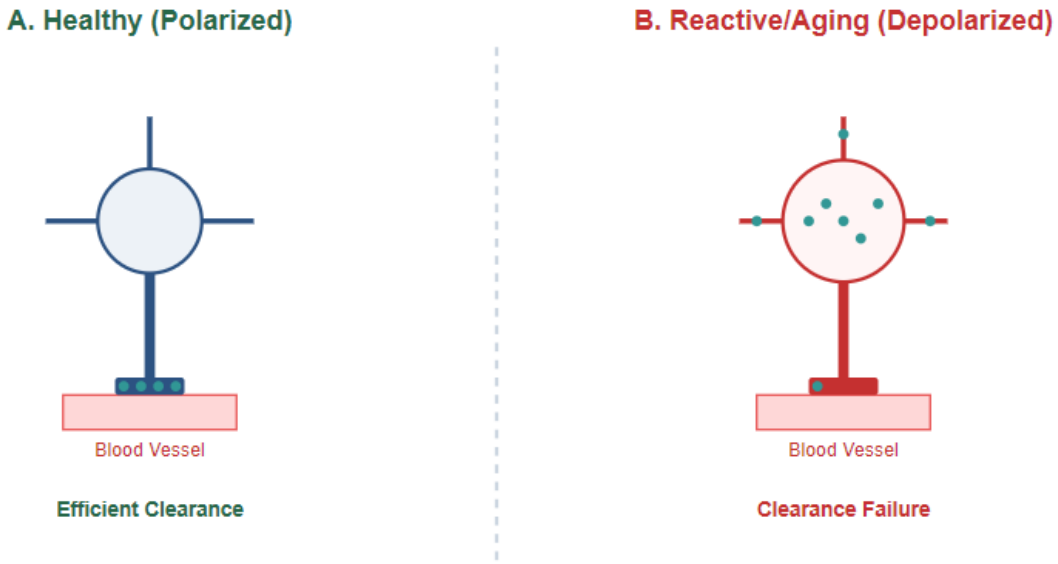

Figure 3. Impact of Aquaporin-4 (AQP4) polarization on clearance efficiency.

(A) In the healthy brain, AQP4 channels (teal dots) are strictly polarized to the astrocytic endfeet facing the blood vessel, ensuring a low-resistance pathway for fluid exchange. (B) In aging or reactive gliosis, AQP4 expression becomes depolarized, redistributing across the soma and non-vascular processes. This loss of polarization increases resistance to fluid flow and results in the failure of metabolic waste clearance.

Convective Bulk Flow versus Diffusion

A critical distinction in understanding CNS clearance is the mechanism of fluid movement. The brain utilizes advection (bulk flow) rather than relying solely on diffusion.

Limitations of Diffusive Transport

Diffusion facilitates the movement of small molecules over short distances but is inefficient for transporting large, polar molecules like peptides and proteins across the brain parenchyma. The time required for a large protein to diffuse from the center of the brain to the cortical surface would theoretically exceed the lifespan of the organism if diffusion were the sole mechanism [9]. The glymphatic system overcomes this by operating via convective bulk flow, where a pressure gradient drives the movement of fluid and its dissolved solutes together, ensuring rapid clearance regardless of molecular weight.

Table 1. Comparison of Solute Transport Mechanisms in the CNS

Feature	Passive Diffusion	Glymphatic Convective Flow
Primary Driver	Concentration gradients and thermal motion	Hydrostatic pressure gradients driven by arterial pulsation
Transport Speed	Slow; time increases exponentially with distance	Rapid; facilitates brain-wide clearance

Size Selectivity	Highly selective; favors small, lipophilic molecules	Non-selective; clears large macromolecules (e.g., Amyloid-β, Tau)
Distance Efficacy	Effective only over microscopic distances (<100 μm)	Effective over macroscopic distances (entire parenchyma)
Energy Dependence	Passive process (no energy required)	Indirectly active (relies on metabolic energy for ion gradients and arterial pressure)

Arterial Pulsatility as a Pump Mechanism

Arterial pulsation provides the primary driving force for this bulk flow. The rhythmic expansion of the arterial wall during the cardiac cycle creates a "perivascular pumping" effect that propels CSF down the peri-arterial spaces. Experimental reduction of arterial pulsatility, such as through internal carotid artery ligation, significantly attenuates perivascular flow [10]. This indicates that the stiffening of arterial walls common in atherosclerosis and aging may mechanically impede glymphatic clearance, linking cardiovascular health directly to neurodegenerative risk.

The Meningeal Lymphatic Vessels

While the glymphatic system manages fluid dynamics within the parenchyma, the ultimate egress of these fluids from the cranial vault relies heavily on meningeal lymphatic vessels. Historically, lymphatic vessels were believed to terminate at the base of the skull, leaving the brain without a conventional drainage pathway. However, high-resolution imaging and immunohistochemistry have revealed an extensive network of functional lymphatic vessels lining the dural sinuses, fundamentally altering our understanding of neuroimmunology [11].

