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Reviews

The Role of the Glymphatic Clearance System in the Mechanisms of the Interactions of the Sleep–Waking Cycle and the Development of Neurodegenerative Processes

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Selective and progressive neuron death is a characteristic feature of the neurodegenerative process and leads to corresponding neuron dysfunctions. Neurodegenerative diseases constitute a heterogeneous group of nosologies with different clinical presentations but similar molecular mechanisms of pathogenesis. They are based on processes of abnormal protein aggregation and the formation of fibrillar insoluble structures and their deposition as histopathological inclusions in nervous system tissues. Disruption of homeostatic functions regulating neuron ion and energy metabolism, protein and nucleotide biosynthesis and degradation, chronic hypoxia, and penetration of toxic and inflammatory substances into the brain from the bloodstream not only cause age-related metabolic changes and disturbances in the sleep–waking cycle, but also contribute to the development of neurodegenerative processes. Animal studies have identified pathways of clearance in which solutes and specific tracers are cleared by a perivascular pathway into meningeal lymphatic vessels. The glymphatic network facilitates the clearance of metabolites, including beta-amyloid and tau protein, from the extracellular space of the brain. The glymphatic system is more efficient during natural sleep; fluid dynamics through this pathway display daily fluctuations and are under circadian control. The review systematizes the key aspects and scientific data from recent studies on the role of the glymphatic pathway and astroglial aquaporin type 4 as its main determinant in maintaining homeostatic fluid circulation in the brain in normal and pathological conditions, particularly in relation to the regulatory role of the sleep–waking cycle and during the development of neurodegenerative processes.

Keywords: glymphatic system, aquaporin-4, neurodegenerative diseases, sleep–waking cycle, amyloid, blood–brain barrier.

Glymphatic clearance is a pathway for the removal of fluids and metabolites from the brain and is believed to be a central mechanism for extravascular transport in the brain for substances unable to cross the blood–brain barrier (BBB). This pathway supports entry of cerebrospinal fluid (CSF) into the brain through arterial perivascular spaces and from there into the interstitium of the brain, this process being mediated by aquaporin type 4 (AQP-4) water channels. It is hypothesized that the glymphatic system then directs fluid into venous perivascular and perineuronal spaces, ultimately removing dissolved substances, including amyloid proteins, into the lymphatic drainage vessels. Animal experiments and theoretical network models have shown that the glymphatic pathway is active primarily during sleep, when the clearance of harmful metabolites and pathological molecules increases twofold as compared with the waking state [1–5].

Studies of the fundamental processes underlying aging and neurodegenerative diseases (NDD), particularly the role of glymphatic clearance, using modern experimental and clinical diagnostic neuroimaging and modeling methods is driven by the need for new knowledge on the molecular mechanisms of their development, followed by translation of the experience gained into practical applications.

The aim of the present review was to systematize the latest research data on the role of the glymphatic pathway and astroglial AQP-4 as its main determinant in maintaining homeostatic fluid circulation in the brain in normal and

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pathological conditions, particularly in relation to the regulatory role of the sleep–waking cycle and in the development of neurodegenerative processes.

Glymphatic Clearance of Metabolites. Alzheimer's disease (AD), the main clinical manifestation of which is dementia, and Parkinson's disease (PD), a predominantly motor disorder of the nervous system, are the most common human NDD. These pathologies affect more than 50 million people around the world, and the vast majority of cases are sporadic. Most NDD are associated with impaired processing and aggregation of specific proteins and the formation of insoluble fibrillar forms of these proteins, so they are regarded as conformational diseases, or proteinopathies [6–8]. Pathological proteins initially associated with a specific disease have subsequently been found to be involved in many neurodegenerative processes, suggesting the existence of common pathways in the pathogenesis of these diseases. Among these proteins, those of particular note are amyloid Aβ, α-synuclein, tau protein, and the non-amyloid proteins TDP-43 and FUS, whose clearance from brain tissue is impaired in neurodegeneration and neuroinflammation. Age has a direct effect on the progression of NDD and also plays an indirect role, taking concomitant diseases into account, with the result that age is seen as the most important non-modifiable risk factor for their development [8–13].

