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Astroglial water channel aquaporin 4-mediated glymphatic clearance function: A determined factor for time-sensitive treatment of aerobic exercise in patients with Alzheimer's disease

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ABSTRACT

Currently, there are no effective drug therapies for Alzheimer's disease (AD). Thus, exploring new non-pharmacological strategies, including the neuroprotective mechanisms of aerobic exercise, to enhance therapeutic treatment of AD are essential. Previous studies have shown that the beneficial efficiency of aerobic exercise in the prevention and treatment of AD is time-sensitive, but its mechanism is not clear. Recent studies revealed that the water channel protein aquaporin 4 (AQP4) mediates the glymphatic system to clear interstitial solutes, including β-amyloid, from the brain. More recently, voluntary exercise has been shown to promote glymphatic clearance function in mice. However, glymphatic function is reduced in the mid- or late-stage of AD due to the loss of the polarity distribution of AQP4. Based on this, we hypothesized that AQP4-mediated glymphatic system clearance function is a determining factor for time-sensitive treatment of aerobic exercise in patients with AD. While further studies are necessary, the potential results are important for elucidating the new pro-cognitive mechanism of aerobic exercise, but also help to establish a new strategy for treatment of AD via regulation of glymphatic clearance function by targeting AQP4.

Background

Aerobic exercise, such as swimming, running and bicycling, are low to high intensity physical exercises that depends primarily on the aerobic energy-generating process [1]. There are a number of recognized benefits in regular aerobic exercise. For instance, strengthening cardio-pulmonary function, increasing the total number of red blood cells and facilitating transport of oxygen [2–5]. Indeed, aerobic exercise has been shown to reduce the incidence of aeroerlipidemia, atherosclerosis and diabetes [6–7].

Aerobic exercise also has multiple protective effects on the brain, such as increasing cerebral blood flow, oxygen uptake and glucose utilization, improvement of growth factor production, angiogenesis and neurogenesis, and decreasing oxidative stress [8–10]. Aerobic exercise can also improve mental health, reduce stress, lower the incidence of depression, and increase cognitive capacity [11–12]. Several population-based cohort studies found that aerobic exercise reduces the potential risk for Alzheimer's disease (AD) [13–14]. Clinical investigations also indicate that exercise could improve the cognitive function of AD patients, especially in the early stage, but do not mitigate memory deficits in patients with advanced AD [15].

In agreement with epidemiological and clinical studies, animal experiments demonstrate that aerobic training, such as wheel running or treadmill running, can reduce memory impairment of AD transgenic mice, Aβ deposition in the cortex and hippocampus, increase the number of cortical capillaries and improve brain perfusion [16]. An early study from our laboratory reported that voluntary exercise counteracts the impairment of working memory ability in mice intracerebroventricularly injected $A\beta_{25\text{-}35}$, which is associated with reducing oxidative stress and glial inflammatory reaction, and increasing hippocampal angiogenesis [10]. However, a subsequent study revealed that aerobic exercise, combined with antioxidant therapy, could not mitigate the middle-stage AD-like pathophysiology processes of APP/PS1 mice without alleviation of spatial cognitive malfunction, oxidative stress, glial inflammatory response, synaptic loss, and Aβ load [17].

The aforementioned evidences highly suggest the timeliness of aerobic exercise in the prevention and treatment of AD. Aerobic exercise successfully prevents or delays the occurrence and development

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of AD, but there are no obvious therapeutic effects on patients in the middle and late stages of AD. The mechanism underlying timeliness of aerobic exercise for treatment of AD needs further analysis.

The glymphatic system in efficient clearance of interstitial waste solutes from the brain

Abnormal deposition of Aβ and Tau in the brain is the core pathological changes of AD [18]. Sporadic AD constitutes the majority of all AD cases, but lacks a genetic mutation associated with the production of Aβ [18]. Therefore enhancing clearance of Aβ from the brain is currently the primary treatment strategy for AD. It is well known that the brain clears extracellular Aβ through various mechanisms, including uptake of neurons and glial cells, enzymatic degradation and elimination, and transportation crossing the blood-brain-barrier (BBB) and blood-cerebrospinal fluid barrier [18]. Nevertheless, there has been increasing evidences in recent years supporting the glymphatic system removing a major proportion of Aβ, Tau protein and other metabolites from the brain parenchyma [19].

