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EDITORIAL

Kalawatia M, Mehrunkar A, Lucke-Wold B. Harnessing resilience in patient treatment and long-term recovery: Psychosocial and neurobiological pathways to enhanced outcomes. *World J Psychiatry* 2025; 15(10): 109462 [DOI: [10.5498/wjp.v15.i10.109462](https://doi.org/10.5498/wjp.v15.i10.109462)]

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ORIGINAL ARTICLE

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Glymphatic system dysfunction in alcohol use disorder: Current understanding and future directions

Jia-Yu Lin, Hai-Bo Zhang, Ling Luo, Ren-Jie Li, Xiao-Guang Wang

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Abstract

The glymphatic system, a recently discovered cerebrospinal fluid-mediated pathway, plays a crucial role in fluid exchange and waste clearance in the brain. Its dysfunction has been implicated in various neurological disorders, including Alzheimer's disease and traumatic brain injury. Recent studies suggest that alcohol intake has a biphasic effect on the glymphatic system: Low doses of alcohol enhance glymphatic function, whereas high doses lead to glymphatic suppression and cognitive decline, mirroring patterns seen in alcohol-related dementia, providing valuable insights into the dose-dependent effects of alcohol on glymphatic function, but significant gaps persist, particularly regarding the mechanistic understanding and the influence of confounding factors such as sex, age, blood pressure, and wakefulness. Here, we synthesize and critically evaluate the important research findings within this field to gauge its progress and identify new research opportunities. We discuss the specific mechanisms by which alcohol affects the glymphatic system, including how alcohol influences cerebrospinal fluid-interstitial fluid exchange and waste removal. We also discuss the potential

of the glymphatic system as a new target, such as through pharmacological or lifestyle interventions aimed at enhancing glymphatic function to treat alcohol use disorder and other neurological disorders associated with glymphatic dysfunction.

Key Words: Alcohol use disorder; Glymphatic system; Aquaporin 4; Perivascular space; Mitochondrial dysfunction

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Core Tip: The glymphatic system, a critical pathway for fluid exchange and waste clearance in the brain, is linked to neurological disorders when dysfunctional. Alcohol has a biphasic effect: Low doses enhance glymphatic function, while high doses suppress it and cause cognitive decline, mirroring alcohol-related dementia. Studies explore how alcohol affects cerebrospinal fluid-interstitial fluid exchange and waste removal. Despite progress, gaps remain in understanding mechanisms and confounding factors like sex, age, and blood pressure. The significance of this review lies in deepening the understanding of the relationship between alcohol and glymphatic system disorders and offering possible targets for developing new treatments.

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INTRODUCTION

Alcohol is the most commonly used addictive substance worldwide. Alcohol use disorder (AUD), a prevalent psychiatric condition, is characterized by compulsive alcohol consumption, loss of control over drinking, and withdrawal-related negative emotions[1]. It poses a significant threat to public health, contributing to more than 140000 deaths annually in the United States[2]. The history of mechanistic understanding of AUD is long, complex, and full of controversies. Records from ancient biblical, Egyptian, and Babylonian sources document early recognition of alcohol misuse. By the 18th century, habitual intoxication was moralized as weakness, necessitating punitive re-education (moral model). The 19th century temperance movement reframed AUD as a pharmacological vulnerability, advocating regulatory control. Modern biological frameworks emerged in the 20th century, culminating in Leshner's "brain disease model", which recognized AUD as a neurobiological disorder with behavioral and social dimensions[3]. Recently emerging research highlights the glymphatic system in AUD pathophysiology. This system, newly identified as a mechanism responsible for clearing metabolic waste in the brain, can lead to the accumulation of metabolic waste when dysfunctional, thereby affecting cognitive function and potentially exacerbating the progression of neurodegenerative diseases[4,5]. Currently, the effects of alcohol on the glymphatic system have not been fully summarized.

This review examines alcohol's potential mechanisms of action on glymphatic regulation, aiming to identify novel therapeutic targets for patients with AUD with glymphatic impairment.

