Rev Mex Neuroci ahora en CONACyT

Vol. 19, issue. 1 (january-february 2018)

Revista Mexicana de Neurociencia

Publicación oficial de la Academia Mexicana de Neurología A.C.

Revista Mexicana de Neurociencia; 19,1 (2018):102-113

Órgano Oficial de Difusión de la AMN

Academia Mexicana de Neurología, A.C.

www.revmexneuroci.com / ISSN 1665-5044

Review

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A new pathway for cerebral drainage: the glymphatic system. Historical and conceptual review

Una nueva vía de drenaje cerebral: el sistema glinfático. Revisión histórica y conceptual

Abstract

For more than 100 years the works carried out by Santiago Ramón y Cajal supported the nervous system studies to focus on a single cell, the neuron, resulting in a "neurocentric" perspective, averting the sight from other important cellular components of nervous tissue such as neuroglia. At the same time, significant advances were made in the field of immunology, consolidating concepts such as blood-brain barrier, generating the idea of the nervous system as an immunologically privileged site, thus relegating to the background the research between the interactions in these systems.

Nowadays the scientific and technological advance has enabled to show that the neuron, although an essential component both morphologically and functionally, is not the only actor in the functioning nervous system. Today the glymphatic system, a brain drainage system that relies on the adequate neuroglia functioning, particularly the astrocytes, must be paid attention if we want to know about the integral view of how the nervous system works and how it interacts with the immune system.

This paper aims to show the current state of the art regarding knowledge of the glymphatic system, and how this knowledge is changing paradigms of study and is also giving birth to several questions previously hidden by the "neurocentric" approach.

Keywords

Glymphatic system, blood-brain barrier, neurovascular unit, immune privilege.

Resumen

Por más de 100 años los trabajos realizados por Santiago Ramón y Cajal hicieron que los estudios del sistema nervioso se enfocaran en una sola célula, la neurona, generándose una visión de tipo "neurocéntrica" y provocando que se desviara la mirada de otros componentes celulares importantes del tejido nervioso como la neuroglia. Al mismo tiempo, avances importantes en el campo de la inmunología, terminaban por consolidar conceptos como el de barrera hematoencefálica que llevaron a considerar al sistema nervioso como un sitio "inmunológicamente privilegiado", por lo que las investigaciones sobre la interacción entre estos sistemas quedaron en un plano secundario.

Actualmente el avance científico-tecnológico ha permitido mostrar que, si bien la neurona continúa siendo un componente importante, tanto morfológico como funcional, no es la única célula de la que depende el correcto funcionamiento del sistema nervioso. Recientemente se ha descubierto el sistema glinfático, una vía de drenaje cerebral que depende del adecuado funcionamiento de la neuroglia y en especial de los astrocitos. Este sistema de drenaje amerita prestarle gran atención si se quiere conocer de manera integral la forma en cómo funciona el sistema nervioso y su interacción con el sistema inmune.

Este trabajo pretende mostrar el actual estado del arte en lo que se refiere al conocimiento del sistema glinfático y cómo, por un lado, está cambiando los paradigmas de estudio, y por otro está dando a luz a varios cuestionamientos que estaban obscuros a raíz de este enfoque "neurocentrista".

Palabras clave

Sistema glinfático, barrera hematoencefálica, unidad neurovascular, privilegio inmune.

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Introduction

In recent decades there has been an increasing interest in the study of neuroglia, previously believed to be simple support cells for neurons mainly due to the "neurocentric" approach generated from the works of Santiago Ramón y Cajal. Nowadays, thanks to advances in technology and the development of a more integrative vision, we know that their functions are much more complex and have descriptions of this relatively "new" cerebral drainage system.

