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Editorial

The glymphatic system: A hidden pathway for brain health

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1. Introduction

The clearance of metabolic waste, excess fluid and interstitial solutes is very crucial in maintaining immune defence and homeostasis in the human body. This work is well completed by the “lymphatic system” in the peripheral tissues of the body. The lymphatic network in extended to all parts of the peripheral tissues and the density of the lymphatic vessels is directly proportional to the metabolic activity of that tissue. However, in spite of the higher metabolic activity of the central nervous system, there is lack of conventional true lymphatic drainage system. Traditionally, it was considered that cell debris, potential neurotoxic proteins, and other metabolic end products like amyloid beta (Aβ) proteins and tau oligomers were considered to be removed in a different clearance pathway than brain vasculature. In 2012, Nedergaard and group discovered that cerebrospinal fluid (CSF) can enter brain parenchyma and exchange the interstitial fluid with the help of Aquaporin-4 (AQP-4) water channels expressed in a highly polarized manor in astrocytic endfeet that encase the cerebral vasculature.[1] Maiken Nedergaard named this unique glial dependant lymphatic drainage system of the central nervous system as ‘Glymphatic system’.[2,3] It was named by combining "glia" (referring to glial cells, which are non-neuronal cells in the brain that provide support and protection for neurons) and "lymphatic" (referring to the lymphatic system, which clears waste from other parts of the body). This recently discovered system, plays a crucial role in maintaining brain health and has profound implications for our understanding of neurological diseases.

The glymphatic system operates primarily during sleep, utilizing a network of perivascular channels formed by astroglial cells. These channels facilitate the flow of cerebrospinal fluid (CSF) through the brain, effectively flushing out metabolic waste products, proteins, and other potentially harmful substances. This process is essential for preventing the accumulation of toxic materials that could impair brain function. Over the past decade, an increasing number of studies have shown that, the glymphatic system acts as a ‘lymphatic system’ in clearing the metabolic waste and modulating water transport in the brain, and the dysfunction of the glymphatic system is involved in causation of various neurological conditions through animal experiments, such as Alzheimer’s disease (AD), Parkinson’s disease (PD), epilepsy, stroke, traumatic brain injury (TBI), mood disorder, traumatic brain injury (TBI) and infectious or autoimmune disease in the CNS. Besides the clearance of the metabolic waste of the brain, the glymphatic system is involved in the modulation of intracranial pressure and the transport of excess interstitial fluid in the brain. Moreover, the glymphatic system’s activity is highly dependent on sleep, highlighting the importance of healthy sleep patterns for brain health. Disrupted sleep can impair glymphatic

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clearance, increasing the risk of cognitive decline and neurodegeneration.[4]

2. Mechanism of Action

The glymphatic system is a perivascular pathway driven by AQP4 water channels located on astrocytic endfeet in the entire brain. It delivers essential nutrients and neuroactive substances to the brain parenchyma via the peri-arterial CSF influx pathway and removes metabolic wastes through peri-venous clearance routes. The functioning of the glymphatic system is closely related to the two important structures in the brain namely, the Aquaporin-4 water channels on astrocyte endfeets and the perivascular spaces.[1,5,6] The PVS surrounds the cerebral vasculature and is lined by astrocyte end-feet plastered alongside the pericytes and endothelial cells that form the blood brain barrier. In 2012, researchers injected fluorescent tracers with different molecular weights into the cisterna magna of anesthetized mice, followed by in vivo two-photon imaging and immunofluorescence techniques to track the CSF circulation through the brain interstitial space.[1] They concluded that this waste clearing glymphatic system consists of three main components : (1) the CSF is continuously drained from the basal cisterns into the subarachnoid spaces around the cerebral hemispheres, then from the subarachnoid spaces CSF in propelled into the periarterial spaces in a bulk-flow-driven manner; (2) CSF is driven from the periarterial spaces into the interstitial spaces with the help of aquaporin-4 water channels located on astrocyte endfeets; (3) Finally this CSF mixed with metabolic waste products in the interstitial fluid is propelled into the perivenous spaces of large cerebral veins, and then eventually into the systemic circulation through the conventional lymphatic vessels. Aspelund et al. found a network of lymph vessels in the dura mater that drain CSF from the subarachnoid spaces and brain interstitial fluid through the glymphatic system to the deep cervical lymphatic channels via foramina at the skull base.[7] AQP4 plays an important role in brain water transport and waste clearance. Analysis of genetically modified mice that lacked the AQP-4 gene revealed that the clearance of interstitial solutes in the brain parenchyma decreases by 70% in the absence of AQP4.[1,8,9]