GLYMPHATIC SYSTEM

In 2012, Iliff *et al*[6] discovered that cerebrospinal fluid (CSF) enters the brain parenchyma *via* perivascular spaces around arteries, and interstitial fluid (ISF) is cleared along paravenous pathways. This system, resembling a brain lymphatic system and reliant on astrocytes, was named the glymphatic system. It comprises three components: CSF inflow pathways (PVSs/Virchow-Robin spaces[7] around arteries), ISF outflow pathways (around veins), and fluid exchange pathways connecting the two, mediated by aquaporin 4 (AQP4) on astrocyte endfeet (Figure 1)[8].

The Virchow-Robin space, formed by endothelial cells, basement membrane, astrocyte endfeet, and extracellular fluid, serves as the CSF entry pathway[9]. As pial arteries penetrate the brain parenchyma, arterial pulsations and AQP4 water channels on astrocyte endfeet drive CSF influx[10-12], where it mixes with ISF containing metabolic waste. Waste-laden fluid is subsequently cleared through three efflux routes: Along cranial/spinal nerve sheaths to lymphatic vessels[13,14], along olfactory nerves to nasal lymphatics[15], or absorption by arachnoid granulations into venous blood[16,17]. By maintaining ISF homeostasis and cerebral metabolic balance *via* convective CSF transport, the glymphatic system prevents neurotoxic waste accumulation. Dysfunction in this system is implicated in neuroinflammation and neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD).

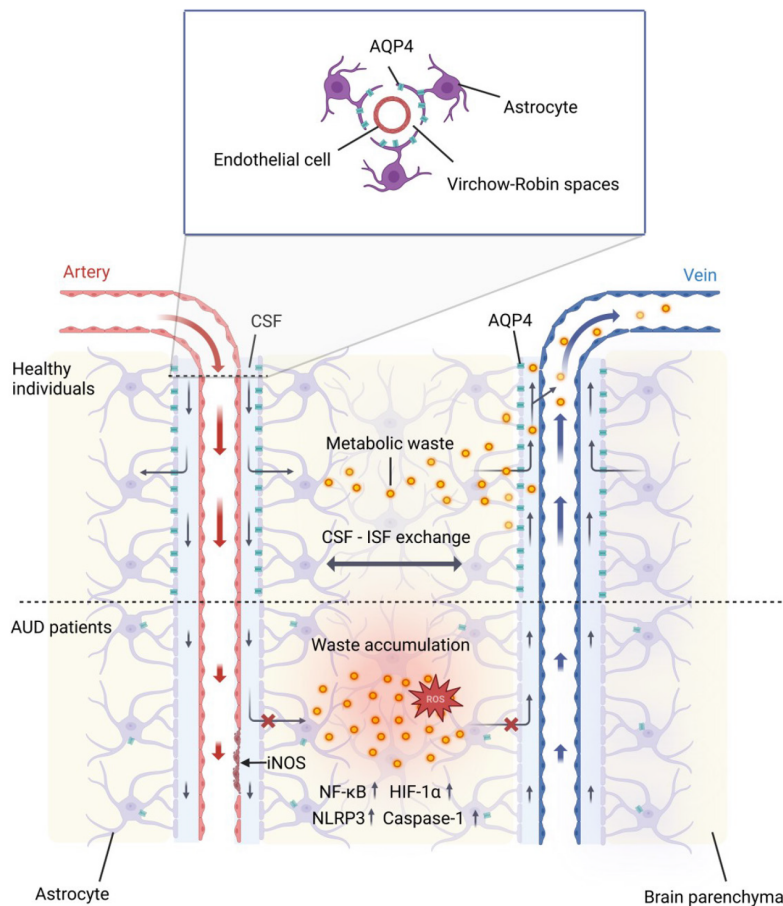


Figure 1 The glymphatic system in healthy individuals and alcohol use disorder patients. AQP4: Aquaporin 4; AUD: Alcohol use disorder; CSF: Cerebrospinal fluid; HIF-1 α : Hypoxia-inducible factor-1 alpha; iNOS: Inducible nitric oxide synthase; ISF: Interstitial fluid; NF- κ B: Nuclear factor kappa B; NLRP3: NOD-like receptor protein 1.

