Acta Pharmaceutica Sinica B 2024;14(7):3291−3293

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

COMMENTARY

Commentary: The central lymphatic drainage in pharmacological, surgical and physical therapies of Alzheimer's disease

KEY WORDS

Aβ;
Central lymphatic drainage;
Surgery;
NPLP;
AD

Alzheimer's disease (AD) is a prevalent neurodegenerative disease in the aged population[1]. Etiology of AD remains largely unknown and no effective drugs are available in clinical settings to reverse or delay the disease progress[2]. In recent years, the brain's lymphatic systems, including glymphatic[3] that exists in the brain interstitial space and meningeal lymphatic vessels[4] that presents within the dural sinuses, have been found to play an important role in the AD pathogenesis. Dysfunction of the lymphatic drainage led to the cognitive decline, whereas improvement of the drainage function rescued the learning abilities in aged mice[5]. The lymphatic drainage of central nervous system has emerged as a potential target in the treatment of AD. However, translation of the laboratory findings into clinical practice is limited by our understanding of the central lymphatic structure of the human brain. This issue is addressed in a recent study in *Nature*[6].

Amyloid-β (Aβ) protein accumulation is one of the key factors in etiology of AD. Aggregation of Aβ protein together with misfolding of neurofibrillary Tau proteins (Tau tangles) is the histological features of AD brain[7]. It is hypothesized that imbalance between Aβ production and clearance causes the Aβ accumulation[8]. Aβ clearance is conducted by several pathways, including hydrolysis by local proteases, uptake and degradation by microglia, drainage crossing the blood−brain barrier, and clearance through perivascular spaces surrounding the cerebral arteries[9]. The blood vessel system may count for half Aβ protein clearance in the brain[10]. The role of Aβ protein is enforced in AD pathogenesis by recent studies. Aβ-specific monoclonal antibodies for removal of the protein deposition are able to slow down AD progression at the early stage[7]. A 2024 *Nature* article reports that an excessive stress response in the brain is responsible for neuronal death in the presence of the Aβ protein deposite[11]. The team identified a large E3 ligase complex by the name "silencing factor of the integrated stress response (SIFI)", which inhibits general stress response by promoting proteasomal degradation of unimported mitochondrial precursors and stress response components. SIFI inactivation leads to a persistent stress response for a widespread neuronal loss[11]. The loss was attenuated in the mice by induction of SIFI activity with a SIFI activator (ISRIB). In another study, Tony Wyss-Coray's team analyzed the result of single-nucleus RNA-sequence (snRNA-seq) of the AD brain tissue, finding that Aβ triggers the synthesis of triglyceride (TAG) lipid in microglia, leading to accumulation of lipid droplet, and subsequent secretion of neurotoxic factors in an APOE-dependent manner[12]. These lipids might be transferred to neurons thereby inducing neurodegeneration as neurons can't metabolize TAG. This finding presents a new mechanism in the pathogenesis of AD mediated by lipid droplet accumulating microglia (LDAM)[12]. These studies suggest that the neuron damage in AD involves two new mechanisms: the first is the Aβ-dependent stress response from inactivation of SIFI activity; the second is neurotoxic factors derived from lipid containing microglia in response to Aβ accumulation. Accumulation of Tau protein is another feature of AD brain pathology and induction of Tau protein clearance by ubiquitination-mediated degradation is able to attenuate neurodegeneration and cognitive dysfunction[13]. Obesity may increase

Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2024.04.018

the AD risk through disorders in glucose, lipids and hormones. In obesity, adipose tissue-derived products are able to impair the cognitive function in type 2 diabetes (T2D) models[14].

