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The brain's glymphatic system: significance for physiology and pathology

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Summary. This review aims to summarize the world's scientific sources that highlight the current vision of the role of the brain glymphatic system in the utilisation of end metabolites from the central nervous system. It has been reported that protein clots or aggregates that are produced in brain cells and, importantly, failure of their elimination can cause cognitive problems in neurodegenerative diseases. In particular, Alzheimer's and Parkinson's disease, as well as the other neurodegenerative diseases, the aging process can be reproduced in experimental models by overproducing these conglomerates.

Current investigations are focused as well on clarifying changes in brain glymphatic drainage in the condition of traumatic brain injury. Modern research has shown that acute brain injury, including traumatic brain injury, subarachnoid hemorrhage, or stroke, dramatically alters glymphatic function. It is evident that aging is a critical risk factor for neurodegenerative diseases. It has also been experimentally proven that glymphatic activity decreases with aging. Accordingly, this can lead to the accumulation of misfolded and hyperphosphorylated proteins, and thus the brain becomes vulnerable to the development of neurodegenerative pathology. Comprehensive analysis of the causes and mechanisms of glymphatic system dysfunction will help to predict and develop methods for diagnosing and treating serious neurodegenerative diseases and traumatic brain injuries.

Keywords: glymphatic system, neurodegenerative diseases, aquaporins 4 (AQP-4).

Ґлімфатична система мозку: роль у фізіології та патології

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Резюме. В огляді представлені аналіз та узагальнення світових наукових джерел, що висвітлюють актуальне бачення ролі ґлімфатичної системи мозку в утилізації кінцевих метаболітів з центральної нервової системи. Обговорюються порушення кліренсу мозку за умов деяких нейродегенеративних нозологій, а також при інсультах і травматичному ушкодженні мозку. Показано, що кліренс асоційованих, до прикладу, з хворобою Альцґеймера, білків амілоїду β (Aβ) і тау (tau) знижується внаслідок порушення функції ґлімфатичної системи через відсутність, зокрема AQP. Відповідно, водні канали типу аквапорину-4 (AQP-4) є важливою складовою цієї системи і порушення їх функції викликане низкою нейропатологій. Виявлені зміни в експресії AQP-4, які пов'язують з певними нозологіями, дають можливість прогнозувати, що цей водний канал може бути важливою фармакологічною мішенню. Також засвідчено, що біомаркери черепно-мозкової травми дренуються через ґлімфатичні шляхи. Ґлімфатична дисфункція за даних умов може визначати ймовірний прогноз після перенесеної черепно-мозкової травми. Аналіз та поглиблене вивчення змін ґлімфатичного дренажу за умов травми обґрунтовує можливість фармакологічних маніпуляцій з ґлімфатичною системою за даних умов. Експериментально підтверджено, що при старінні знижується активність ґлімфатики, що може сприяти накопиченню неправильно згорнутих і гіперфосфорильованих білків і, отже, мозок стає вразливим до розвитку нейродегенеративної патології. Аномальне розширення периваскулярного простору значно частіше виявляють при хворобі Альцґеймера у суб'єктів похилого віку, що може свідчити про можливе порушення функції ґлімфатичної системи і подальше зниження кліренсу білка.

Ключові слова: ґлімфатична система, нейродегенеративні захворювання, аквапорини 4 (AQP-4).

The central nervous system is unique in being the only functional system lacking conventional lymphatic pathways and thus has no discrete routs for the clearance of substances dissolved in the interstitium. Recent scientific publications have highlighted the concept of the existence of a glymphatic system that enables the brain to be drained of extracellular harmful substances and waste products [1, 2, 3]. Water channels such as aquaporin-4 (AQP-4) are an important component of this system, and their dysfunction is associated with a number of neuropathologies [4, 5].

The purpose of the study. To analyze and systematize the world scientific sources over the past decade on the processes and mechanisms of functioning, as well as clinical prospects for the evaluation of the glymphatic brain drainage system.