DOSE-DEPENDENT AND TIME-DEPENDENT EFFECTS OF ALCOHOL ON THE GLYMPHATIC SYSTEM

The dose-effect and time-effect of alcohol on the glymphatic system remain unclear. Lundgaard *et al*[18] found that both acute and chronic low-dose alcohol exposure improved glymphatic system function without affecting the polarization of AQP4. Additionally, chronic high-dose alcohol exposure reduced glial fibrillary acidic protein (GFAP) expression. He proposed that these improvements may be attributed to low-dose alcohol reducing neuroinflammation and enhancing cerebral arterial pulsatility[18]. In contrast, acute high-dose alcohol exposure significantly inhibited glymphatic function [18,19]. Lundgaard *et al*[18] attributed this inhibition to reduced cardiac output and pulse pressure caused by acute alcohol intoxication, leading to diminished CSF flow. However, Liu *et al*[19] suggested that elevated β -endorphin release and reduced cerebrovascular pulsatility following acute alcohol consumption played an important role[19]. Notably, neither acute high-dose nor chronic low-dose exposure affects GFAP or AQP4 expression.

In a mouse model, chronic high-dose alcohol exposure increased GFAP expression, facilitated AQP4 polarization, promoted reactive astrocytosis and enlarged PVS, and inhibited glymphatic function[18-20]. In human clinical samples, chronic high-dose alcohol consumption has been shown to impair the glymphatic system. Histopathological examination of the brains of chronic alcoholics reveals enlargement of Virchow-Robin spaces, which may be associated with personality changes[21]. Consistently, patients exposed to alcohol long term with alcohol-related brain damage demonstrate a significant enlargement PVS in the frontal cortex and basal ganglia, indicating that glymphatic function may be impaired[20]. We recently investigated whether diffusion tensor imaging (DTI) along the PVS (ALPS) index can be used as a translational biomarker for glymphatic dysfunction in AUD. The results showed that the AUD group had a lower ALPS index than the control group, and there was a positive correlation between the ALPS index and Montreal Cognitive Assessment/Mini-Mental State Examination scores, suggesting that chronic high-dose alcohol consumption can induce glymphatic impairment and cognitive deficits[22]. However, longitudinal studies are needed to disentangle causal relationships in the future. Consistently, it was found that individuals with AUD exhibited widespread astrocytic reactive proliferation and neuroinflammation[23]. In summary, these studies highlight the dose-dependent and time-dependent effects of alcohol on the glymphatic system. Acute and chronic low-dose alcohol exposure improved glymphatic function, while acute and chronic high-dose exposure inhibited it, albeit through differing mechanisms.

MECHANISMS BY WHICH ALCOHOL MEDIATES GLYMPHATIC DYSFUNCTION

Alcohol induces the dysfunction of the glymphatic system through a variety of mechanisms, including the loss of AQP4 polarization, expansion of the PVS, astrocyte dysfunction, reduced cerebrovascular pulsation, metabolic disturbance, and mitochondrial dysfunction (Figure 2).

AQP4 depolarization

Alcohol disrupts the spatial distribution of AQP4 in astrocytes. Chronic alcohol consumption reduces AQP4 polarization, characterized by diminished localization to perivascular foot processes and increased expression in the brain parenchyma. This depolarization causes irreversible impairment of glymphatic fluid flow[18,19]. A study indicates that long-term drinking (intragastric administration of alcohol for 2 months in mice) downregulates AQP4 expression, increased blood-brain barrier permeability, and aggravated cognitive decline[24]. However, another study found that “binge drinking” induces brain edema and neuroinflammation by upregulating AQP4 in astrocytes in the hippocampal-entorhinal cortical[25,26]. These findings indicate that short-term and long-term drinking have different effects on the regulation of AQP4 expression.

Moreover, alcohol’s regulation of astrocytic AQP4 varies across disease conditions. In traumatic brain injury (TBI), pre-injury ethanol exposure increases post-trauma AQP4, particularly in astrocyte endfeet, and activates transcription factors nuclear factor- κ B and hypoxia-inducible factor-1 α , worsening brain edema and neuroinflammation[27,28]. Conversely, post-trauma alcohol consumption significantly reduces AQP mRNA and protein levels, correlating with improved brain edema[29]. These opposing outcomes likely reflect differences in alcohol exposure timing (pre-injury *vs* post-injury) and the dynamic regulatory interplay in disease states, necessitating further mechanistic investigation. In summary, alcohol’s effects on AQP4 are highly complex and influenced by dosage, duration, and pathological conditions.