Broadly speaking, neuroglia fulfill several important functions in the central nervous system (CNS). For example, astrocytes provide metabolic support to neurons promoting glucose uptake and are responsible for the recapture of neurotransmitters and the buffering of K+, among other functions. On the other hand, microglia, the resident macrophage of the CNS, is responsible during the development of "synaptic pruning" and of cellular debris removal after damage during pathological states. Finally, oligodendrocytes, responsible for the production of myelin, contribute to the facilitation of signaling between neurons.

This article reviews, from a historical point of view, the most relevant investigations that led to the generation of this neurocentric perspective and the concepts that promoted the perception that the CNS was an immunologically privileged site. It also briefly describes the main structures in which the operation of the glymphatic system was found.

Historical perspective

Absence of lymphatic circulation

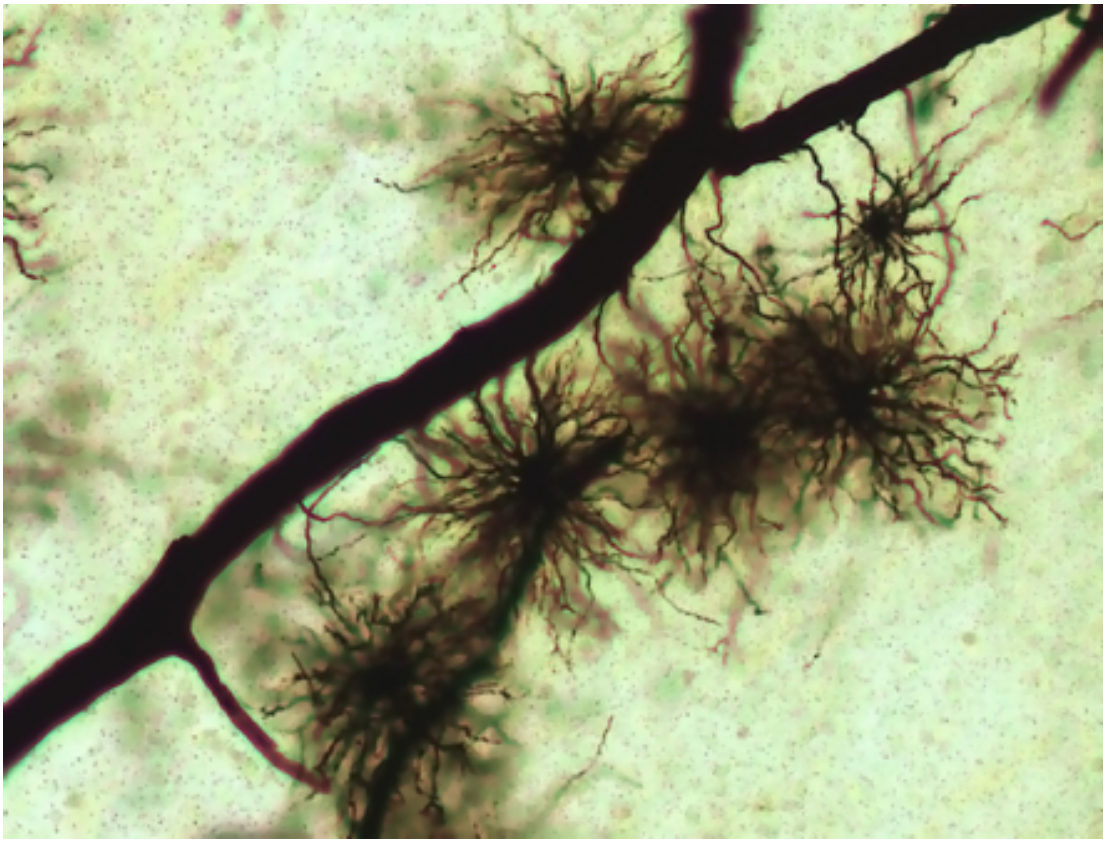
During the 18th century, the Italian physician and anatomist Giovanni Paolo Mascagni (1755-1815) published in his work "Vasorum lymphaticorum corporis humani historia et iconographia" the first great systematic description of the lymphatic system that included the existence of lymphatic vessels in the meninges and on the surface of the brain.[1-3] Although after this work there were attempts to corroborate his observations, it wasn't until the 19th century that the lack of lymphatic circulation in the brain was concluded.[4]