The glymphatic system, also termed as paravascular pathway, is located in the narrow gap between small vascular adventitia and vascular end feet of astrocytes [20]. In comparison with the BBB composed by tight junctions of capillary endothelial cells, the glymphatic system has greater permeability, which contributes to the clearance of macromolecules from the brain parenchyma [20]. Recent studies demonstrated that the glymphatic system links the dural lymphatic vessels, which eventually drains toward the deep cervical lymph nodes [21–23]. Functional studies further demonstrated that the clearance capacity of the glymphatic system is associated with the fluidity of interstitial fluid (ISF) [24]. Previous studies found that astrocytes undergo contraction during the sleep state, which enlarges the extracellular space and improves ISF flow, in turn facilitating the clearance of macromolecular metabolic proteins from the brain [25].

Aerobic exercise increases heart rate, cerebral pulse pressure and perfusion flow, thereby enhancing brain interstitial fluid flow, which potentially promotes the glymphatic system to clear Aβ and Tau in the brain [26–27]. This hypothesis is proven by a recent study revealing that voluntary exercise enhances glymphatic clearance of amyloid beta in aged mice [26]. Furthermore, another study demonstrated that voluntary exercise increases the influx of CSF tracers into the brain of young, freely behaving, and awake mice relative to sedentary mice [27]. Together, all these evidences suggest that glymphatic clearance might mediate neuroprotective effects of aerobic exercise.

Aquaporin 4-mediated glymphatic clearance function

Further studies also show that the clearance function of the glymphatic system depends on astroglial water channel aquaporin 4 (AQP4) that lines the paravascular CSF pathways [28–30]. AQP4, the most abundant water channel in the brain, is crucial for maintaining brain water homeostasis [31,32]. We demonstrated that AQP4 gene knockout ($AQP4^{-/-}$) in mice results in slightly increased brain water content, reduced CSF production rate, and delayed postnatal brain water uptake [33–34]. $AQP4^{-/-}$ mice exhibit slowed CSF influx from the subarachnoid space into the brain parenchyma, as well as ISF outflow into the subarachnoid space again [28]. Apart from maintaining brain water balance, AQP4 facilitates ISF entering into astrocyte processes surrounding the synapses, which might drive astrocyte Ca^{2+} signaling transduction and reuptake of K^+ and glutamate, thus regulating synaptic plasticity [35,36]. AQP4 is also involved in the regulation of neurotrophic factor-dependent synaptic plasticity [37]. Adult $AQP4^{-/-}$ mice exhibit defects in consolidation memory and location-specific object memory [38,39].

Furthermore, AQP4 is necessary for the glymphatic system to clear Aβ and Tau [28–30]. Adult $AQP4^{-/-}$ mice show a ~45% reduction in clearance of intrastriatal injected radio-labeled $Aβ_{1-40}$, compared with aged-match wild-type (WT) mice [28]. In order to define the function of AQP4 in AD pathology, we successfully established $AQP4^{-/-}$/APP/PS1 mice. Twelve-month-old $AQP4^{-/-}$/APP/PS1 mice exhibit heightened spatial learning and memory impairment along with increased Aβ plaques deposition, amyloid angiopathy, synaptic protein loss and atrophy of astrocytes in the hippocampus and cortex [30]. This revealed a mitigating role of AQP4 in Aβ pathogenesis, suggesting that regulating the glymphatic system via targeting at AQP4 may be an effective therapeutic strategy for clearing soluble Aβ in the brain of patients with AD.

Previous studies have indicated that perivascular AQP4 polarization is the structural basis of the glymphatic clearance function. Astrocytes are activated, causing abnormal expression of AQP4 at the astrocyte soma and presynaptic processes in the brain of aged mice, AD mouse model or following brain trauma injuries [29,40,41]. The mislocalization of AQP4 disrupts the high expression feature of AQP4 along blood vessels and under the pia mater, impairing astroglial water flux, which would subsequently reduce the clearance efficiency of interstitial soluble Aβ and Tau from the brain parenchyma [41]. Consistent with animal studies, human brain research has revealed that abnormal polar expression of AQP4 is age-dependent, and closely associated with the aggregation of Aβ and Tau [42]. Recently, a few literature has reported that variations in the AQP4 gene may modulate the progression of cognitive decline in AD and relationship between sleep and brain Aβ burden [43,44].

Hypothesis

Based on the above analysis and previous work, we believe that glymphatic clearance function is a critical factor for the time-sensitive treatment of aerobic exercise for patients with AD. Under normal physiological conditions, or the early stage of AD, aerobic exercise increases cerebral arterial pulsation and enhances rapid transport of water from the extracellular space into the paravascular space via perivascular polarization of AQP4. Subsequently, this might facilitate the clearance of toxic solutes, including Aβ and Tau from the brain parenchyma (Fig. 1A-B). In contrast, in the mid- or late-stages of AD, glymphatic clearance function is impaired due to loss of AQP4 polarization caused by reactive astrogliosis, which would destroy the neuroprotective mechanism of aerobic exercise (Fig. 1C). To test this hypothesis, it would be interesting to compare improving effects of aerobic exercise on the glymphatic clearance function between AQPP/PS1 and $AQP4^{-/-}$/APP/PS1 mice at various ages.

