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Structural and Functional Features of the Glymphatic System: A Contemporary Perspective

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ABSTRACT

The aging of the population in developed countries is a trend of major medical and social significance. In this regard, the study of the etiology and pathogenesis of neurodegenerative diseases, as well as the search for effective treatment methods, is of particular relevance. For a long time, it was believed that metabolic waste products were drained from the brain parenchyma's interstitial fluid into the ventricular system. However, the discovery of the brain's glymphatic system has significantly advanced our understanding of the mechanisms underlying pathologies associated with impaired clearance of metabolites from the brain. This scientific review outlines the main directions in the study of the functional morphology of the glymphatic system under normal conditions. It provides a detailed description of two theories of cerebrospinal fluid outflow and presents a critical analysis of both Russian and international research data. Under normal conditions, the function of the glymphatic system is influenced by heart rate, intracranial pressure, pulse and arterial pressure, as well as the phase of the respiratory cycle. In addition, sleep quality, head position during sleep, and exposure to toxic substances directly affect glymphatic system activity. The review also highlights recent data on the glymphatic system of the visual organs. Further research into the morphofunctional characteristics of the glymphatic system under normal conditions may greatly expand our fundamental understanding of disease pathogenesis and contribute to the development of new approaches to treatment and prevention.

Keywords: glymphatic system; perivascular space; Virchow–Robin space; cerebrospinal fluid.

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Структурные и функциональные особенности глимфатической системы головного мозга: современный взгляд на проблему

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АННОТАЦИЯ

Большую медико-социальную значимость имеет тенденция к старению населения развитых стран. В связи с этим особенную актуальность имеет изучение этиологии и патогенеза нейродегенеративных заболеваний, а также поиск методов их лечения. Долгое время считалось, что продукты метаболизма дренируются из интерстициальной жидкости паренхимы мозга в систему желудочков. Однако открытие особой глимфатической системы головного мозга позволило значительно продвинуться в понимании природы патологий, связанных с нарушением процесса очищения головного мозга от метаболитов. Научный обзор отражает основные направления в изучении функциональной морфологии глимфатической системы в норме. В нём детально описаны две теории оттока ликвора и критически проанализированы данные отечественных и зарубежных исследований. В норме функция глимфатической системы зависит от частоты сердечных сокращений, уровня внутричерепного, пульсового и артериального давления, а также от фазы дыхательного цикла. Кроме того, на работу глимфатической системы оказывают непосредственное влияние качество сна, положение головы во время сна и токсические вещества, потребляемые человеком. В обзоре приведены «свежие» данные о глимфатической системе органов зрения. Дальнейшие исследования морфофункциональных особенностей глимфатической системы в норме могут существенно расширить фундаментальные представления о патогенезе заболеваний, а также способствовать разработке методов их лечения и профилактики.

Ключевые слова: глимфатическая система; периваскулярное пространство; пространство Вирхова–Робина; ликвор.

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脑部淋巴系统的结构与功能特点：问题的现代视角

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摘要

发达国家人口老龄化的趋势具有重要的医学与社会意义。因此，研究神经退行性疾病的病因和发病机制，以及探索其治疗方法，尤为重要。长期以来，代谢产物被认为是通过脑实质间质液进入脑室系统而被清除的。然而，脑部特殊的脑淋巴系统（glymphatic system）的发现，极大地推动了人们对脑部代谢产物清除机制障碍相关疾病本质的理解。本综述反映了脑淋巴系统在正常状态下功能形态学研究的主要方向。文中详细介绍了两种脑脊液回流理论，并对俄罗斯与国外的研究数据进行了批判性分析。在正常情况下，脑淋巴系统的功能取决于心率、颅内压、脉压、动脉压以及呼吸周期的阶段。此外，脑淋巴系统的功能还直接受到睡眠质量、睡眠时头部位置以及人体摄入的毒性物质的影响。文中还列举了有关视觉器官脑淋巴系统的最新研究数据。对脑淋巴系统在正常状态下形态与功能特点的进一步研究，将有助于拓展对疾病发病机制的基本认识，并促进治疗与预防方法的开发。

关键词：脑淋巴系统；血管周围间隙；Virchow－Robin间隙；脑脊液。

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INTRODUCTION

Neurosciences remain a top priority in modern research. Research into the etiology and pathogenesis of neurodegenerative diseases, as well as the search for treatment options, is particularly relevant because of the aging population and the tendency to remain socially and professionally active in older age, characteristic of developed countries. For a long time, it was believed that the central nervous system (CNS) lacked a network of lymphatic capillaries, with metabolic products draining from the cerebral interstitial fluid into the ventricular system containing cerebrospinal fluid (CSF). However, this explanation was not convincing enough because the ventricular wall area is relatively small compared with the brain parenchyma, and the CNS is one of the most metabolically active systems in the human body. In 2015, Louveau et al. [1] and Aspelund et al. [2] first described lymphatic vessels in the dura mater alongside the venous sinuses in mice and humans. However, Iliff et al. [3, 4] formulated the main concepts of the "glymphatic system" hypothesis back in 2012. They described a unique system of paravascular channels formed by astroglial cells. These channels facilitate the efficient removal of soluble proteins and metabolites from the CNS parenchyma.