Hydrodynamics characteristics and exchange between the CSF and interstitial fluid, as well as the composition of these proteins, change with brain age, alterations in health status, and chronic sleep disorders. The complex system for fluid circulation and clearance of metabolic by-products from the cerebral parenchyma normally not only maintains brain health, but also plays an important role in the pathogenesis of many diseases [3, 12, 14–18]. The perivascular spaces of the brain form a complex network of communication channels around cerebral blood vessels and capillaries, which serve as pathways for movement of substances and exchange between CSF and interstitial fluid, as well as for the removal of metabolic waste from the brain [10, 19–22]. The so-called glymphatic pathway is a glial-mediated and highly organized fluid transport system and has recently come to be seen as the central clearance system in the brain in both animals and humans. Research into and confirmation of the key features of the functioning of the glymphatic system have employed dynamic contrast-enhanced MRI, providing visualization the para-arterial influx of fluid [1, 2, 16, 23–25]. Contrast medium injected directly into the cerebral parenchyma, mixing with the interstitial fluid, goes on to enter the paravascular spaces, the rate of elimination by this route being quite high – too high to be explained by simple diffusion. Consideration of various mechanisms of transport of substances from the intercellular spaces contributed to the discovery that a significant part of the CSF penetrates into cerebral tissues via the perivascular route and is removed in the same way. Astroglia, with their terminals surrounding brain blood vessels, form a type of coupling which additionally separates the vascular bed from neurons. Astrocyte processes surround synapses and cover both the relatively open perivascular spaces surrounding penetrating vessels and the basement membrane and the extracellular matrix around microvessels deep in the parenchyma. Thus, pial vessels penetrating deep into the brain substance form a perivascular space around them, filled with CSF. Perivascular spaces offer little resistance to flow and are connected to the subarachnoid spaces, from which CSF quickly moves into the deep parts of the brain due to pulsations of arterial vessels [22, 26, 27].

Data obtained in the last decade indicate that the glymphatic system plays an important role in health and in the pathogenesis of neurological diseases, by maintaining homeostatic fluid circulation in the brain. Even before the onset of clinical manifestations, the genesis of neurodegenerative processes includes self-aggregation of proteins under the influence of various physicochemical factors directly promoting assembly and their gradual accumulation. At the same time, reduced fluid transport and impaired glymphatic clearance not only increase the local amyloid concentration, but also increase the risks of subsequent aggregation. Studies of the glymphatic pathway of movement of tracers from the CSF have noted that movement correlates with the local pattern of formation of fibrillar forms [26, 28–30].

During transport of fluid through the cerebral parenchyma, diverse factors, in particular solute size, binding of ligands to receptors, protein aggregation, and the distance of molecular transport, have significant influences on the hydrodynamics and exchange between the CSF and the interstitial fluid. The main functionality in the complex system of fluid circulation and clearance of metabolic products is associated with the expression of AQP-4 water channels, the highest concentration of which is seen in the terminal regions of astrocyte processes (end-feet) [31, 32]. Astrocytes are essential for maintaining BBB functions and glymphatic clearance. Astrocyte terminals are attached to cerebral vessel walls and nutrients can be exchanged between endothelial cells and the cerebral parenchyma. Thus, astrocytes are key components not only of the neuroglia, but also of the vasculature, and are critical for BBB integrity. Astrocytes release a number of biologically active substances (BAS), including cytokines and neurotrophic factors (TGF-β, fibroblast growth factor-β, IL-6); they express transport proteins and receptors, in particular AQP-4 water channels. A close correlation between this protein and glymphatic function was found in studies on mice with AQP-4 gene knockout, while deletion of the water channel in these mice significantly aggravated dysfunction of glymphatic clearance and intraneuronal amyloid accumulation [33, 34].

AQP-4 as a Major Determinant of the Glymphatic System. AQP-4, which mediates water transport in cells and tissues, is a bidirectional transmembrane water channel. AQP-4 is located predominantly at the perivascular terminals of astrocytes as a result of its association with the dystro-

phin-associated complex (DAC). The area of astrocyte terminals also varies, depending on cerebral vessel diameter, and this is most marked in the arterial vasculature. It has been suggested that this ensures a relatively constant glymphatic flow despite changes in pressure in the cerebrovascular system. Astrocyte volume, particularly of their terminal sections, changes in response to osmotic stimuli by a process involving AQP-4, and this may be one of the means of dynamic regulation of perivascular metabolism. Recent studies have shown that the dynamic translocation of astroglial AQP-4 from the intracellular vesicle pool to the plasma membrane is responsible for water homeostasis in health and disease, while pharmacological inhibition of water channels promotes the formation of edema [31, 35–37]. It has been suggested that the key role of AQP-4 is precisely that of mediating the movement of solutes and electrolytes and, to a lesser extent, its function as a true water channel for the flow of fluid (water) between the perivascular space and the interstitium [38].