Structural Characteristics and Molecular Profile

The meningeal lymphatic network is not uniform; it exhibits distinct anatomical and molecular features that facilitate its unique role in clearing central nervous system waste.

Lymphatic Endothelial Markers

Meningeal lymphatic vessels (mLVs) are composed of a specialized endothelial monolayer that expresses classical lymphatic markers. These include the transcription factor PROX1, the hyaluronan receptor LYVE1, and the vascular endothelial growth factor receptor 3 (VEGFR3) [12]. Unlike blood endothelial cells, these cells lack tight junctions. Instead, they possess distinct "button-like" junctions at their cell borders, which function as primary valves. This discontinuous basement membrane architecture allows for the unimpeded entry of macromolecules, immune cells, and excess fluid from the cerebrospinal fluid (CSF) compartment into the lymphatic lumen without disrupting the vessel integrity.

Table 2. Cellular and Molecular Components of the CNS Clearance Axis

Component	Primary Localization	Functional Role
Aquaporin-4 (AQP4)	Astrocytic endfeet (perivascular)	Facilitates low-resistance water exchange between PVS and ISF
Alpha-Syntrophin	Astrocytic endfeet (intracellular)	Anchors AQP4 to the endfoot membrane, ensuring polarization
PROX1	Meningeal lymphatic endothelial cell nuclei	Master transcription factor determining lymphatic identity
LYVE1	Meningeal lymphatic endothelial cell membrane	Hyaluronan receptor involved in fluid uptake and leukocyte trafficking

VEGFR3	Meningeal lymphatic endothelial cell membrane	Receptor for VEGF-C; critical for lymphangiogenesis and vessel maintenance
Glia Limitans	Perivascular boundary	Functions as a molecular sieve regulating solute entry into the parenchyma

Table 3. Anatomical and Functional Distinction Between Glymphatic and Meningeal Systems

Feature	Glymphatic System	Meningeal Lymphatic System
Location	Intraparenchymal (deep brain tissue)	Extraparenchymal (dura mater)
Primary Cell Type	Astrocytes (glial cells)	Lymphatic Endothelial Cells
Fluid Source	Cerebrospinal Fluid (CSF) and Interstitial Fluid (ISF) mixing	CSF and ISF draining from the subarachnoid space
Primary Function	Waste mobilization from tissue to perivascular spaces	Waste collection and drainage to cervical lymph nodes
Immune Role	Solute transport; limited immune cell trafficking	Major route for immune cell trafficking and antigen presentation
Drainage Destination	Perivenous spaces and subarachnoid space	Deep Cervical Lymph Nodes (dCLNs)

Dorsal versus Basal Networks

Anatomically, the vessels are distributed into two primary functional networks: the dorsal and basal meningeal lymphatics. The dorsal vessels run alongside the superior sagittal sinus and transverse sinuses. While these were the first to be characterized, recent evidence suggests that the basal meningeal lymphatic vessels, located at the skull base, may be more critical for CSF drainage. The basal vessels possess valves similar to peripheral collecting lymphatics and are situated near the arachnoid granulations and cranial nerve exit points, placing them in an optimal position to absorb CSF accumulating at the base of the brain due to gravity and bulk flow dynamics [13].

Drainage Pathways to the Periphery

The transport of fluid from the meninges to the systemic circulation follows a specific anatomical route that bridges the CNS and the immune system.

The Deep Cervical Lymph Node Connection

Once fluid enters the meningeal lymphatic network, it is transported out of the skull via the foramina, particularly the jugular foramen and stylomastoid foramen. From there, the fluid drains primarily into the deep cervical lymph nodes (dCLNs) [14]. This connection establishes a direct physical link between the central nervous system and the peripheral immune system. It allows for the trafficking of CNS-derived antigens and T-cells to the lymph nodes, facilitating immune surveillance. The ablation of these vessels in murine models results in impaired clearance of macromolecules from the subarachnoid space and correlates with cognitive deficits, indicating that these vessels are integral not just for waste removal, but for maintaining the immunological privilege of the brain.

Physiological Modulation of Clearance

The efficiency of the glymphatic-meningeal clearance axis is not static; it is highly dynamic and modulated by specific physiological states, with sleep and aging playing opposing roles.

The Role of Sleep and Circadian Rhythms

The most profound regulator of glymphatic function is the sleep-wake cycle, transforming the brain from a state of metabolic activity to one of metabolic cleaning.