3. Driving Forces of the Glymphatic System

The process of fluid transport and waste clearance of the glymphatic system is dependent of several factors such as perivascular aquaporin-4 water channels, sleep wake cycle, hydraulic forces generated by the arterial pulsations, rate of CSF production and absorption, respiration and the pressure differences.[10]

The polarized high expression of the aquaporin-4 water channels on astroglial endfeets is very crucial for efficient influx and efflux of glymphatic. In a study by Illif et al., he showed that influx of amyloid beta (Aβ) is reduced by 40% in AQP-$4^{-/-}$ mice, and the clearance of Aβ is reduced by 20% in AQP-$4^{-/-}$ mice as compared to controls.[1] Also, the immunohistochemistry studies of AQP-4 water channels on mice brain revealed that the expression of AQP-4 water channels in not uniform across the brain, which might explain the regional heterogenicity in the glymphatic transport function.

Xie L et al. in 2013 published an article indicating the importance of sleep in the glymphatic activity. They first showed that the clearance of interstitial waste is dramatically enhanced during sleep. In vivo 2-photon imaging of glymphatic function showed that the CSF influx in the awake state was reduced by 90% compared to anesthetized mice.[4] Xie and Nedergaard demonstrated that the improved glymphatic function in anaesthetized and sleeping mice is due to the expansion of the interstitial space by around 60% in resting brain.[1,4] On the basis of these findings, they concluded that the restorative function of the brain during sleep is linked to the increased clearance of the interstitial metabolic waste generated during awake and active brain. The speed of glymphatic flow varies with the depth stage of the sleep. The glymphatic flow is highest in the NREM 3 stage of the sleep and decreases as the depth stage of sleep decreases. This highlights the importance of the duration and quality of the sleep in prevention of the neurodegenerative disorders.

Glymphatic function is also linked to the arterial pulsation and heart rate. A study on mice models showed that the ligation of internal carotid artery slowed down the rate of exchange of the waste products at CSF-ISF interface whereas injection of dobutamine, an inotropic agent, increased the heart rate and the perivascular CSF-ISF exchange, thus increasing the glymphatic function.[11–13] Various cardiac conditions such as congestive cardiac failure, hypertension and cardiac arrythmias disrupts the glymphatic function which could be explained by the reduced compliance and pulsatility of the blood vessels in these conditions. Humberto et al. found that the pulsation of the arterial wall matched that of the CSF flow rhythm and thus concluded that arterial wall motion is an important factor in the glymphatic function via a process known as “perivascular pumping”. All these findings demonstrate that arterial pulsation is a key driver of glymphatic flow.[13,14]

4. Implications of Glymphatic Function in Neurological Conditions

Dysfunction of the glymphatic system has been implicated in various neurological conditions. Impaired waste clearance can lead to the accumulation of toxic proteins, contributing to the pathogenesis of diseases like Alzheimer’s, Parkinson’s, and Huntington’s disease. Moreover, the glymphatic system’s activity is highly

dependent on sleep, highlighting the importance of healthy sleep patterns for brain health. Disrupted sleep can impair glymphatic clearance, increasing the risk of cognitive decline and neurodegeneration.

Alzheimer's disease (AD) is a neurodegenerative condition characterized by the impaired memory function shrinkage of brain volume. Pathologically Alzheimer's disease is characterized by accumulation of Aβ plaques and neurofibrillary tangles of tau proteins. Various research studies suggests that glymphatic pathway is a substantial factor in the clearance of Aβ. A malfunction of the glymphatic system preceded significant amyloid-β deposits, which may be an early signal of AD. Researchers have demonstrated through the mice studies that proper functioning of the glymphatic system is necessary for the clearance of soluble Aβ from the interstitial spaces of the brain and thus prevention of the Alzheimer's disease. In mice lacking the AQP4 gene, clearance of amyloid-beta is reduced by around 55%. One of the important factor in AD is decreased sleep.[1,12,13,15] In a study by Xie et al., it was shown that the clearance of Aβ was double during sleep compared with wakefulness.[4] The glymphatic system has been implicated in alleviating the symptoms in parkison's disease as well by increasing the clearance of α-syn. In an experimental model with genetically altered mice, when meningeal lymphatic drainage was blocked by ligating the deep cervical lymphatic vessels, the glymphatic inflow of CSF tracer in the mice's brain was significantly decreased which resulted in increased α-syn accumulation, inflammation, loss of dopaminergic neurons and dyskinesia. Also the deletion of the AQP-4 inhibited the clearance of the α-syn in the mice brain.[12,14]