Another theory of the glymphatic system structure suggests that interstitial fluid in the brain parenchyma flows retrograde into the bloodstream through perivascular spaces within the basement membrane stratification of smooth muscle cells in the middle layer of vascular walls [5–8]. The development of the glymphatic system is assumed to be closely related to the formation of the lymphatic channel, which is stimulated by the signaling cascade of vascular endothelial growth factor C / vascular endothelial growth factor receptor 3 (VEGF-C/VEGFR-3) during embryogenesis. This assumption is based on the finding that transgenic mice with disrupted VEGF-C/VEGFR-3 signaling exhibited impaired development and function of meningeal lymphatic vessels and dysfunctional CNS glymphatic clearance [9].

The importance of the glymphatic system cannot be overestimated. Since its discovery, it has become apparent that this system plays a critical role in clearing proteins produced by cellular metabolism from the brain parenchyma. For example, beta-amyloid, alpha-synuclein, and tau proteins play key roles in the pathogenesis of Alzheimer disease, Parkinson disease, and other neurodegenerative disorders [10, 11]. The exchange between tissue and CSF facilitates the removal of this so-called metabolic waste [12]. Gymphatic clearance is thought to significantly impact the distribution of glucose, lipids, amino acids, growth factors, and neuromodulators in the brain [4, 9]. Given the high density of lipoproteins and lipid transporters associated with astrocytes, the glymphatic system also contributes to lipid transport and glucose uptake [10, 13].

In addition to clearance, the glymphatic system modulates intracranial pressure in cases of excess interstitial fluid in the brain [10, 14]. It is known that increased fluid pressure stimulates calcium flux through N-methyl-D-aspartate (NMDA) receptors in astrocytes, which plays a role in signal transmission [10, 15].

For modern neuroscience, it is crucial to investigate the morphology and function of the glymphatic system, as well as the factors that contribute to or interfere with its effective functioning. A healthy glymphatic system delays the accumulation of metabolic waste and specific proteins in the brain. However, glymphatic system dysfunction plays a key role in the early degeneration of brain parenchyma [16].

STRUCTURE OF THE GLYMPHATIC SYSTEM

Our knowledge about the glymphatic system has improved greatly since its discovery. However, a review of numerous publications on this topic revealed significant discrepancies in the terminology. There are two main theories of the CSF outflow. The paravascular theory describes the drainage of interstitial fluid through slit-like channels located between the walls of blood vessels and adjacent brain tissue, also known as Virchow—Robin spaces. The perivascular theory considers the CSF flow through channels formed by the middle layer of the arterial wall, the basement membranes of single smooth muscle cells of arterioles, and the basement membranes of endothelial cells of capillaries. The two terms are often used interchangeably in most foreign papers [15–22], which makes it difficult to clearly define and determine the relationship between these two mechanisms. However, it is clear that an unambiguous understanding of the basic mechanisms of the glymphatic system is required to develop new strategies to improve them.

This review describes two non-mutually exclusive theories of the CSF outflow from the brain parenchyma. This article considers drainage through the Virchow—Robin spaces as part of the paravascular theory, consistent with other authors' approach [6, 9]. Notably, some works [5] describe Virchow—Robin spaces in terms of the perivascular theory and report terminological discrepancies in the current scientific discourse.

Paravascular Theory

The paravascular theory describes the glymphatic system as a network of extravascular channels that circulate CSF and interstitial fluid within the brain parenchyma, as well as provide their inflow and outflow (Fig. 1) [15, 17–21, 23, 24].