Adrenergic Regulation by the Locus Coeruleus

In vivo two-photon imaging has demonstrated that glymphatic influx is dramatically enhanced during non-rapid eye

movement (NREM) sleep compared to wakefulness [15]. This state-dependent activation is primarily controlled by the locus coeruleus (LC), a brainstem nucleus that supplies norepinephrine (NE) to the cortex. During wakefulness, high levels of NE maintain astrocytes in a voluminous state, restricting the perivascular and interstitial spaces. During sleep, the firing rate of the LC diminishes, leading to a reduction in adrenergic tone.

Table 4. Physiological Modulators of CNS Clearance

Modulator	Physiological State	Mechanism of Action	Net Effect on Clearance
Sleep (NREM)	Rest/Unconsciousness	Reduced adrenergic tone causes astrocyte shrinkage and increased interstitial space volume (+60%)	Significant increase in glymphatic influx and solute clearance
Arterial Pulsation	Cardiac Cycle (Systole)	Expansion of arterial wall exerts mechanical pumping force on peri-arterial CSF	Drives convective bulk flow into the parenchyma
Aging	Senescence	Loss of AQP4 polarization (reactive gliosis) and arterial stiffening	Reduced CSF-ISF exchange and accumulation of metabolic waste
Norepinephrine	Arousal/Stress	Activation of adrenergic receptors maintains astrocyte cell volume	Constriction of interstitial space; increased resistance to fluid flow

Expansion of the Interstitial Space

The withdrawal of norepinephrine triggers a conformational change in the astrocytic cytoskeleton, resulting in a shrinkage of the cell body. This effectively expands the interstitial space volume fraction by approximately 60% [16]. This expansion significantly reduces tissue resistance to fluid flow, permitting faster convective cleaning of the neuropil. Consequently, sleep deprivation suppresses the clearance of amyloid-beta and other metabolites, providing a mechanistic link between chronic sleep disruption and the risk of developing neurodegenerative conditions.

Aging and the Decline of Fluid Dynamics

Aging acts as a universal suppressor of glymphatic and meningeal function, contributing to the vulnerability of the elderly brain to protein aggregation.

AQP4 Depolarization and Gliosis

In the aging brain, there is a pervasive loss of perivascular AQP4 polarization. Instead of being concentrated at the astrocytic endfeet, AQP4 redistributes across the entire astrocytic soma [17]. This phenomenon is often associated with reactive gliosis, a state of low-grade inflammation common in aging tissues. The depolarization decouples the low-resistance pathway required for efficient CSF-ISF exchange, leading to stagnation of interstitial fluids.

Vessel Regression and Arterial Stiffening

Concurrently, the driving forces of the system weaken. Arterial stiffening (arteriosclerosis) reduces the pulsatile force necessary to drive perivascular fluid movement. Furthermore, meningeal lymphatic vessels undergo regression with age, showing reduced vessel diameter and coverage [18]. This creates a bottleneck at the drainage sites, causing a backup of fluid and waste products within the parenchyma, thereby exacerbating the accumulation of toxic proteins.

Clinical Implications in Neurodegeneration

The failure of protein clearance mechanisms is a hallmark of proteinopathic neurodegenerative diseases, suggesting that these conditions may be fundamentally disorders of "dirty" brain fluid dynamics.

Alzheimer's Disease and Amyloidosis

Alzheimer's disease (AD) is characterized pathologically by the extracellular accumulation of amyloid-beta plaques and intracellular tau tangles.

Impaired Clearance Preceding Plaque Formation

Evidence suggests that glymphatic impairment is an early event in AD pathogenesis, occurring prior to significant plaque deposition. The system contributes to the clearance of soluble amyloid-beta. When this clearance is impaired whether through genetic AQP4 deletion, sleep fragmentation, or aging the concentration of soluble amyloid increases, promoting its aggregation into insoluble plaques [19].

Table 5. Pathological Alterations in Neurodegenerative Disorders

Disorder	Aggregating Protein	Primary Clearance Defect	Consequence
Alzheimer's Disease	Amyloid-beta (Aβ)	Loss of perivascular AQP4 polarization; Meningeal vessel regression	Accumulation of soluble Aβ leading to plaque formation and cerebral amyloid angiopathy
Traumatic Brain Injury	Tau (Microtubule-associated)	Acute disruption of glymphatic flow; Structural damage to meningeal vessels	Failure to clear injury-released tau, promoting aggregation and potential CTE progression
Parkinson's Disease	Alpha-Synuclein	Impaired meningeal lymphatic drainage	Aggregation of alpha-synuclein in the substantia nigra; exacerbated motor deficits
Cerebral Small Vessel Disease	Various / None specific	Arterial stiffening reduces pulsatile drive	General stagnation of ISF and development of white matter hyperintensities