Description of astrocytes and the concept of the blood-brain barrier (BBB)

In 1856, the German scientist Rudolf Virchow described and introduced for the first time the term "Nervenkitt" (neuroglia), conceived as a type of connective tissue that imbibed the elements of the nervous system.[5,6] In 1873, the Italian doctor Camilo Golgi, through his technique of staining with silver nitrate described that certain glial cells projected numerous, long, fine and branch-like extensions to the vessel walls, including capillaries and medium-sized vessels. Based on these findings, he had the theory that glial cells provide the bridge between the parenchyma and the vasculature.[7] Twenty years later, the Hungarian Michael von Lenhossék was the first to coin the term "astrocytes," considering them as support cells or spongiocytes, and that the most common form in vertebrates was that of spider cells or astrocytes, small elements that form the support system of the spinal cord.[8]

Around the same time, the Spanish physician Santiago Ramón y Cajal published his famous work "Texture of the Nervous System of Man and the Vertebrates" (1899-1904) and using the staining techniques developed by Golgi (Figure 1) described in detail almost all the parts of the CNS. When pondering the function of the glial cells, however, he left the question about the functioning of the whole neuroglia unanswered, considering that the problem needed more work to be solved. Cajal cites the previous works of Andriezen, who published in 1893 that "blood vessels of any caliber show neuroglial filaments arranged in irregular bundles forming either complete or incomplete sheathings (neurogliar adventitia)" and at the same time he classified them into fibrous glia (Langstrahler - “long projectors” found in white matter) and protoplasmic glia (Kurzstrahler - “short projectors” found in gray matter).[9-11]

Figure 1. Astrocytes with their astrocytic endfeet projected towards the vessels which are part of the blood-brain barrier. Golgi-Kopsch silver impregnation technique in rat cortex 10x. Photomicrograph courtesy of the Metallic Impregnation Laboratory. Department of Cell and Tissue Biology, School of Medicine, UNAM.



Some years before, in 1885, the German scientist Paul Ehrlich reported incidentally that intraperitoneal injections of various dyes in adult animals stained practically all organs of the animals except the brain and the spinal cord.[12] Subsequently, his student, Edwin Goldmann, complemented these experiments by injecting trypan blue directly into the intraventricular system and observed that the brain of the animal was colored, however, the body remained intact. In subsequent experiments now injecting intravenously, he found that the CNS did not stain,[13] except for the presence of the dye in the choroid plexus and the pineal gland.[14] These experiments showed that the lack of staining was not attributable to a lack of affinity of the dye for the brain tissue, on the contrary, they demonstrated the clear existence of a compartmentalization of the brain against the rest of the organism, proposing the existence of a "physiological limiting membrane."[15] It was also hypothesized that the vehicle transporting substances in the brain was the cerebrospinal fluid (CSF), which had access to nerve tissue through the choroidal plexus.[12,16]

In 1900, Max Lewandowsky described in his work "Zur Lehre der Zerebrospinalflüssigkeit" that the intravenous injection of cholic acid or sodium ferrocyanide had no pharmacological effects on the CNS, while neurological symptoms occurred after the intraventricular application of the same substances[12,16] concluding that: "the cerebral capillaries had very specific restrictive properties with respect to some compounds."[17,18] Recent historical reviews suggest that the first time the term "barrier" is properly used is in the work of Stern and Gautier in 1918: "The barrier which

opposes the movement into the CSF of substances in the blood shows notable differences in different animal species."[18]