According to this theory, fluid transport includes five steps [17]:

- CSF is produced by the choroid plexus, as well as by extrachoroidal sources, such as capillary inflow and metabolic fluid production.
- The CSF moves deeply into the brain through the paravascular spaces (Virchow—Robin spaces) under

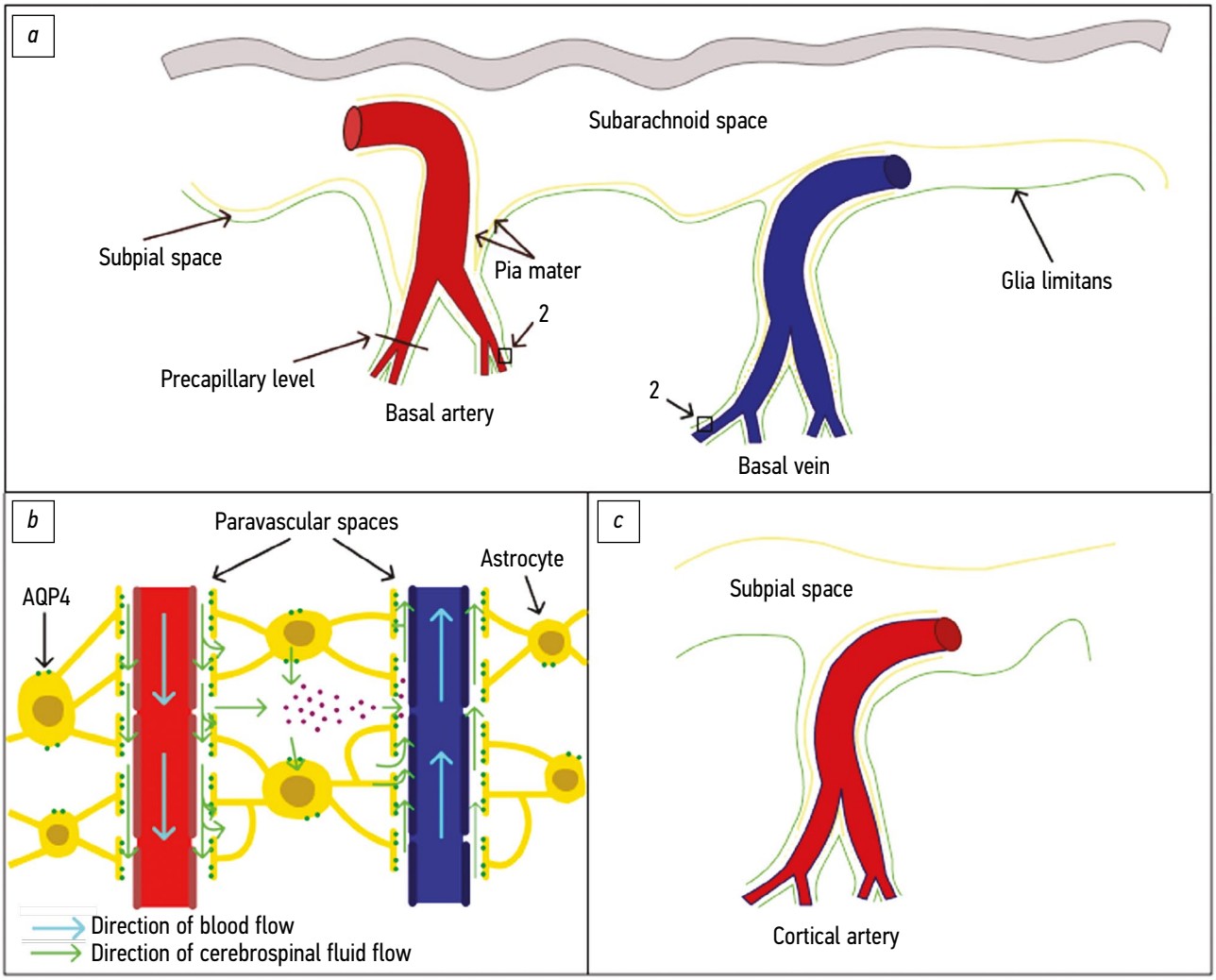

Fig. 1. Structural differences in the pial environment of basal ganglia arteries and cortical arteries: *a* — arteries of the basal ganglia are covered by two layers of the pia mater, whereas veins are covered only by the outer layer; region 2 indicates the area shown in greater detail in part *b*; AQP4 — aquaporin-4; *c* — cortical artery is covered by only one layer of the pia mater. Cortical arteries communicate with the subpial space and indirectly with the subarachnoid space. Original illustration by the authors, part b adapted with modifications from Peng S et al., 2023 [24].

the pulsation of the arterial wall. The paravascular spaces, which have an outer border formed by astrocyte endfeet that express aquaporin-4 (AQP4), are filled with fluid and surround pial arteries, precapillary arterioles that extend from the subarachnoid space deep into the brain parenchyma, and pial postcapillary venules and veins that extend from the parenchyma [18]. At the capillary level, the Virchow—Robin spaces are closed due to the fusion of the basement membranes of endothelial and glial cells [19]. The pia mater surrounding the arteries extends into the paravascular spaces, where it becomes fenestrated and ultimately disappears at the precapillary segment of the vessels [19]. There are some structural differences in the pia mater surrounding the basal ganglia arteries and cortical arteries. The vessels are covered by two layers of the pia mater (outer and inner) in the first case and by one layer in the second case. As a result, the cortical arteries communicate directly with the subpial space and indirectly with the subarachnoid space [25]. A similar structure is characteristic of the basal ganglia veins, which only have the outer layer of the pia mater [19].