Astrocyte dysfunction

Alcohol directly impairs glymphatic function by disrupting astrocyte activity. Chronic alcohol consumption promotes reactive astrocyte proliferation, a hallmark of central nervous system injury, which is associated with neuroinflammation, glymphatic dysfunction, and AQP4 depolarization[18,21,30,31]. Mechanistically, alcohol activates astrocytic connexin 43 hemichannels and pannexin 1 channels, driving the release of inflammatory cytokine, ATP, and glutamate[32]. Moreover, alcohol upregulates cyclooxygenase-2 and inducible nitric oxide synthase expression *via* nuclear factor kappa B activation [33]. Additionally, alcohol promotes mitochondrial reactive oxygen species-mediated NOD-like receptor protein 1/caspase-1 pathway activation and interleukin 1 β /interleukin 18 release in astrocytes[34]. Alcohol also induces cell death. Moderate alcohol doses significantly increase GFAP mRNA level, suggesting exacerbated neuronal damage[35]. Furthermore, alcohol triggers astrocytic oxidative damage *via* mechanisms such as cytochrome P4502E1 upregulation, reactive oxygen species induction, and glutathione depletion[36].

Expansion of the PVS

The Virchow-Robin space is critical for exchanging substances between CSF and brain parenchyma. PVS dilation can impede CSF flow and disrupt the glymphatic function[37]. Consistently, clinical studies show that patients with alcohol-related brain damage have significantly enlarged PVS in the frontal cortex and basal ganglia[20]. Histopathological examinations of chronic alcohol abusers’ brains also reveal Virchow-Robin space enlargement across various brain regions[21]. A cohort study also identified alcohol consumption as a risk factor for PVS expansion in the centrum semiovale of patients with spontaneous cerebral hemorrhage[38]. Animal models corroborate these findings, with long-term alcohol-exposed mice exhibiting PVS enlargement and impaired glymphatic drainage[20]. However, Deike *et al* [39] showed that drinking habits do not affect the PVS volume fraction (PVS volume/brain parenchyma volume). Another epidemiological study involving 5000 healthy middle-aged individuals showed that drinking history does not affect basal ganglia and centrum semiovale PVS enlargement[40]. Therefore, the relationship between alcohol and PVS still requires further investigation.

Weakened cerebral vascular pulsation

Cerebral vascular pulsation is a critical driver of glymphatic fluid exchange and waste clearance[41], and it can enhance CSF axial and radial diffusion coefficients[42]. A previous study showed that unilateral internal carotid artery ligation reduced arterial pulsation by approximately 50% and slowed perivascular CSF-ISF exchange. Conversely, systemic adrenergic agonist dobutamine administration increased arterial pulsation by 60%, boosting perivascular the CSF-ISF exchange[10]. Furthermore, it was found that vascular lesions such as arteriosclerosis and perivascular remodeling caused by chronic hypertension altered the cerebral arterial pulsation and impaired the glymphatic function[43]. Additionally, a study showed that carotid artery stenosis reduced vascular pulsation, impaired glymphatic function, and may lead to cognitive impairment[44].

Alcohol consumption impacts arterial pulsation. Acute moderate alcohol intake (2.0 g/kg/day for 4 weeks, intraperitoneal injection) in mice increases β -endorphin release, reduces cerebral vascular pulsation, and impairs glymphatic function[19]. It was found that 0.75 g/kg ethanol consumption increases systolic blood pressure, diastolic blood pressure, and mean blood flow velocity, while significantly reducing the middle cerebral artery pulsation index[45]. Thus, reduced cerebral vascular pulsation may be a key pathway through which alcohol regulates glymphatic function.

Metabolic disturbance

Alcohol consumption perturbs homeostatic metabolic processes and may induce systemic metabolic dysregulation.