Results and discussion. Modern research has confirmed the existence of an effective mechanism for the utilization of extracellular potentially toxic

brain substances, soluble proteins and metabolites, which uses a unique system of perivascular channels formed by astroglial cells, the so-called glymphatic system [1]. Studies have shown that this system is most active during sleep [2, 6]. The ability to remove toxic metabolites from the brain during sleep will, in fact, contribute to an even deeper understanding of the fundamental biological role of sleep and the consequences of sleep disorders. In addition to the clearance of substances dissolved in the interstitium, other functions of the glymphatic system have been identified. In particular, it has been shown that cerebrospinal fluid inflow is a channel for glucose and other nutrients that are absorbed by neurons and astrocytes [7]. In addition, apolipoprotein E, which is essential for synaptic plasticity and cholesterol transport, can also be transported by the CSF into the brain interstitium [8].

Since the concept of the glymphatic system is relatively new, it is important to consider its basic structural elements, organization, regulation, and functions.

Scientific studies presented in international publications highlight the current understanding of the processes of internal brain cleansing from substances dissolved in the interstitium [9, 10, 11]. Thus, the data showed that CSF (cerebrospinal fluid) and interstitial fluid (ISF) are constantly exchanged. This exchange is facilitated by the convective flow of cerebrospinal fluid along the periarterial space [9]. The perivascular spaces are tunnels that surround each vessel. The inner wall of each space is formed by the surface of vessel cells, mostly endothelial cells, and smooth muscle cells. The outer wall, however, is unique to the brain and spinal cord and is formed by extensions of astrocytes. Astrocytes are known to perform many functions in a highly organized network of neurons. Astrocyte extensions – or pedicles – surround the arteries, capillaries, and veins of the brain and spinal cord. Further transport of CSF into the complex parenchyma of the brain is facilitated by aquaporins – AQP-4, which are expressed in the pedicles of astrocytes, characterizing the polarized distribution of these channels [10, 11]. This localization allows AQP-4 to contact the perivascular space adjacent to blood vessels, facilitating the inflow of CSF into the brain parenchyma and its outflow in the opposite direction into the perivascular space [11]. The attention of scientists was drawn to the multiplicity of astrocytic water channels and their special location facing the vascular wall. Moreover, it was found that vascular endothelial cells bordering the perivascular space do not have these channels. Thus, the fluid cannot be transported directly from the bloodstream to the brain tissue, but only through the perivascular space and through astrocytes, thus gaining access to the brain tissue. The movement of CSF into the parenchyma causes convective flows of interstitial fluid within the tissue to the perivenous spaces surrounding the large deep veins. The CSF-ISF (cerebrospinal fluid-interstitial fluid) then flows through the interstitium, draining through the paravenous highways and through the still poorly understood meningeal lymphatic vessel (MLV) pathway to reach the cervical lymphatic system. This specific movement of fluid through the brain allows extracellular proteins such as Aß and tau to be eliminated from the interstitium.

Returning to an important component of the astrocytic glymphatic system, astrocytic AQP-4, it is the most common water channel in the brain, which has a tetrameric structure [10]. This protein functions as a selectively permeable water channel, maintaining ionic and osmotic homeostasis in the brain [10, 11]. Osmotic homeostasis is important for neural activity, and modulation of water transport changes the concentration of ions in the extracellular fluid, which in turn affects the diffusion of neuroactive compounds to the brain. In addition, disruptions in fluid transport mechanisms can cause cerebral edema, which accompanies certain neurological conditions such as head injury, stroke, and brain cancer [12]. There is strong evidence that AQP-4 is important for neuroexcitation, astrocyte migration, synaptic plasticity, and memory/learning performance [10, 13].

In recent publications, the concept of glymphatic insufficiency is defined as the inability of the glymphatic system to properly perform the function of cleansing the brain [14]. It is believed that this failure can be acute or chronic, depending on the duration of the process. The question arises whether glymphatic dysfunction is caused by the insufficiency of the system itself or by excessive formation of waste substances that exceeds the cleansing capacity of this system. However, regardless of the above question, researchers believe that the result of glymphatic insufficiency is the accumulation of waste substances in the brain parenchyma, in particular in those areas of the brain where glymphatic dysfunction is present [4, 7].

Another interesting area of research is the experimentally confirmed hypothesis that the activity of the glymphatic system decreases dramatically with aging [15]. Reactive gliosis, defined by hypertrophy of astrocyte processes, progresses with aging [15] and may contribute to the age-related decline in glymphatic function, although the detailed mechanisms of this process remain unclear. AQP-4, which in young animals is localized to the astrocyte pedicles, plays a central role in facilitating CSF-ISF exchange along periarterial flow pathways, as well as interstitial clearance of solute through perivascular drainage pathways [15, 16]. However, the vascular polarization of astrocytic AQP-4 is partially lost in reactive astrocytes of the aging brain, i.e., the localization of AQP-4 is no longer limited to astrocytic legs present in the parenchymal processes of astrocytes. The findings that perivascular polarization of AQP-4 is lost with aging, particularly along penetrating arterioles, and that the presence of cortical parenchymal AQP-4 correlates with CSF-ISF exchange, suggest that age-related decline in glymphatic function may be partially related to dysregulation of astroglial water transport.