- The CSF enters the brain parenchyma through AQP4 channels and disperses within the neuropil.
- The CSF mixes with the interstitial fluid.
- Before leaving the brain parenchyma, interstitial fluid accumulates in the paravenous space.

Aquaporin Channels

Recent data show that aquaporin channels (aquaporins) play a key role in the selective permeability of neuronal membranes to water and dissolved substances, as well as create an osmotic gradient. Therefore, aquaporins are involved in the circulation of the CSF and interstitial fluid through the paravascular spaces of the brain.

Three types of aquaporins have been found in the brain: AQP4 [23], AQP1 [26], and AQP9 [27]. AQP4 is a homologous tetramer consisting of monomers that act as independent water molecular channels on the cell membrane. The

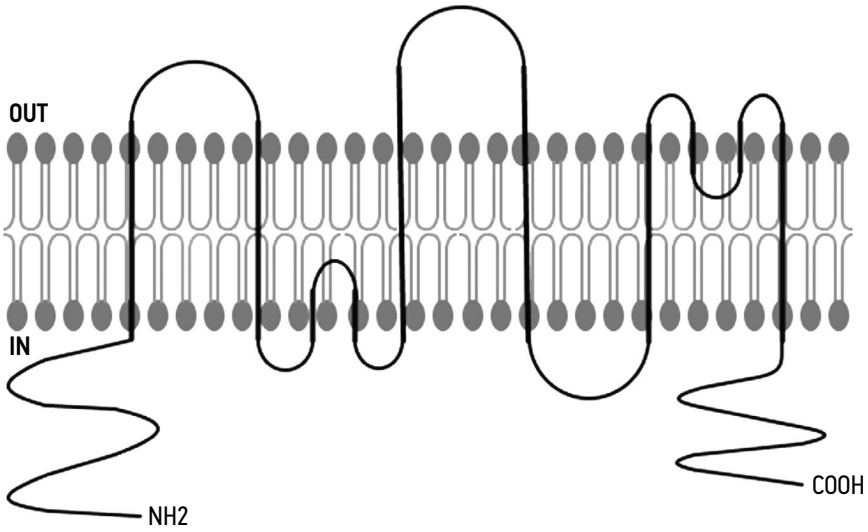

Fig. 2. Structure of the aquaporin-4 monomer: the protein spans the membrane six times, forming two intramembrane and three extramembrane loops. Adapted with modifications from Peng S et al., 2023 [24].

two subtypes of aquaporin-4, AQP4-M1 and AQP4-M23, are expressed at the highest levels in the brain tissue. The molecular weight of the monomer is approximately 30 kDa. Each monomer crosses the membrane six times, forming three extramembrane and two intramembrane rings (Fig. 2) [24].

AQP4 is predominantly located in cell membranes at the interface of the brain parenchyma and the CSF components. For example, it is found in astrocyte podocytes adjacent to microvascular endothelial cells, as well as on the basal side of ependymal cell membranes in ventricles and membranes of brain microvascular endothelial cells [24]. This distribution of AQP4 suggests that it may play a role in regulating the inflow and outflow of CSF in the CNS [24].

Perivascular Theory

The perivascular theory (Fig. 3) describes an alternative way for removing CSF from the brain. Carare et al. [6] injected dextran (3 kDa) and ovalbumin (49 kDa) into the gray matter of the putamen of mice. Five minutes after injection, the markers were detected in the intercellular substance, where they spread diffusely, as well as in the blood vessel walls. The markers were found with laminin in the basement membranes of capillaries and between the smooth muscle