Until then, several studies and reviews proposed that, due to the interaction of astrocytes with brain capillaries, the BBB as such should be found at the astrocytic endfeet.[19,20] However, it wasn't until 1967 that Reese and Karnovsky, using electron microscopy together with the injection of horseradish peroxidase, established where the BBB was, finding that the peroxidase penetrated to the upper interendothelial spaces. They then concluded that it's the presence of tight junctions in the endothelium and not just the astrocytic endfeet or the basement membrane that make up the BBB.[21] In addition, endothelial cells have few pinocytic vesicles compared to the endothelium of noncerebral vessels, so they affirmed that the presence of metabolic "pumps" are necessary to maintain a blood-brain concentration gradient.[12,15]

Concept of immune privilege

With the precedent of the prolonged or indefinite survival of skin grafts in the brain of non-immunized animals, the team of British scientist Peter Brian Medawar in 1948 approached this claim experimentally. Previously immunizing a group of rabbits, he performed skin homografts in three locations: subcutaneous tissue, anterior chamber of the eye, and the brain, finding that in the last two structures, tissue destruction of the homograft by the immune response was delayed until it was transplanted again to skin and revascularized. It is then that he concludes that "skin homografts transplanted to the brain undergo, but cannot provoke, an immune response."[15,22] Finally, it was Barker and Billingham in 1967 who suggested the link between the existence of the BBB and the concept of immune privilege, analyzing that the existence of the BBB, of the tight junctions, and the scarcity of transport vesicles in the cerebral capillaries could restrict diapedesis and, therefore, lymphocyte infiltration and the development of an inflammatory response in the brain, as this would impair the integrity of functional connections between neurons.[15,23]

Blood-brain barrier

Several functions have been proposed for the BBB. One of the main ones is the maintenance of a stable medium since the blood plasma concentrations of various substances can vary depending on several factors such as diet, metabolism, disease, age, or exercise.[24]

The BBB had been considered primarily as an anatomical barrier; however, this concept has been redefined in recent times as a physiological barrier or active interface between the capillaries of the CNS and the extracellular fluid of neurons and glia (blood-brain interface).[25,26] This physiological barrier is mainly composed of the capillary endothelium with tight junctions, the pericytes, the shared basement membrane, a perivascular space (Virchow-Robin), the basement membrane of the astrocytic endfeet, and the limiting glia. (Figure 2) All these components fulfill the function of restricting the transport of potentially harmful substances and cellular elements from the blood to the brain, through a quadruple defense line:[27]

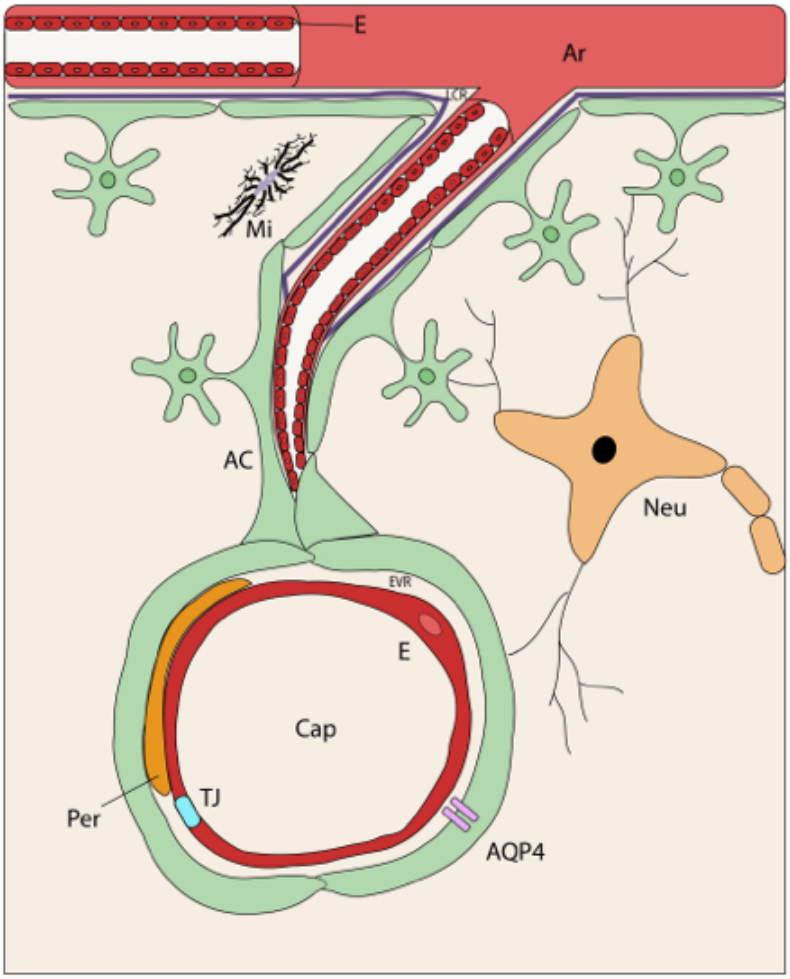
a) A strong paracellular barrier that limits the free movement of solutes and cellular elements between adjacent cells and that is mainly constituted by tight junctions that seal the cleft between endothelial cells.