The brain lymphatic vessel system may count for a significant portion of Aβ clearance under the physiological conditions. In the classical view of anatomy, the brain lacks lymphatic vessel system. However, the view has been updated by a *Nature* study in 2015[4]. While searching for T cell pathways in and out of the brain meninges, Louveau et al. discovered lymphatic vessels within the dural sinuses in the study. These lymphatic structures express all molecular characteristics of lymphatic endothelial cells, carry immune cells out of the cerebrospinal fluid (CSF), and drain into the deep cervical lymph nodes (dcLNs). The finding was introduced into the AD research field in another *Nature* study, in which the meningeal lymphatic vessels were found to transport macromolecules from the central nervous system (CSF and interstitial fluid, ISF) into the cervical lymph nodes[5]. The system dysfunction slowed the perivascular influx of CSF macromolecules and outflow of ISF macromolecules inducing the cognitive impairment. Enhancement of the system function by treating aged mice with the vascular endothelial growth factor C (VEGF-C) improved the CSF macromolecule drainage, improving cerebral perfusion and cognitive abilities. In 2023, the findings of animal studies were translated into a clinical practice in AD treatment by Xie Qingping's team through establishment of a surgical procedure of "cervical lympho-venous anastomosis (LVA)" in AD patients, which was published in the American Society of Plastic Surgeons (ASPS)[15]. The surgical approach is able to improve the drainage function of the brain lymphatic system and improve the cognitive ability of AD patients. Recently, therapeutic value of the brain lymphatic system has been demonstrated in more studies of AD. An article in *Nature* reports that multisensory 40 Hz light and sound stimulation affected arterial pulsation by increasing neuropeptide signals, which promoted clearance of Aβ protein by the glymphatic system in AD[16]. Meanwhile, another study in *Nature Communications* reported that the meningeal lymphatic endothelial cells (mLEC) was improved by 808 nm near-infrared light in aged mice through an impact in mitochondrial functions, which led to an increase in Aβ clearance through the lymphatic drainage and a reduction in neuroinflammation for an improvement in the cognitive ability[17]. These findings suggest that the brain's lymphatic system is a new target for AD treatment in multiple therapies. Nevertheless, the lymphatic structures in the head and neck regions remains to be fully understood. The status has been changed by identification of a new lymphatic network in the brain[6].

In the new *Nature* study by Yoon et al.[6], the nasopharyngeal and cervical lymphatics were identified using a line of prospero-related homeobox 1-green fluorescence protein (Prox1-GFP) reporter mice. The study revealed that the nasopharynx was observed with a fluorescence microscopy and it has a distinctive lymphatic plexus as a major hub for CSF lymphatic outflow from the cribriform plate to dcLNs. They found that the lymphatics in nasopharynx mucosa formed a unique nasopharyngeal lymphatic plexus (NPLP), which is connected to the posterior nasal lymphatic plexus, and covers all posterior nasal and nasopharyngeal surface tissues except the skull base. The NPLP had 45-65 irregular, linearly shaped valves without smooth-muscle coverage and resembled an inverted saddle in a view of three dimension. To determine whether NPLP was a route for CSF outflow, the fluorescence stereomicroscope was used to trace tetramethyl rhodamine-conjugated dextran (TMR-dextran) fluorescence after infusing into the subarachnoid space at the cisterna magna of mice. At 30 min after infusion, fluorescence was detected in the nasopharyngeal lymphatics, deep cervical lymphatics and dcLNs, but not in the oropharyngeal or soft palatal lymphatics. These results suggest that CSF outflow through NPLP, but not the oropharyngeal lymphatic plexus. The route of CSF drainage is that CSF traverse the anterior and middle cranial fossae, enters the NPLP and flows through the medial cervical lymphatic vessels into the discharge pathway of dcLNs. This network mainly links to the internal cervical lymphatic vessels rather than the lateral lymphatic vessels. The conclusion may be influenced by factors such as deep anesthesia and surgical removal of neck muscles, which alter the physiological dynamics of CSF drainage[6]. Therefore, more advanced methods may help to reveal characteristics of CSF drainage under the physiological conditions.

Both blood and lymphatic vessels suffer a functional reduction with age[6,18]. Compared with adult mice (8−12 weeks in age), old mice of 73−102 weeks do exhibit the reduction of CSF outflow and NPLP. Phosphorylated tau and apoptosis (TUNEL) staining in endothelial cells of aged mice were 2.5-fold and 7.4-fold higher in the old mice, respectively, than the young adult mice, increasing the risk of plexus regression in the aged mice. Mice at 75−78 weeks in age were infused with VEGF-C, and the size of plexus and the volume of CSF outflow were both increased in three weeks[6]. The findings demonstrated that the functional reduction of the nasopharyngeal plexus and CSF outflow is reversible in the aged mice. Pharmacological approach in activation of medial cervical lymphatics could promote CSF outflow. α1-Adrehergic agonist phenylephrine could stimulate both phasic and tonic lymphatic contractions, while sodium nitroprusside could induce muscle relaxation and blood vessel dilation. Researchers have successfully utilized these drugs to modulate the cervical lymphatic vessels. Importantly, this characteristic is preserved during the aging process, even when the nasopharyngeal lymphatics are atrophied and functionally impaired.