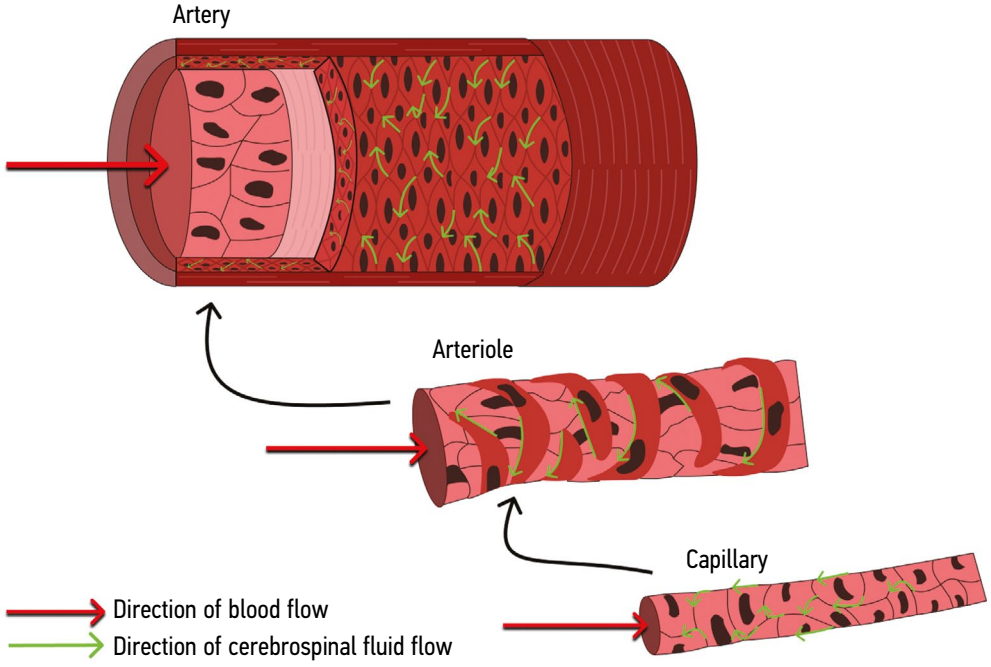

Fig. 3. Cerebrospinal fluid flow through perivascular spaces: the direction of cerebrospinal fluid flow is opposite to that of blood flow; cerebrospinal fluid flow moves along the basal membranes between endothelial cells of capillaries, single smooth muscle cells of arterioles, and between layers of smooth muscle cells in arteries. Original illustration by the authors.

cells of artery media [6, 7]. Furthermore, the injected substances were not found in the perivascular spaces of the veins [5]. Thirty minutes after injection, the markers were no longer present in the intercellular substance of the brain or the basement membranes of blood vessels, such as capillaries and arterioles. However, they remained in perivascular macrophages [6]. Twenty-four hours after injection, perivascular macrophages outlined the CSF outflow pathway near the intracerebral and pial arteries [6].

The CSF has been found to flow through perivascular spaces in the opposite direction of paravascular CSF flow and blood flow [5]. Injecting dextran and ovalbumin of different molecular weights into the brain parenchyma of mice showed that perivascular flow moves outward [6]. However, injecting dextrans with molecular weights of 3 kDa and 2000 kDa into the cisterna magna of a mouse's brain revealed that the CSF flows through the paravascular spaces in the opposite direction [3].

Mathematical modeling shows that counter-reflected waves, which arise after each pulse wave and propagate in the opposite direction, can drive the perivascular transfer of the CSF with substances dissolved in it [8]. However, *in vivo* experiments revealed an extremely low flow rate of the CSF through the perivascular spaces [28]. This is likely caused by their smaller size (100 nm) compared with the paravascular spaces (40 μm) and, consequently, by approximately 108 times lower volumetric flow rate of the CSF [29]. Therefore, the paravascular mechanism plays a more significant role in the functioning of the glymphatic system.

DIRECTION OF THE CEREBROSPINAL FLUID OUTFLOW FROM THE BRAIN

Scientific publications have described several pathways for the CSF outflow from the brain. At the end of the 19th century, studies were conducted on cadaver material stained using methylene blue dye (by Richardson technique). They showed that the CSF outflow may be directed into the venous sinuses through arachnoid granulations, as well as into the lymphatic vessels of the nasal submucosa [30].

Later studies [31] traced the CSF flow through the cribriform plate along perineural pathways. Studies on rodents in 2006 [32] showed that the perineural CSF outflow is possible due to the presence of labyrinthine canals between the olfactory filaments and the periosteum of the ethmoid bone. These canals result from the transition of the dura mater into the periosteum of the cribriform plate and the arachnoid mater into the perineurium [32]. A 2020 study found that only 2 out of 18 participants had a perineural pathway for CSF flow through the cribriform plate, suggesting that this mechanism is secondary [33]. Ringstad and Eide proposed that this difference may be caused by the fact that the human olfactory system is less developed than that of rodents. In addition, research has shown that both humans and animals have a perineural pathway for the CSF outflow through openings in the cranial base, including the hypoglossal canal and the jugular foramen [33].