b) A transcellular barrier, characterized by low levels of endocytosis and transcytosis of brain endothelial cells.

c) An enzymatic barrier, provided by a complex set of enzymes including acetylcholinesterase, alkaline phosphatase, y-glutamyl transpeptidase, monoamine oxidase, and other drug metabolizing enzymes.

d) Efflux transporters, mainly expressed on the apical membrane of endothelial cells where they excrete different xenobiotics from the endothelium into the bloodstream. The most important is the P-glycoprotein (P-gp), which contributes to the

Figure 2. Structural conformation of the blood-brain barrier. E: endothelium; AR: artery; TJ: tight junctions; Per: pericyte; VRPS: Virchow-Robin perivascular space; AC: astrocyte; Neu: neuron; Mi: microglia; AQP4: Aquaporin-4; Cap: capillaries.



transport of several potentially harmful substances such as amyloid beta protein and also different drugs such as antiepileptics, psychotropics, antivirals, and chemotherapeutics.

Currently, a large amount of work suggests that brain functions are largely determined by a complex interaction of different cell types including neurons, glial cells, brain endothelial cells, and pericytes, which led to the development of the neurovascular unit concept.[28-31]

Glymphatic system

The glymphatic system (term coined for the first time by Nedergaard M *et al.* in 2013), acquires great importance since it is presented as a complex set of structures whose main function is to serve as drainage and thereby contribute to the homeostasis of the brain and its immunological surveillance. This changed the previously-held concept of the CNS as an immunologically privileged site, since it considered that the BBB inhibited the immune system's incoming arm by blocking the migration of cells such as lymphocytes to the CNS, while the absence of a

conventional lymphatic drainage blocked the immune system's outgoing arm by not draining CNS antigens to the peripheral lymphatic tissues.[32]

On this last point, the absence of a lymphatic system contrasted radically with what was known about the lymphatic circulation in peripheral organs, since it contributes to the elimination of extracellular proteins and excess interstitial fluid (ISF), a fundamental role for the homeostasis of tissues.[33] On the other hand, it had also been observed that the density of lymphatic vessels correlated with the local tissue metabolism rate[34] counterposing what happened in the CNS, which can require up to 15-25% of cardiac output and reach an average glucose use ten times higher than the total body average.[35,36]

It is important to mention that, initially, it had been proposed that molecules that had specific transporters in the barrier were quickly cleared from the brain,[37] while other compounds that were found in the interstitium could be drained through the CSF, which ended up being eliminated by the bloodstream in the arachnoid villi[38] or finally drained to peripheral lymphatic vessels through the extensions of the meninges in cranial nerves.[39,40] However, this did not entirely clarify how much of the brain tissue in deep structures—such as the basal nuclei or the deeper layers of the cortex—drained into the CSF compartments, mainly due to the large distance between them, so simple diffusion could not explain how large molecules such as peptides, proteins, and other solutes dissolved in the brain ISF could be eliminated.