In summary, as the most common neurodegenerative disease, AD has an enormous negative impact on society, patients and their families. Targeting at AQP4 may serve as a prospective strategy aimed at this catastrophic disease. Therefore, further studies are necessary to explore the contribution of AQP4 mediated glymphatic clearance function in AD pathology, and find corresponding new therapeutic drugs and methods.

Conflict of interest

We have no conflict of interest to declare.

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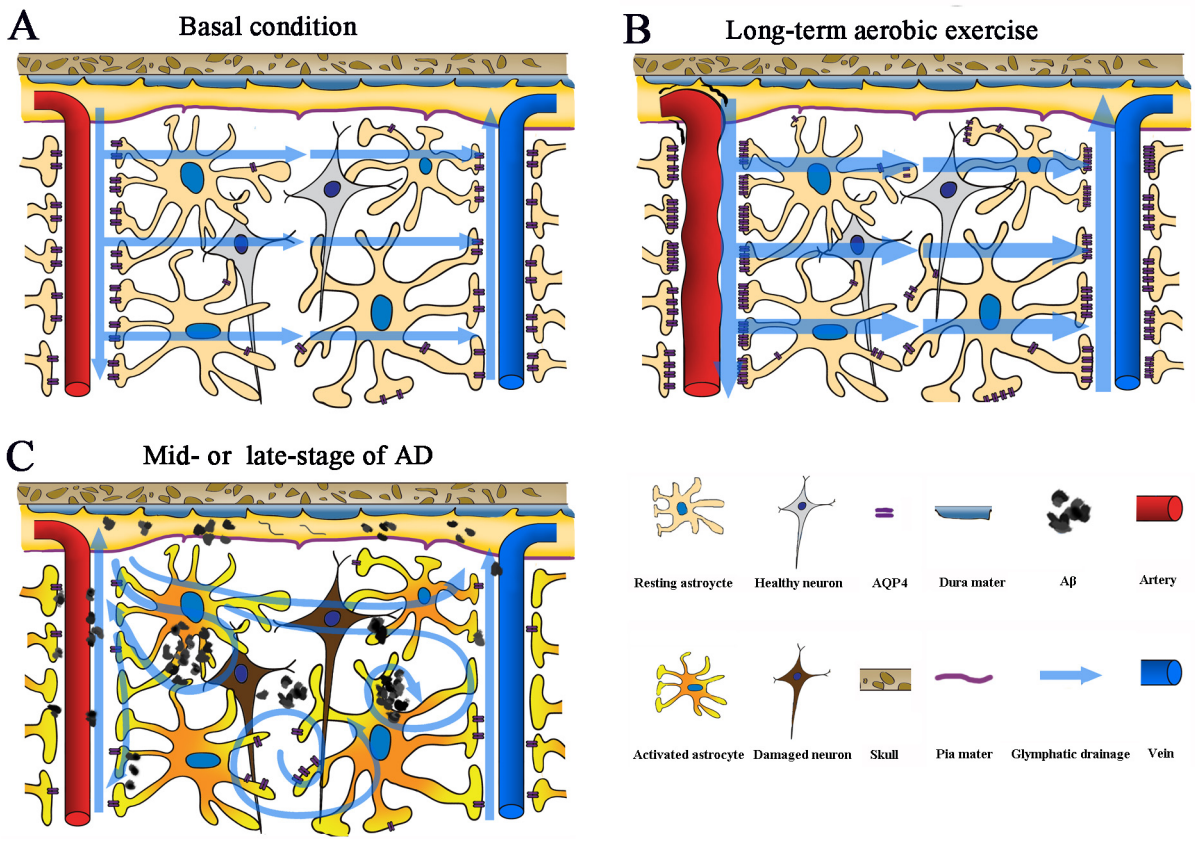

Fig. 1. Summary of the clearance function of glymphatic system. **A.** Under basal condition, the polarity distribution of AQP4, together with arteriopalmus, pushes CSF into the brain parenchyma via periarterial pathways. Wastes are washed out from the interstitial space within the veins. **B.** During aerobic exercise, arteriopalmus accelerates, and pushes additional CSF into the brain parenchyma. Velocity and the volume of flow are both increased. After an extended period of aerobic exercise, the expression and polarity distribution of AQP4 are both increased. As a result, the clearance function of CSF is enhanced. **C.** In AD, glymphatic function is reduced due to the accumulation of toxic proteins and the loss of the polarity distribution of AQP4. CSF flow becomes turbulent, resulting in toxic product accumulation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.mehy.2018.07.016.

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