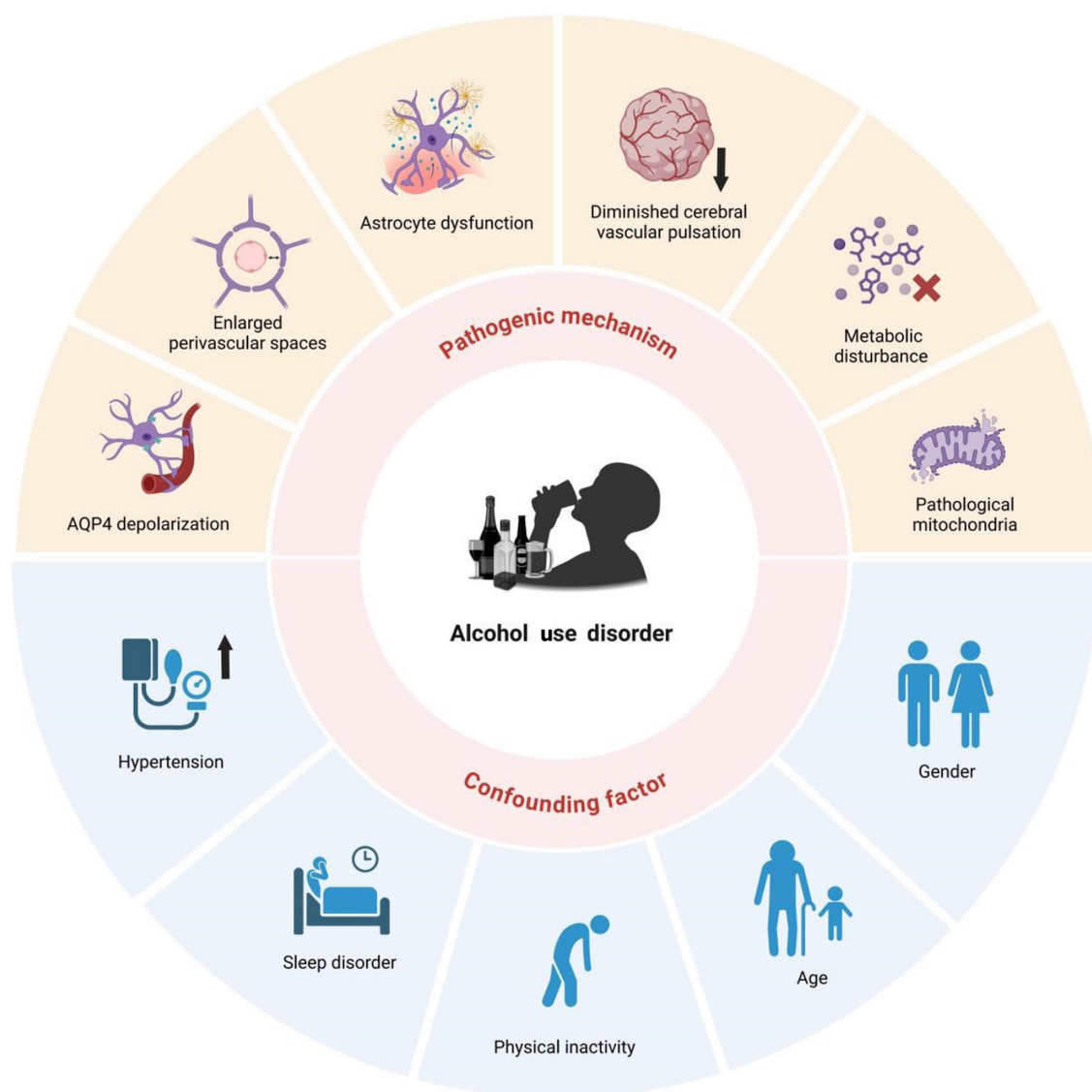


Figure 2 Pathogenic mechanism and confounding factor in alcohol-induced glymphatic dysfunction. AQP4: Aquaporin 4.

Hepatic ethanol metabolism constitutes the principal source of circulating acetate. Alcohol-derived acetate modulates neuronal histone acetylation through chromatin-bound acetyl-CoA synthetase 2, driving the transcription of synaptic plasticity-related genes, and facilitates ethanol-induced conditioned place preference[46]. Alcohol may also induce brain metabolic disturbance by reducing omega-3 (n-3) fatty acid[47]. Docosahexaenoic acid, the predominant n-3 fatty acid in neural membranes, structurally stabilizes lipid bilayers while modulating membrane protein activity, intracellular signaling, and transcriptional regulation. Recent reports support the protective effects of n-3 fatty acids on the glymphatic system. Chronic unpredictable mild stress induced depression-associated glymphatic impairment in mice, manifesting as decreased cerebral arterial pulsatility, reduced vascular compliance, and perivascular AQP4 depolarization[48]. Notably, supplementation of polyunsaturated fatty acid (PUFA) alleviated neuroinflammation and glymphatic dysfunction in mice, ultimately improving cognitive abilities[48]. Studies indicate that n-3 PUFA improves the brain lymphatic clearance rate in mice possibly by reducing amyloid- β (A β) 42 accumulation[49,50]. Additionally, genetic variation in n-3 PUFA biosynthesis genes (glucokinase regulator, fatty acid desaturase 2 enzyme, acyl-CoA oxidase 1) is associated with AUD diagnosis, and externalizing behaviors[51], implicating endogenous lipid metabolism in addiction vulnerability. Thus, alcohol may indirectly disrupt glymphatic function by altering n-3 fatty acid levels.