Recent studies by Iliff and Nedergaard define for the first time an anatomical pathway in the brain that facilitates the exchange and allows the elimination of solutes between CSF and ISF. This pathway consists of three main elements: I) a para-arterial influx route for CSF; II) a para-venous ISF clearance route; III) and a transparenchymal pathway dependent on astrocytic water transport through aquaporin-4 (AQP4) channels, also known as convective flow (collective movement of water and solutes either as a result of diffusion and/or advection).(Figure 3) The latter refers to the mass movement of fluid driven by any combination of pressure gradients such as hydrostatic, gravitational, of cardiovascular origin, osmotic, oncotic, and/or temperature.[33,41,42]

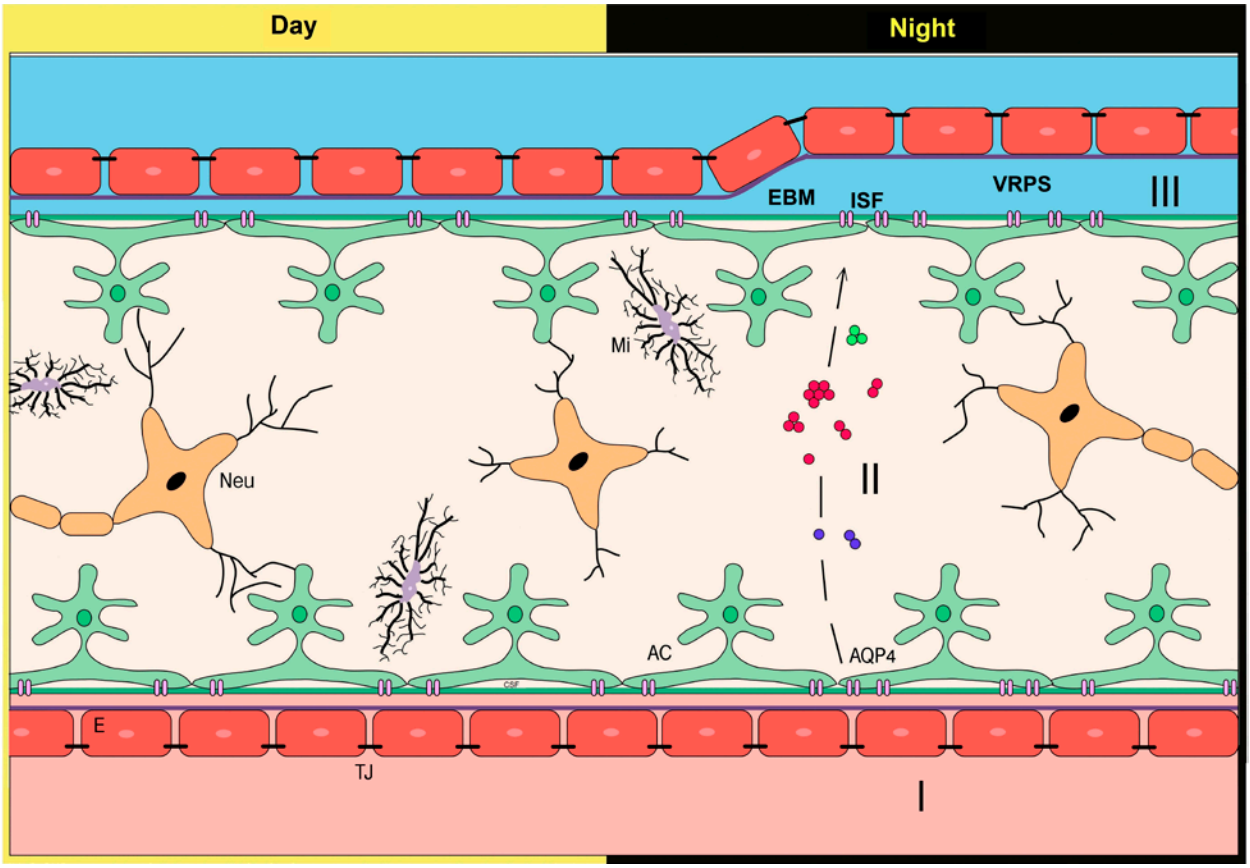
It is through the Virchow-Robin perivascular space that the CSF comes into contact with the ISF due to its continuity with the subarachnoid space, mainly due to a unique feature of the CNS vasculature in which all the arterioles, capillaries, and venules within of the cerebral parenchyma are surrounded by astrocytic vascular feet. These create the outer wall of the perivascular space resembling a donut-shaped tunnel surrounding the vasculature; when penetrating arterioles narrow deeper down in the brain parenchyma, the Virchow-Robin spaces containing CSF become continuous with the basal lamina. Due to the loose structure of the extracellular matrix, the basal lamina provides minimal resistance to the flow of CSF, which will flow from the Virchow-Robin space along the periarterial space, enter the basal lamina surrounding the capillaries, and come out through the perivenous space.[42]