The discovery of meningeal lymphatic vessels in 2015 led to a reassessment of ideas about the anatomical pathways for the CSF outflow from human brain tissue [1]. The meningeal lymphatic vessels are located between the wall of the superior sagittal sinus and the parasagittal dura mater that serves as a link between the subarachnoid space and the lymphatic vessels of the dura mater and an important pathway for the CSF outflow from the brain [33]. The CSF enters the parasagittal dura mater itself through the arachnoid granulations.

A 2023 study used intravenous gadolinium-based contrast agents (GBCAs) to visualize the perisinusoidal lymphatic vessels of the dura mater near the sigmoid and transverse sinuses. It should be noted that the expansion of meningeal lymphatic vessels along the sigmoid sinus occurred when GBCA elimination was delayed and outflow of substances from the interstitial space was impaired [34].

The deep cervical lymph nodes play a key role in regulating the immune response of the CSF circulating in the brain. Their connection to the subarachnoid space was first demonstrated in the 19th century by injecting methylene blue using the Richardson technique into the subarachnoid space [30]. In the 20th century, red blood cells were found in the deep cervical lymph nodes of a patient who died from a subarachnoid hemorrhage [35]. Another study found that patients who died from brain hemorrhage had significantly higher iron content in their deep cervical lymph nodes than patients without brain lesions [36].

A 2018 study used magnetic resonance imaging with the intrathecal contrast enhancement with gadobutrol as a CSF tracer to demonstrate glymphatic drainage of CSF from the brain to the deep cervical lymph nodes [37].

CHARACTERISTICS OF THE REGULATION OF THE GLYMPHATIC SYSTEM

Some studies have been conducted to determine the regulatory patterns of individual glymphatic system links. The velocity of CSF flow in the paravascular space has been shown to correlate with blood flow velocity. This indicates that the periodic increases and decreases in the CSF flow velocity are synchronized with phases of the cardiac cycle [20, 21]. Peaks in velocity are associated with cardiac output. In other words, the pulse wave that propagates along the arteries is the main driving force of the CSF inflow. In fact, the displacement of the arterial wall when a pulse wave passes corresponds to the pattern of CSF movement in terms of velocity and timing, suggesting that the CSF moves through paravascular spaces when the arterial wall stretches during pulse wave propagation [20, 21]. The correlation between the cardiac cycle and CSF movement in the paraarterial spaces is also confirmed by the fact that changes in the general hemodynamics resulting from pharmacological effects

impact CSF circulation. For example, in rats, administration of dobutamine, a beta1-adrenergic receptor agonist, has been shown to increase heart rate and cardiac output, as well as stimulate the CSF flow into the paravascular spaces [15, 21]. The use of angiotensin II causes hypertension by narrowing the arteries, but reduces the rate of CSF inflow [21]. Therefore, the effects of the pulse wave on CSF movement depend on the heart rate, blood pressure, pulse pressure, and fluctuations in intracranial pressure. The isolated effects of each factor on CSF movement through the paravascular spaces have not been thoroughly studied [20, 21]. Notably, the respiratory cycle also modulates the size of the lumen of the arterial paravascular space [15, 20, 21]. Depending on the respiratory rhythm, the centripetal flow of venous blood can increase the volume of veins and stimulate glymphatic outflow [38]. However, the cardiac cycle makes the most significant contribution to regulating CSF circulation in the glymphatic system [20].

GLYMPHATIC SYSTEM AND SLEEP

Sleep is known to play a key role in metabolite elimination [22]. The volume of the interstitial space increases by 60% during sleep. This increases the efficiency with which the interstitial fluid transitions into the CSF, as well as the elimination rate of beta-amyloid [39]. The effect of sleep on glymphatic clearance was first investigated in 2013 [39]. The work used *in vivo* two-photon imaging to compare the CSF flow into the cerebral cortex of awake, sleeping, and anesthetized mice [39]. The mice were injected with dextran, an indicator with a molecular weight of 3 kDa. Then, electrocorticography and electromyography were performed to monitor brain activity continuously. Dextran was administered during daylight via a cannula implanted in the cisterna magna of the brain because mice primarily sleep during the day. A strong influx of the fluorescent indicator was noted in the periarterial spaces, subpial areas, and brain parenchyma of sleeping and anesthetized mice with slow-wave sleep and delta waves. The mice were awakened by touching their tails. After awakening, there was a sharp decrease (by 95%) in the dextran influx into brain tissue, associated with a strong decrease in delta waves. A similar experiment was later conducted in the evening when mice are usually awake. This experiment showed a complete absence of the CSF entering the brain tissue. It should be noted that the CSF flow through the paraarterial spaces increased significantly under anesthesia [39]. The experimental results concluded that changes in glymphatic transport are associated with the state of consciousness, rather than with circadian rhythms [21, 39].