The field of brain lymphatic system study has made significant progress in recent years, providing new insights into the structure, function, and application of this system. Several recent studies have consistently indicated that the brain lymphatic drainage system holds great promise as a target for pharmacological, surgical, and physical therapies for AD. In addition to its role in clearing the Aβ protein, the brain lymphatic drainage system may also play a crucial role in removing other metabolites, particularly lipids, in the maintenance of the microenvironment of neurons in the brain.

Acknowledgment

This study is supported by a project (32271220) from the National Natural Science Foundation of China to Jianping Ye.

Author contributions

Lixuan Ren: Writing − review & editing, Writing − original draft. **Jianping Ye:** Writing − review & editing, Supervision, Conceptualization.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. *Alzheimers Dement* 2016;**12**:459−509.
2. Dos Santos Picanco LC, Ozela PF, de Fatima de Brito Brito M, Pinheiro AA, Padilha EC, Braga FS, et al. Alzheimer's disease: a review from the pathophysiology to diagnosis, new perspectives for pharmacological treatment. *Curr Med Chem* 2018;**25**:3141−59.
3. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med* 2012;**4**:147ra11.
4. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015;**523**:337−41.
5. Da Mesquita S, Louveau A, Vaccari A, Smirnov I, Cornelison RC, Kingsmore KM, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature* 2018;**560**:185−91.
6. Yoon JH, Jin H, Kim HJ, Hong SP, Yang MJ, Ahn JH, et al. Nasopharyngeal lymphatic plexus is a hub for cerebrospinal fluid drainage. *Nature* 2024;**625**:768−77.
7. Jucker M, Walker LC. Alzheimer's disease: from immunotherapy to immunoprevention. *Cell* 2023;**186**:4260−70.
8. Huang Y, Mucke L. Alzheimer mechanisms and therapeutic strategies. *Cell* 2012;**148**:1204−22.
9. Guo X, Zhang G, Peng Q, Huang L, Zhang Z, Zhang Z. Emerging roles of meningeal lymphatic vessels in Alzheimer's disease. *J Alzheimers Dis* 2023;**94**:S355−66.
10. Cheng Y, Wang YJ. Meningeal Lymphatic Vessels: a drain of the brain involved in neurodegeneration?. *Neurosci Bull* 2020;**36**:557−60.
11. Haakonsen DL, Heider M, Ingersoll AJ, Vodehnal K, Witus SR, Uenaka T, et al. Stress response silencing by an E3 ligase mutated in neurodegeneration. *Nature* 2024;**626**:874−80.
12. Haney MS, Pálovics R, Munson CN, Long C, Johansson PK, Yip O, et al. APOE4/4 is linked to damaging lipid droplets in Alzheimer's disease microglia. *Nature* 2024;**628**:154−61.
13. Li L, Jiang Y, Wang JZ, Liu R, Wang X. Tau ubiquitination in Alzheimer's disease. *Front Neurol* 2021;**12**:786353.
14. Wang J, Li L, Zhang Z, Zhang X, Zhu Y, Zhang C, et al. Extracellular vesicles mediate the communication of adipose tissue with brain and promote cognitive impairment associated with insulin resistance. *Cell Metabol* 2022;**34**:1264. 79.e8.
15. Xie Q, Louveau A, Pandey S, Zeng W, Chen WF. Rewiring the brain: the next frontier in supermicrosurgery. *Plast Reconstr Surg* 2024;**153**:494e-5e.
16. Murdock MH, Yang CY, Sun N, Pao PC, Blanco-Duque C, Kahn MC, et al. Multisensory gamma stimulation promotes glymphatic clearance of amyloid. *Nature* 2024;**627**:149−56.
17. Wang M, Yan C, Li X, Yang T, Wu S, Liu Q, et al. Non-invasive modulation of meningeal lymphatics ameliorates ageing and Alzheimer's disease-associated pathology and cognition in mice. *Nat Commun* 2024;**15**:1453.
18. Wang J, Gu BJ, Masters CL, Wang YJ. A systemic view of Alzheimer disease—insights from amyloid-β metabolism beyond the brain. *Nat Rev Neurol* 2017;**13**:612−23.

Lixuan Ren[a], Jianping Ye[a,b,*]

[a]*Metabolic Disease Research Center, Zhengzhou Central Hospital Affiliated to Zhengzhou University, Zhengzhou 450000, China*

[b]*Tianjian Laboratory of Advanced Biomedical Sciences, Academy of Medical Sciences, Zhengzhou University, Zhengzhou 450001, China*

*Corresponding authors.

E-mail addresses: yejianping@zzu.edu.cn (Jianping Ye)

Received 20 March 2024

Revised 18 April 2024

Accepted 19 April 2024