This transport is a process that requires energy, so multiple mechanisms come into play. The two principal ones can be highlighted. First, the constant production of CSF creates a pressure that dictates the direction of fluid flow through the ventricular system into the subarachnoid space. Second, the pulse generated by smooth muscle cells creates waves along the entire length of the pial artery and penetrating arteries that are immersed in the brain from the cortical surface, pushing CSF specifically into the arterial perivascular space and not into the venous space.[42]

Both processes make it clear that this system establishes a flow in the brain capable of "washing" it of several substances, besides contributing to the distribution of important components such as ions, glucose, and lipids, aiding good cerebral functioning.

Last but not least, we must highlight the role of AQP4 in this system. It has been observed that the limiting glia has a water permeability four times

Figure 3. Main components of the glymphatic system. I) para-arterial influx route for CSF. II) transparenchymal pathway dependent on astrocytic transport of AQP4. III) para-venous ISF clearance route.
E: endothelium; EBM: endothelial basement membrane; TJ: tight junctions; VRPS: Virchow-Robin perivascular space; AC: astrocyte; Neu: neuron; Mi: microglia; CSF: cerebrospinal fluid; AQP4: Aquaporin-4; ISF: interstitial fluid.



greater than the BBB endothelium, mainly due to the presence of this protein that is expressed in about 40% of its surface.[43,44] Also, other works have observed that the deletion of AQP4 decreases the movement of solutes to the glymphatic system by more than 60%.[45] Thus, this system provides a novel explanation for the paradoxical localization of AQP4, which is only expressed on the astrocytic feet adjacent to the vessel wall, while at the endothelium it is completely devoid of aquaporins.[41]

Variation in the activity of the glymphatic system

A fundamental condition for the functioning of the glymphatic system is that its activity depends on the time of day, since it has been shown that during sleep the activity of this system drastically improves, while during wakefulness it is suppressed. The difference between sleep and wakefulness in the glymphatic flow was correlated with the volumetric fraction of the interstitial space (IS), which was 13-15% in the awake state and expanded to 22-24% in mice both sleeping and anesthetized, which indicates that the dream state leads to convective flows of fluids and, therefore, to the elimination of metabolites. This suggests that a main function of sleep would be to increase the activity of the glymphatic system, promoting the brain to clear neurotoxic waste products produced during the waking state, such as beta-amyloid.[45-47]

Future study of the glymphatic system

Recent studies show that during pathological

processes such as ischemia or post-traumatic brain injury (TBI) physiopathological cascades are unleashed that involve the increase of several substances which could be used as biomarkers of damage or even neuroprotection; however, the glymphatic system in its drainage function could be clearing these substances, which prevents their correct measurement. However, if we thought about applying a blocker to this system, these biomarkers could be maintained in the brain to be detected and measured objectively.[42]