Mitochondrial dysfunction

Alcohol can induce brain mitochondrial dysfunction *via* multiple mechanisms, thereby impairing glymphatic function. High ethanol exposure alters mitochondrial permeability transition pore component expression, resulting in the impairment of mitochondrial bioenergetics[52]. Alcohol also reduces the activity of mitochondrial complexes I, III, and IV, inhibits Na⁺/K⁺-ATPase function, and depletes cardiolipin content, which is critical for maintaining oxidative phosphorylation and coupled respiration[53].

Notably, chronic alcohol exposure dysregulates genes regulating mitochondrial energy metabolism and neurodegeneration pathways linked to neurodegenerative diseases like AD and PD[54]. Given the glymphatic system's role in

neurodegenerative pathology, alcohol-induced mitochondrial damage may exacerbate glymphatic dysfunction, potentially accelerating neuropsychiatric disease progression. Supporting this hypothesis, patients with PD exhibit a significantly reduced ALPS index[55] and increased mitochondrial DNA levels, indicating glymphatic dysfunction is linked to oxidative stress[56]. Similarly, in patients with idiopathic intracranial hypertension, pathological astrocyte endfoot mitochondria significantly increase and are positively correlated with astrocyte reactive proliferation[57]. These studies indicate that mitochondrial dysfunction may cause glymphatic system dysfunction.

CONFOUNDING FACTORS IN ALCOHOL MODULATION OF THE GLYMPHATIC SYSTEM

Given numerous comorbid or confounding factors also modulate the glymphatic system, we explored the complex interconnections between AUD, the glymphatic system, and confounding factors such as hypertension, sleep disorders, lack of exercise, age, and sex (Figure 2).

Hypertension

Studies indicate a significantly increased risk of hypertension in patients with AUD[58]. Hypertension may impair glymphatic function through specific mechanisms. A study used dynamic contrast-enhanced magnetic resonance imaging to assess the impact of hypertension on brain glymphatic transport kinetics in young/adult spontaneously hypertensive male rats *vs* age-matched normotensive Wistar-Kyoto rats, and found the glymphatic transport was significantly impaired in spontaneously hypertensive male rats[43]. Another study demonstrated that increased blood pressure increases reflux by reducing arterial wall pulsatility, thereby decreasing PVS net flow[59]. Moreover, a clinical study calculated the ALPS index along blood vessels in hypertension and healthy control groups, finding that the hypertension group exhibit a significantly lower average ALPS index than the control group. The average PVS analysis index in all subjects was significantly negatively correlated with the blood pressure[60]. Consistently, a study found that intensive systolic blood pressure treatment, targeting a reduction to less than 120 mmHg[61], decreases the PVS volume fraction (PVS volume/total regional volume)[62].

Sleep disorders

Sleep disorders are highly prevalent among individuals with AUD[63]. Alcohol disrupts sleep through mechanisms like damaging the electrophysiological sleep structure, causing insomnia, circadian rhythm abnormalities, short sleep duration, reduced slow-wave sleep duration, and increased respiratory-related sleep disorders[64-66]. Patients with AUD have a higher risk of obstructive sleep apnea, linked to glymphatic dysfunction[67]. Studies also found that patients with obstructive sleep apnea have a significantly lower ALPS index than healthy controls, which was significantly negatively correlated with the apnea-hypopnea index and sleep N period oxygen saturation index[68-70]. Alcohol may disrupt sleep homeostasis, causing sleep fragmentation and affecting glymphatic function[71]. The sleep fragmentation group had a lower ALPS index than the healthy control group, and it was negatively correlated with the Pittsburgh Sleep Quality Index[72], a self-administered questionnaire evaluating sleep quality and patterns over the past month[73]. These findings suggest that AUD may indirectly impair human glymphatic function through sleep disorders. Thus, treating sleep disorders and AUD is crucial for preventing potential cognitive decline.