Studies in genetic knockout animals have shown that mice lacking AQP-4 have a 70% reduction in CSF influx and a 55% reduction in parenchymal clearance of ^{125}I-labeled beta-amyloid (amyloid Aβ). As compared with young mice, the clearance of injected amyloid in older mice is impaired by 40%, and this is accompanied by decreased perivascular polarization of AQP-4 along penetrating arteries and a progressive decrease in the efficiency of the cerebral hydrodynamics of dissolved substances in the aging brain. Tau protein, which is able to spread from neuron to neuron through the extracellular space by a prion-like mechanism, is also a substrate for clearance through the glymphatic pathway. Disruption of glymphatic metabolism has been found in mouse models of tauopathy; pharmacological blockade of AQP-4 leads to decreased clearance of tau protein, revealing the therapeutic targeting of AQP-4 as a target for glymphatic modulation in neurodegenerative tauopathies. Preclinical studies suggest that the normal functioning of the glymphatic pathway significantly influences the clearance of amyloidogenic proteins in humans [1–3, 28, 29, 39–42].

The perivascular localization of AQP-4 is decreased in people with clinically confirmed NDD, while age-associated loss of the required localization of AQP-4 leads to worsening of patient status and disease staging. A postmortem immunohistochemical study of patients with AD revealed impaired expression of AQP-4, similar to that seen in aging mice [43]. Thus, total immunoreactivity and, consequently, the number of AQP-4 molecules increased with age, while the polarity of the transport protein was preserved only in cognitively healthy elderly people; loss of perivascular localization of AQP-4 correlated with clinically confirmed cases of AD and the stage of disease. Loss of AQP-4 polarization and disruption of its dynamic redistribution are believed to alter synaptic activity and astrocyte function, subsequently contributing to the development of neurodegeneration and endothelial dysfunction in humans [12]. In-life CSF AQP-4 levels are significantly higher in patients with NDD than in controls, and this simultaneously correlates with tau protein concentrations. This may be either a consequence of reactive astrogliosis, which induces increased expression of water channels, or a result of impairment to the protein selectivity of astrocytes and a decrease in the rate of glymphatic metabolism – the homeostatic restoration of which requires overexpression of AQP-4 [44]. It is of note that the question whether impaired AQP-4 localization is a consequence of the accumulation of amyloidogenic proteins or whether AQP-4 pathology causes the accumulation of such proteins due to a decrease in glymphatic function remains open and requires further study.

Glymphatic Function and the Sleep–Waking Cycle. The sleep–waking cycle changes significantly throughout development and aging, sleep disturbances being a common feature of many NDD and an early correlate of them. Research has shown that sleep disturbance may not simply be a sign of brain aging, but may also be a factor in the aging brain's vulnerability to the development of neurodegenerative processes. Sleep quality and structure undergo age-related changes; for example, the proportion of deep slow-wave sleep decreases with age, while the superficial stages become significantly predominant. Even short periods of sleep loss have long-term consequences, such as impairments to memory consolidation and other cognitive functions. Sleep deprivation leads to a decrease in dendritic spines and synaptic proteins in the hippocampus, deposition of abnormal proteins, and activation of astrocytes and microglia as the main source of the secretion of proinflammatory cytokines in the brain; however, the molecular mechanisms of brain disorders caused by changes in the sleep–waking cycle continue to be studied [45–49].

It has been suggested that glymphatic clearance is regulated by the sleep–waking cycle because the movement of CSF through brain tissue occurs more rapidly in the sleeping and anesthetized brain than in the awake brain. Similarly, clearance of interstitial dissolved substances, including amyloid Aβ, occurs more rapidly during sleep. Natural sleep is associated with an increase in the size of the interstitial space, which in turn increases the convective exchange of CSF with the interstitial fluid and macromolecule clearance. Thus, studies in mice revealed a doubling of the glymphatic clearance of radioactively labeled amyloidogenic proteins during sleep compared to the waking state. The glymphatic system is not only more efficient during natural sleep, but the fluid dynamics through this pathway exhibit daily fluctuations and are under circadian control. AQP-4 is believed to maintain this rhythm by a specific mechanism, and its perivascular polarization is most marked during sleep. Moreover, deletion of AQP-4 in knockout mice eliminates the day-night differences in both glymphatic influx and fluid outflow. At the same time, studies in humans have demonstrated that poor sleep quality is a risk factor for cognitive decline and the development of dementia in humans. Progression of the neurodegenerative process in older people can be explained in terms

of age-related disturbances in the sleep–waking cycle, where changes in the architecture and depth of sleep directly reduce the glymphatic clearance of metabolites and promote amyloid formation [16, 34, 36, 49–52].