The above could have great clinical relevance since it would allow establishing better therapeutic processes. For example, at least four mechanisms have been recently described by which the glymphatic system can be blocked including the use of acetazolamide to inhibit the production of CSF, puncture of the cisterna magna, genetic deletion of AQP4,[48] and a much more practical process, sleep deprivation. Although it could be thought at first that this would cause the inhibition of the system, our group has reported two important aspects in a model of TBI in rats. First, the total deprivation of sleep for short periods (of 24 hrs) in rats subjected to TBI promotes a better recovery.[49] One possible explanation is that inhibiting the glymphatic system allows the retention of several substances, including some that produce neuroprotective effects such as ©-aminobutyric acid (GABA), a neurotransmitter that would oppose the excitotoxic effect of glutamate, or even some anti-inflammatory cytokines or growth factors, essential for tissue recovery.

The second important aspect that our group documented is that the time of day in which the trauma occurs is fundamental for the recovery (or lack thereof) of the individual, since we have found a greater recovery if the TBI occurs during the hours of darkness compared to the hours of light.[50] The explanation of this finding based on the functioning of the glymphatic system is evident, since as previously mentioned, the system is active during the night, therefore it contributes to the washing of products such as glutamate produced in excess after a TBI. Glutamate causes damage by excitotoxicity, so if this neurotransmitter is drained, it would lessen the damage. However, for both cases, where sleep deprivation happens post-TBI as well as due to the time of day in which trauma happens, the hypotheses of the possible beneficial role of the glymphatic system still needs to be corroborated by experiments aimed at direct observation in this pathological state.

The knowledge of its functioning could contribute to improve the manipulation of CSF flow appropriately in order to promote either the retention of drugs or the washing of harmful substances in the brain, which could have implications in various pathological processes such as cancer, neurodegenerative diseases such as Alzheimer's or Parkinson's, cerebrovascular diseases, TBI, etc.[51]

It would also allow us control of the cerebral metabolism by contributing to the distribution of ions, glucose, and lipids throughout the brain.[52,53]

Conclusion

The neurocentric approach established by Santiago Ramón y Cajal led to great advances in the understanding of the neuron, but neglected to research other CNS components such as neuroglia. Although the existence of neuroglia had been glimpsed at the same time as the neuron, looking into its functions was neglected for a long time.

A little more than a century ago, when the foundations for the development of modern neurosciences were consolidated, the knowledge of structures like the BBB, the meninges, and the neuroglia achieved such progress that it is possible for us to conceive today the concept of this glymphatic system.
We must emphasize that the knowledge of this system was due largely to the technological breakthrough in the 1960s. Thanks to electron microscopy, Reese and Karnofsky could observe and describe the structure of the BBB.

On the other hand, the concept of "immune privilege" was preserved for years. The work of Medawar during the 40s maintained the view that the CNS could not mount an immune response similar to the one presented in peripheral tissue such as the skin.

In the case of neuroglia, it's the works of Virchow from which the concept is developed. His works advance the knowledge of the multiple functions that are today recognized in that tissue.
Currently, the discovery of the glymphatic system explains how the brain controls the flow of CSF and thereby clears out several substances such as excess neurotransmitters or antigens, while at the same time establishes an adequate distribution of lipids, ions, glucose, and amino acids. Finally, we can highlight the participation of this system in various diseases such as Alzheimer's, Parkinson's, multiple sclerosis, cancer, and multiple neurological diseases—in short, the possibilities are enormous.

Acknowledgments

We are grateful for the help of Dr. Marcela Ramírez Escoto, who provided the plates with silver impregnations from which the photograph was taken for this article.

This research is carried out thanks to the Program UNAM-DGAPA-PAPIIT IN223417.

Conflicts of interest

The authors state that there are no relevant conflicts of interest in this study.

Funding sources

There was no particular funding source for this scientific report.

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Revista Mexicana de Neurociencia, 2017; 18(6): 1-19
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