Physical inactivity

Exercise is crucial for glymphatic system regulation[74], and AUD may indirectly affect this system through physical inactivity. Studies have shown that individuals with AUD exhibit a significant decline in physical fitness and impaired motor function, which is specifically manifested in the shortened distance of the 6-minute walk test[75-77]. The benefits of motor behavior on the glymphatic system are well-documented. Exercise enhances glymphatic function and A β clearance by inhibiting transient receptor potential vanilloid 4 expression, promoting AQP4 polarization, and regulating astrocyte phenotype[78]. Similarly, swimming training enhances hippocampal glymphatic clearance of A β deposition by upregulating laminin subunit alpha 1 and dystrophin 71 transcription, reducing AQP4 depolarization, and enhancing CSF-ISF exchange[79]. Given exercise effectively repairs and improves glymphatic function, physical inactivity in patients with AUD may worsen glymphatic dysfunction.

Sex

Sex differences significantly influence AUD susceptibility, driven by variations in sex hormone signaling and neuroanatomical organization[80,81]. A study showed sex-specific mechanisms and functional manifestations of alcohol exposure on astrocytes. In females, alcohol exposure activated astrocytes, increased pro-inflammatory cytokine tumor necrosis factor expression, decreased neuroprotective cytokine transforming growth factor- β 1 expression, impaired bioenergetics, and reduced excitatory amino acid uptake. By contrast, male mice exhibit astrocyte inactivation marked by reduced GFAP expression[82]. Thus, sex differences must be considered in studying and treating alcohol-mediated glymphatic dysfunction.

Age

Studies have shown that aging is linked to a sharp decline in subarachnoid CSF and brain parenchyma exchange efficiency in mice. Compared to young mice, aged mice exhibit a 40% reduction in injected A β clearance rate, a 27% decrease in cortical small artery vascular wall pulsation, and widespread AQP4 depolarization around penetrating

arteries[83]. Moreover, aging affects the balance between glymphatic system inflow and outflow. Human studies reveal an age-dependent imbalance in glymphatic dynamics. Participants over 45 exhibit higher glymphatic inflow but significantly lower outflow compared to younger adults (ages 21-38). This mismatch may result from age-related changes of the arterial pulsation and AQP4 polarization[84].

GAINING TREATMENT INSIGHTS FROM OTHER NEUROPSYCHIATRIC DISEASES

Although accumulating evidence implicates glymphatic dysfunction in the pathogenesis of AUD, few studies have directly targeted this system for therapeutic intervention. However, emerging research on glymphatic modulation in other neuropsychiatric disorders may provide valuable insights for developing novel interventions against AUD. A previous study found that AUD increases cerebral A β deposition[85] and AD risk[86]. Notably, AD progression involves glymphatic impairment, indicating a bidirectional relationship between AUD, AD, and glymphatic dysfunction. For example, studies have shown that the DTI-ALPS index in patients with AD is negatively correlated with positron emission tomography-imaged amyloid and tau deposition and positively correlated with cognitive scores[87-90]. Moreover, similar to AUD, AQP4 mislocation occurs in both AD animal models and patients[91,92]. TBI is a brain functional disorder or pathological change caused by external physical forces[93]. It is frequently accompanied by glymphatic system dysfunction[94]. A study using the DTI-ALPS method assessed glymphatic system activity in patients with TBI. The results showed that patients with TBI had a significantly lower ALPS index than healthy controls. Multivariate analysis indicated that subarachnoid hemorrhage and diffuse axonal injury were associated with a lower ALPS index[95]. Thus, the glymphatic system may be an emerging target for AD and TBI treatment. Recently, various interventions, such as low-intensity ultrasound, electroacupuncture, fingolimod, *etc.*, have been confirmed to improve pathological conditions by regulating glymphatic function (Table 1)[96-105]. These emerging glymphatic-focused approaches are poised to serve as investigative tools in animal models to elucidate the role of glymphatic dysfunction in AUD pathogenesis, and also as promising clinical strategies for translating these mechanistic insights into effective AUD treatments.