Other factors that may affect the dynamics of glymphatic drainage with aging are a 66 % decrease in CSF production and a 27 % decrease in CSF pressure [15]. Aging is also accompanied by stiffening of the arterial wall, which leads to a decrease in arterial pulsatility, which is one of the enhancers of glymphatic inflow [17]. Observations of the age-related decline in glymphatic activity are important because aging is a critical risk factor for neurodegenerative diseases. Impaired function of the glymphatic system in aging can lead to the accumulation of misfolded and hyperphosphorylated proteins, and thus the brain becomes vulnerable to the development of neurodegenerative pathology or, possibly, the progression of cognitive dysfunction [17].

It is known that neurodegenerative diseases are characterized by the accumulation of aggregated proteins [4, 5]. Numerous studies on protein degradation in the CNS have mainly focused on intracellular processes, i.e., proteosomal or lysosomal degradation. However, it is now known that toxic protein monomers, oligomers, and aggregates are also present in the interstitial fluid and CSF: misfolded ß-amyloid and fibrillar tau aggregates in Alzheimer's disease, misfolded α-synuclein in Parkinson's disease, and misfolded superoxide dismutase enzyme in experimental models of amyotrophic lateral sclerosis [4, 5, 18]. ß-amyloid deposits are found in hippocampal synapses, which serve as a source of extracellular ß-amyloid [19]. According to this, ß-amyloid production is maximal during wakefulness, when neuronal activity is highest [20]. However, ß-amyloid is produced not only by neurons. In fact, all cells produce ß-amyloid, including oligodendrocytes and their progenitor cells. The latter may, at least in part, explain the changes in myelin structure observed in Alzheimer's disease. The concept of prion-like spreading of neurotoxic protein aggregates emphasizes the importance of the interstitial space in relation to deposits of aggregated protein, such as ß-amyloid, in Alzheimer's disease [5,18]. In the human body, the synthesis and metabolism of ß-amyloid is extremely intense. In healthy young adults, 8.3 % of total ß-amyloid is eliminated with the CSF [4]. Perivascular drainage pathways function as drain path for interstitial ß-amyloid in Alzheimer's disease [21]. The volumetric clearance by the glymphatic system in

combination with transport across the blood-brain barrier [1, 16] can provide the necessary and adequate removal of extracellular ß-amyloid until the end of the reproductive period of life. Abnormal expansion of the perivascular space is more common in Alzheimer's disease compared to control elderly subjects, indicating a possible deformation of the glymphatic pathways and a subsequent decrease in protein clearance and development of pathology [15, 17].

There is a hypothesis that sleep disorders in dementia may not only be a side effect of the disorder, but also contribute to the development of the disease itself. Moreover, if the glymphatic system clears beta-amyloid during sleep at a higher rate than during wakefulness, it is possible that poor sleep in patients with neurodegenerative disorders can cause disease progression [22]. Many patients with Alzheimer's disease experience sleep disturbances long before their dementia becomes apparent. In older people, sleep becomes more fragmented and superficial and has a shorter duration. Epidemiologic studies have shown that patients with dyssomniatic disorders in middle age had a higher risk of developing cognitive impairment than control subjects [23, 24, 25]. Even healthy people who have been deprived of sleep experience symptoms more typical of neurological and mental illnesses, such as lack of concentration, memory lapses, fatigue, irritability, and emotional swings. Deep sleep deprivation can lead to confusion and hallucinations, which can potentially lead to epileptic seizures and even death. The role of sleep in the clearance of glymphatic fluid has been convincingly demonstrated, and since the rate of clearance is highest during sleep, the glymphatic system simply cannot be studied without studying the basic aspects of sleep [15, 17, 23].