A study of the hydrodynamics of CSF containing fluorescently labeled lipidated isoforms of apolipoprotein E (ApoE) [53] demonstrated significant decreases in the clearance of many substances from the interstitium during sleep deprivation. The glymphatic fluid transport system delivers ApoE to the brain, primarily during sleep, via periarterial spaces, and an imbalance in this physiological clearance may contribute to the development of ApoE isoform-specific disorders in the long term. Sleep fragmentation causes progression of the symptoms of AD and induces neuroinflammation, accumulation of amyloid Aβ, and phosphorylation of tau protein, while in wild-type mice it has adverse influences on cognitive behavior, particularly learning and memory [5]. This is associated with the modulation of AQP-4, a key participant in the activity of the glymphatic system, expression of water channels varying depending on the stage and severity of the process; it is also associated with microglial activation and reactive astrogliosis. On the other hand, deletion of astroglial AQP-4 led to disruption of glymphatic transport and accumulation of amyloidogenic proteins in the brain in a mouse model of chronic sleep disorder. In an experiment in AQP-4 null rodents, neurochemical and behavioral analyses revealed microglial activation, neuroinflammation, and loss of synaptic proteins in the hippocampus, along with decreases in working memory, as compared with wild-type mice [36]. The relationship between variation in the AQP-4 gene with cognitive functions and sleep quality and parameters has also been studied in humans [54, 55]. Genetic variation in AQP-4 has been shown not only to be associated with cognitive decline on development of NDD, but also to modulate the relationship between sleep and brain amyloid Aβ levels. Findings from in vivo models open up the opportunity for new clinical studies, as the expression levels of astroglial aquaporin and its role in the glymphatic system as a whole may represent a prognostic marker for the onset of the neurodegenerative process for early diagnosis. Furthermore, studies of the relationship between the sleep–waking cycle and metabolite transport in the context of the development of NDD should take genetic variations in AQP-4 and their impact on sleep architecture into account [4, 5, 49, 52–59].

The mechanisms of suppression of glymphatic clearance during waking remain unknown, though EEG activity is closely correlated with glymphatic influx. It may be the case that the synchronous characteristics of slow-wave sleep result in the movement of extracellular ions through the cortex, maintaining a pulsatile influx of CSF. Conversely, this process is incompatible with asynchronous patterns of neural activity during waking [34, 52].

Conclusions. Disturbances in cerebral fluid dynamics and glymphatic clearance are involved in the pathophysiology of a number of brain diseases, including neurodegenerative and demyelinating diseases, dementia, and sleep pathology. However, the data supporting these findings are currently inconclusive and sometimes contradictory. It is of note that analysis of glymphatic activity in animals and humans remains difficult, as the requirements for neuroimaging, including the invasive introduction of fluorescent indicators and contrast agents into the brain, have a number of technical and time limitations; neuroimaging can be accompanied by neurotoxic effects and even damage to the BBB when gaining access to the parenchyma of the brain. Organ-on-a-chip technology has potential for solving the problems of finding suitable models in humans and for creating new models for further research into complex intercellular interactions as the basis for the functioning of glymphatic clearance [60, 61].

Ongoing progress in basic research is driving the translation of this knowledge into clinical applications, as numerous studies have been conducted over the past decade to explore new molecules as promising diagnostic biomarkers for various NDD and as therapeutic targets for biological therapies. Given the involvement of amyloidogenic proteins, various genetic markers, and pathology of glymphatic clearance and disorders of the sleep–waking cycle in the final common pathways leading to neurodegeneration, the contribution of these abnormalities and disorders of the molecules and processes discussed here is increasingly being investigated in order to find new solutions and alternative approaches for the diagnosis and treatment of a heterogeneous group of diseases of neurodegenerative origin.

The authors declare no conflict of interest.

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