The glymphatic system also may be impaired after acute brain insults such as traumatic brain injury, ischemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage. A group of researchers from the French Institute of Health and Medical Research (INSERM) demonstrated by MRI that the glymphatic system was impaired after subarachnoid hemorrhage, because of the presence of coagulated blood in the paravascular spaces.[16] Following traumatic brain injuries, there is accumulation of Aβ and tau protein which can lead to the development of neurodegenerative diseases. Similarly, injury to the mice brain causes loss polarity distribution of AQP-4 on astrocyte endfeet leading to decrease in the functioning of the glymphatic system by around 60%.[17] These indicate that chronic injury of the glymphatic system after TBI may be a key factor leading to tau protein aggregation and neurodegenerative attacks in the brain after trauma. Improper functioning of the glymphatic system also explains the pathological mechanism in amyotropic lateral sclerosis. More than 97% cases of ALS cases show the presence of insoluble proteins such as TDP-43 and Tau proteins in the brain. Also, elevated tau proteins in the CSF indicates upper motor neuron degeneration leading to ALS. Hence, clearing of Tau proteins in the glymphatic system may be an effective mechanism for the treatment of ALS.[12,14] Disruption of sleep in patients of ALS may also attribute to impaired clearance of tau proteins leading to elevated tau proteins in brain. Diabetics patients usually develop memory loss and cognitive decline and are at a higher risk of developing neurodegenerative vasculopathy and AD. Researchers have demonstrated that MRI of type-2 diabetic rats showed reduced clearance of contrast agent in CSF from interstitial spaces in hippocampus as compared to non-diabetic rats, which was also confirmed using fluorescein imaging analysis. These experiments confirm that type-2 diabetes can slow down the exchange flow of CSF and ISF leading to dysfunctional glymphatic system.[12,18] Thus, these findings indicate that further research into the functional mechanism of the glymphatic system will be beneficial to better understand and explain the physiological and pathological mechanism of neurodegenerative diseases. More studies could focus on both the pathogenic mechanisms and therapeutic function of the glymphatic system in neurological disease and can help in better management of these diseases in the future.

5. Future Directions

The discovery of the glymphatic system has opened new avenues for research and potential therapeutic interventions. It has provided a new direction for better understanding the brain diseases by shifting the focus from changes in specific structures in the brain to the overall fluid circulation in the brain. Current studies are exploring ways to enhance glymphatic function, such as optimizing sleep patterns, developing drugs that target aquaporin-4 channels, and utilizing lifestyle interventions to support brain health. Additionally, advanced imaging techniques are being employed to better understand the system's functioning and its role in disease progression. New methods of drug delivery are emerging based on the understanding of the glymphatic system.

As our knowledge of the glymphatic system expands, it holds promise for revolutionizing our approach to preventing and treating neurological diseases. By unveiling the intricate mechanisms of brain waste clearance, scientists and medical professionals can develop more effective strategies to maintain cognitive function and enhance overall brain health.

6. Conclusion

The glymphatic system represents a groundbreaking discovery in neuroscience, shedding light on the brain's sophisticated waste clearance processes. Besides waste elimination, the glymphatic system may also function to help distribute non-waste compounds, such as glucose,

lipids, amino acids, and neurotransmitters related to volume transmission, in the brain. Interestingly, the glymphatic system functions mainly during sleep and is largely deactivated during wakefulness. Impaired glymphatic clearance contributes to the risk of developing neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, ALS etc, due to reduced removal of aggregated proteins such as amyloid-beta and tau. Thus, a well functional waste clearing system like glymphatic system is very crucial in better understanding and management of these conditions.

However, the studies on the functional role of the glymphatic system are only based on experimental rodent animal models and has not been applied to humans. Thus, we need follow-up experiments to prove that the glymphatic system is also important for the steady-state maintenance of the human brain by supplementing subsequent experiments. There are many controversies and unsolved questions in the lymphatic system which require constant high-quality and dedicated research in this field. Continued research into this hidden pathway promises to unlock further mysteries of the brain and pave the way for innovative therapeutic approaches, ultimately enhancing the quality of life for individuals worldwide.

7. Conflict of Interest

None.

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