Experimental studies have shown that glymphatic function is highly active both in anesthetized mice and in the state of natural sleep, indicating that glymphatic activity is regulated by physiological differences in the states of sleep and wakefulness themselves, rather than by fluctuations in circadian rhythms. The main driver of awakening is the neuromodulator norepinephrine [25, 26]. Literature data suggest that norepinephrine is also a key regulator of glymphatic activity and may be a major factor in the suppression of glymphatic activity during wakefulness. An increase in the volume of interstitial space in the sleeping state reduces tissue resistance to convective flows, promoting efficient CSF-ISF exchange. Thus, the release of norepinephrine during awakening increases the cell volume fraction, reducing the interstitial space. In turn, the resistance to convective CSF-ISF exchange increases, which acts to suppress of glymphatic flows during wakefulness [20].

Traumatic brain injury is also the subject of modern research to clarify the functioning of the glymphatic system. It is known that traumatic brain injury increases the risk of premature development of dementia and Alzheimer's disease [27]. Numerous studies have shown that repeated traumatic events and even single cases of moderate to severe traumatic brain injury can lead to progressive neurodegeneration. Traumatic brain injury causes the release of ß-amyloid peptide and tau protein, a proteolytically cleaved product of MAP-tau, which is an intracellular microtubule protein in neuronal axons [27, 28]. C-tau is a biomarker of brain damage, as it is produced in large quantities and directly correlates with the severity of traumatic brain injury [27]. As a result, a hypothesis has emerged that a significant increase in interstitial tau levels leads to cellular uptake and initiation of fibrillar aggregates, which attracts additional tau, and this in turn leads to the formation of neurofibrillary tangles and ultimately causes a prion-like spread of pathology [29]. It is striking that in a model of repetitive moderate traumatic brain injury, the decrease in glymphatic function persisted at least until 28 days after the injury. The prolonged decline in glymphatic function was associated with glial scarring, characterized by hypertrophic GFAP-positive (glial fibrillary acidic protein) processes in the ipsilateral hemispheres. In addition, mislocalization of AQP-4 from the vessel pedicles to the parenchymal processes was observed, similar to

the mislocalization of AQP-4 observed in aging [24]. Human tau accumulated around large veins, and the amount of tau remaining in the tissue correlated with decreased clearance of glymphatic fluid [27, 30]. This suggests that the elimination of tau through glymphatic pathways is crucial for limiting secondary neuronal damage after traumatic brain injury. Another study using magnetic resonance imaging (MRI) to assess glymphatic function found additional evidence that head trauma, such as subarachnoid hemorrhage, severely impairs glymphatic function [31, 32, 33]. In this «subarachnoid hemorrhage» model, the use of tissue plasminogen activator, which removes fibrin clots, improved glymphatic perfusion. Embolic ischemic stroke caused transient inhibition of lymphatic flow within an hour after ischemia, but the function was spontaneously restored 24 hours after transient ischemia. Thus, studies have shown that acute brain injury, including traumatic brain injury, subarachnoid hemorrhage, or stroke [34, 35], dramatically alter glymphatic function and impair convective fluid flow. The impaired CSF-ISF exchange has direct consequences for the limitations of the diagnostic value of plasma biomarkers in traumatic brain injury [36, 37, 38]. Most importantly, impaired glymphatic function can further exacerbate the injury through the accumulation of both common metabolites and injury-induced accumulation of neurotoxic compounds.

Conclusions. The data obtained over the past decade indicate that age-related decline in the activity of glymphatic drainage largely causes the accumulation and pathological aggregation of ß-amyloid and tau proteins. The literature also suggests that the concentration of ß-amyloid in the CSF changes during the sleep-wake cycle in humans. It is expected that future studies focused on the glymphatic system will reveal other important functions of convective cerebrospinal fluid flows, which, in addition to removing metabolic products, are involved in the regulation of lipid, glucose, and other metabolic processes. It can be assumed that the glymphatic system provides an important pathway for the distribution of electrolytes, macromolecules, and other high molecular weight compounds that enter the brain mainly with the CSF system. Similarly, the glymphatic system can serve as a highway for the transportation and distribution of targeted drugs in the brain, including anticancer drugs. The analysis of current scientific studies has shown that intrathecal lumbar injections, which are routinely used in clinical studies, provide a valid alternative way to assess the main parameters of glymphatic function. Much remains to be studied, but the ability to evaluate glymphatic activity in patients after traumatic brain injury will allow to identify patients with the most severe suppression of glymphatic activity and thus predict the contingent of patients at higher risk of developing chronic traumatic encephalopathy.

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