Table 1 Treatments targeting the glymphatic system

Treatment	Outcome	Mechanism	Ref.
High-intensity interval training	Alleviate cognitive dysfunction of STZ-induced AD rats, promote clearance of abnormal tau and A β	Shift astrocyte phenotype from A1 to A2, improve AQP4 polarization	[96]
Electroacupuncture therapy	Improve cognitive function of SMAP8 AD model mice, mitigate neuropathological damage in brain tissue	Suppress astrocyte reactivity, improve AQP4 polarity	[97]
VLIUS	Enhance influx of CSF tracer into perivascular spaces, promote clearance of brain interstitial solutes	TRPV4 in astrocytes activated by VLIUS, induce Ca ²⁺ influx and CaM activation to promote AQP4 polarization	[98]
OAB-14	Improve cognitive impairment of 9-10-month-old APP/PS1 transgenic mice, promote A β clearance	Upregulate PPAR γ -P2X7r-AQP4 pathway to increase AQP4 expression, promote AQP4 polarization by raising Agustin, SNTA-1 and ABCA1 Levels	[99]
L-3-n-butylphthalide	Enhance glymphatic clearance rate of APP/PS1 mice, reduce parenchymal A β deposition	Increase brain pulsatility, improve perivascular AQP4 Localization	[100]
Yuanzhi powder	Clear excessive A β deposits, improve cognitive defects and pathological damage of APP/PS1 mice	Improve AQP4 polarity distribution, upregulate transport function of MLV	[101]
Nano-plumber encapsulating pro-DHA and VEGF-C	reverse inflammatory microenvironment, enhance glymphatic system function	Reverse microglial inflammatory phenotype, restore phagocytic ability and protect vasculature, stimulate angiogenesis of meningeal lymphatics	[102]
GLP-1R agonists	Improve post-traumatic cognitive function in mice, increase fluid drainage in perivascular spaces	Suppress reactive gliosis, improve AQP4 polarization, reduce axonal injury and neuronal apoptosis	[103]
Cannabidiol	Improve motor, memory and cognitive functions, promote clearance of p-tau and A β	Improve AQP4 polarization, reduce inflammation, increase cerebral blood flow	[104]
Fingolimod	Reduce brain edema of DBI rats, mitigate axonal injury, restore glymphatic function	Improve AQP4 polarization, reduce inflammation, increase cerebral blood flow	[105]

A β : Amyloid- β ; ABCA1: ATP-binding cassette subfamily A-1; AD: Alzheimer's disease; APP/PS1: Amyloid precursor protein/presenilin 1; AQP4: Aquaporin 4; CaM: Calmodulin; CSF: Cerebrospinal fluid; DBI: Diazepam-binding inhibitor; DHA: Docosahexaenoic acid; GLP-1R: Glucagon-like peptide-1 receptor; MLV: Murine leukemia virus; P2X7r: P2X7 receptor; PPAR γ : Peroxisome proliferator-activated receptor gamma; p-tau: Phosphorylated tau; SMAP8: Smooth muscle-associated protein 8; SNTA-1: Syntrophin alpha 1; STZ: Streptozotocin; TRPV4: Transient receptor potential vanilloid 4; VEGF-C: Vascular endothelial growth factor-C; VLIUS: Very low-intensity ultrasound.

CONCLUSION

Alcohol exerts dose-dependent and time-dependent effects on the glymphatic system. In AUD, glymphatic dysfunction exacerbates neuroinflammation, metabolic dysregulation, and neurodegeneration. Current evidence on the effects of alcohol on the glymphatic system predominantly stems from animal studies that adopt administration paradigms discordant with the pathophysiological features of human chronic alcohol intoxication. Future studies should prioritize developing chronic alcohol intoxication animal models with higher translational relevance, such as long-term voluntary alcohol consumption models. To systematically delineate the dose-dependent, temporal, and modality-specific impacts of alcohol exposure on glymphatic dynamics, large-scale longitudinal cohort studies are imperative. These should integrate multimodal neuroimaging approaches to quantify spatiotemporal variations in glymphatic clearance efficiency. Such investigations will advance mechanistic insights into alcohol-associated neurodegenerative processes and inform the development of glymphatic-targeted therapeutic interventions.

FOOTNOTES

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