However, more recent studies have demonstrated that circadian rhythms also contribute to the regulation of glymphatic clearance [40], and differences in the function of the glymphatic system in rodents depend not only on state of arousal, but also on circadian rhythm. Even after 10 days of constant light exposure, the patterns of the CSF influx, clearance of substances, and AQP4 expression, are maintained, suggesting the circadian control of the glymphatic system. This control is maintained by regulating AQP4 polarization (the position of aquaporins in astrocyte membranes). There was no difference in CSF flow between day and night in AQP4 knockout (AQP4 KO) animals [40].

The differences in glymphatic system activity during sleep and wakefulness are related to hemodynamic characteristics. For example, during non-rapid eye movement (NREM) sleep, fluctuations in cerebral blood flow volume have a much greater amplitude than during wakefulness [21, 41].

Turner et al. [41] evaluated behavior and measured neural activity, blood volume, and arteriolar dilation in head-fixed mice while they were awake and during NREM and rapid eye movement (REM) sleep. The authors discovered that arteriolar dilation and blood volume fluctuations during NREM and REM sleep phases can be 2–5 times greater than in awake animals. This increases blood flow, allowing more CSF to enter the brain during sleep than during the awakening period. In animals with Parkinson disease and Alzheimer disease, long-term stimulation of slow-wave sleep improves glymphatic transport, increases paravascular AQP4 expression, and reduces the accumulation of alpha-synuclein and beta-amyloid. Epidemiologists report that the importance of proper sleep habits is also illustrated by the direct correlation between frequent benzodiazepine use, which suppresses slow-wave sleep, and the development of dementia [38].

Notably, the position of the head during sleep also affects the function of the glymphatic system. Dynamic contrast-enhanced magnetic resonance imaging revealed that contrast agent retention in the interstitium is lower, or clearance is better, in the lateral position than in the supine position in mice [42]. In addition, an increased flow of fluorescent CSF markers into the brain was observed in the lateral position [42]. Therefore, postural and gravitational factors are also involved in regulating glymphatic clearance [15].

Sleep disturbances are associated with various chronic diseases, such as Alzheimer disease, Parkinson disease, multiple sclerosis, and traumatic brain injury [21, 43–46]. The causal relationship between sleep disorders and neurodegenerative diseases is not fully understood. However, it has been noted that sleep problems often precede the onset of these diseases, and poor sleep is also considered a risk factor for Alzheimer disease.

GLYMPHATIC SYSTEM AND AGING

The duration and quality of sleep decreases with age. This negatively affects the efficiency of the glymphatic system [47]. Since poor sleep quality can inhibit glymphatic clearance, which is a potential risk factor for some neurodegenerative diseases, aging itself can be considered a key factor in the development of many neurological disorders [21].

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In 2014, data was obtained showing a decrease in the CSF inflow into the paravascular spaces and a decrease in the transpial CSF flow in middle-aged and older animals compared with young animals. This decrease is associated with a 40% reduction in the elimination rate of beta-amyloid from the brains of aging rodents [47].

Two main factors that cause age-related suppression of the glymphatic system have been identified: mislocalization of AQP4 in astrogliosis and decreased arterial wall elasticity with increased cerebral artery rigidity [47, 48]. These processes independently reduce fluid transport through astrocyte endfeet into the brain interstitium and decrease the efficiency of pumping the CSF from the para-arterial space by weakening arterial wall pulsations [47–49]. Altered expression of astroglial AQP4 has also been detected in aging human brains [50].

GLYMPHATIC SYSTEM AND THE EFFECTS OF ALCOHOL

Available research data shows that alcohol affects the glymphatic system in two ways. A study in mice showed that acute and chronic exposure to etanol at 1.5 g/kg (equivalent to the level of binge drinking) significantly suppressed the glymphatic system function [51]. In addition, chronic exposure to this level of ethanol increases the expression of the glial fibrillary acidic protein (GFAP) gene, thereby increasing the amount of GFAP protein in astrocyte membranes, leading to the abnormal distribution of AQP4 aquaporins [52].

Notably, acute exposure to a low dose of ethanol (0.5 g/kg) improved the glymphatic system function in mice, while chronic exposure to the same dose over one month reduced GFAP expression [51]. It was also found that low doses of alcohol significantly increase the movement of the fluorescent marker toward paravascular spaces and promote its clearance from brain tissue [53]. Two-photon linear scanning demonstrated that higher marker accumulation in paravascular spaces is associated with substantial vasodilation caused by elevated nitric oxide (NO) levels [53].

Therefore, consuming small amounts of alcohol can potentially benefit the glymphatic system, while long-term excessive consumption can suppress its function [54].