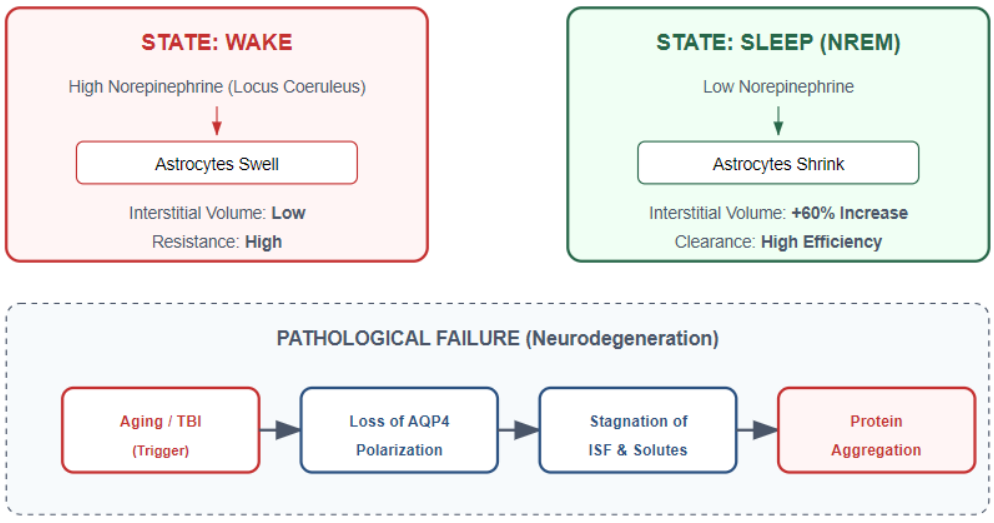

Figure 4. Physiological Regulation & Pathological Failure

(Top) The influence of the sleep-wake cycle on glymphatic efficiency. During wakefulness, norepinephrine maintains astrocytic volume, minimizing the interstitial space. During sleep, reduced adrenergic tone leads to astrocyte shrinkage, expanding the extracellular volume and facilitating clearance. (Bottom) The pathological cascade initiated by aging or traumatic brain injury (TBI),

leading to the loss of AQP4 polarization, fluid stagnation, and the subsequent aggregation of neurotoxic proteins like amyloid-β and tau

The Feed-Forward Loop of Toxicity

Once formed, amyloid-beta can deposit within the perivascular spaces, a condition known as cerebral amyloid angiopathy (CAA). These deposits physically obstruct the perivascular channels, increasing resistance to flow and further impeding clearance. This creates a vicious feed-forward cycle where initial accumulation damages the drainage system, leading to further accumulation and toxicity.

Traumatic Brain Injury (TBI)

Traumatic brain injury causes acute disruption of glymphatic function which may have long-term consequences.

Acute Disruption and Tau Accumulation

Following impact, there is often a sustained loss of AQP4 polarization and structural damage to meningeal vessels [20]. This disruption can persist for weeks or months post-injury. TBI releases large amounts of tau protein from damaged axons. If the clearance system is compromised by the injury itself, this tau cannot be effectively removed.

Link to Chronic Traumatic Encephalopathy (CTE)

The resulting accumulation of hyperphosphorylated tau is a key driver of chronic traumatic encephalopathy (CTE). This suggests that post-traumatic neurodegeneration is not merely a result of the initial mechanical force, but a failure of the clearance systems to recover and remove the toxic byproducts of that injury.

Parkinson's Disease and Synucleinopathies

While less studied than AD, Parkinson's disease involves the aggregation of alpha-synuclein.

Alpha-Synuclein Dynamics

Recent evidence suggests that alpha-synuclein is also cleared via the glymphatic pathway. Dysregulation of meningeal lymphatic drainage exacerbates alpha-synuclein pathology in the substantia nigra and other regions. Enhancing lymphatic function in animal models via growth factor treatment (e.g., VEGF-C) has shown promise in reducing aggregation and ameliorating motor deficits, identifying the meningeal lymphatics as a potential therapeutic target [21].

Conclusion

The conceptualization of CNS waste clearance has evolved from a passive, diffusion-reliant model to a complex, regulated system of fluid dynamics involving the glymphatic system and meningeal lymphatic vessels. This integrated network utilizes astrocyte-mediated convective flow and dural lymphatic drainage to maintain the delicate homeostatic balance of the brain. The sensitivity of this system to sleep, arterial pulsatility, and aging underscores its physiological relevance. The identification of clearance failure as a common denominator in Alzheimer's disease, traumatic brain injury, and other neurodegenerative conditions is a remarkable finding in our treatment and management approach to these disorders. Restoring AQP4 polarization, enhancing meningeal lymphatic drainage, or mimicking the fluid dynamics of sleep may offer potent avenues to halt or reverse the progression of proteinopathies.

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