GLYMPHATIC SYSTEM OF THE EYE

It was previously believed that the eyes, like the brain, lacked typical lymphatic vessels. However, the production of beta-amyloid and tau protein by electrically active retinal neural tissues has prompted some experimental works to identify an intraocular glymphatic/lymphatic system that could remove these metabolites.

Wang et al. [55] injected HiLyte-594-tagged human beta-amyloid (hAβ) into the vitreous body of mice and visualized ultimate three-dimensional (3D) imaging to evaluate its location within the eyeball [55]. The study showed that hAβ is transported from the vitreous body through the paravenous space of the optic nerve, along axons, and out through the orbital and meningeal lymphatic vessels located in the outer layer of the dura mater that covers the optic nerve [55]. In addition, the absence of AQP4 was shown to decrease the clearance of hAβ along the optic nerve.

Therefore, the structural and functional characteristics of the glymphatic system in the eye are similar to those in the brain. AQP4 plays a key role in its function. It is expressed on astrocytes in the paravascular spaces of the optic nerve. The transport of CSF occurs through paravenous and paraarterial spaces. However, because of unique structural and functional organization of the eyes and brain, there are differences in glymphatic clearance between these two organs [56]. Fluid flow from the eye along the optic nerve is driven by translaminar pressure (the difference between intraocular and intracranial pressure). The plate between the retina and the optic nerve serves as a semipermeable barrier that allows certain substances, such as β-amyloid, to pass through [56, 57]. Various factors influence the clearance of beta-amyloid. An increase in intracranial pressure reduces clearance, while a decrease has the opposite effect [55]. In addition, light-induced pupillary constriction has been shown to positively impact ocular glymphatic clearance [55].

As mentioned above, the efficiency of anterograde glymphatic clearance (the removal of metabolites from the eye) depends on both the pupillary response and translaminar pressure. A decrease in intraocular pressure reduces anterograde glymphatic clearance [57]. In addition, an association was discovered between the optic disc edema and decreased intraocular pressure resulting from short sleep duration [57]. The highest intraocular and translaminar pressure is observed during the slow-wave phase, indicating the important role that proper sleep structure plays in the effective functioning of the glymphatic system.

Given the functional relationship between the glymphatic system and intraocular pressure regulation, impaired glymphatic clearance could significantly contribute to the development of glaucoma and age-related macular degeneration [55, 58, 59]. Research into the glymphatic system of the eye is important for developing treatment and prevention options for diseases associated with impaired function of this system.

CONCLUSION

Although the glymphatic system was discovered relatively recently, research over the past decade has demonstrated its crucial role in maintaining brain tissue homeostasis. First, the components of the glymphatic system provide clearance of metabolites. The accumulation of these metabolites leads to neurodegenerative diseases. Furthermore, the glymphatic system modulates intracranial pressure and transports lipids and glucose. Its mechanisms of functioning are not fully understood. The data provided in foreign and Russian

publications are sometimes controversial, and discrepancies in terminology is also observed [9, 60–62]. This review closely evaluates two theories of the CSF outflow. The paravascular theory describes the drainage of interstitial fluid through the Virchow—Robin spaces in the direction of blood flow. In contrast, the perivascular theory states that CSF flows in the opposite direction through channels formed by the middle layer of arteries, the basement membranes of single smooth muscle cells of arterioles, and the basement membranes of endothelial cells of capillaries. In addition, the CSF flow from the subarachnoid space into the meningeal lymphatic vessels through the parasagittal dura mater is described.

The article presents data on the regulation of the glymphatic system and its relationship with wakefulness, age, circadian rhythms, and alcohol consumption. New data on the morphology of the glymphatic system of the eyes is also reported. The normal functioning of this system is associated with reference values of intraocular and intracranial pressure.

Further research in this area will contribute to our basic understanding of the mechanisms of neurodegenerative diseases, as well as the potential to modulate glymphatic system functions. This research will also evaluate the state of the glymphatic system in organic disorders, traumatic brain injuries, and strokes in order to develop appropriate treatment options. Understanding how lifestyle, genetic status, and medication influence the functioning of the glymphatic system will help develop new preventive and diagnostic tools for neurosurgery, pathology, neurology, anesthesiology, resuscitation, and psychiatry.

ADDITIONAL INFORMATION

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Вклад авторов. Д.А. Аверин, Л.А. Клюева — перевод текста англоязычных статей; Л.А. Клюева, Д.А. Аверин — написание статьи; К.А. Васянина — окончательная редакция текста статьи форматирование в соответствии с правилами журнала. Все авторы одобрили рукопись (версию для публикации), а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части.

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