What Do We Understand about the Brain Barrier in both Health and Sickness, and What We Do Not?

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Editorial

The human brain, despite its relatively small size, comprises approximately 2% of the total body weight. It is notable that the brain consumes nearly one-fifth of the body's oxygen and calorie supply, indicating its high energy requirements [1]. To meet this demand, the brain possesses a rich network of blood vessels that play a crucial role in delivering oxygen and nutrients. These blood vessels exhibit distinct characteristics known as the Blood-Brain Barrier (BBB), which regulates the exchange of molecules, such as ions and proteins, between the brain and peripheral tissues.

The BBB acts as a barrier separating the Central Nervous System (CNS) from the surrounding peripheral system. Over a century ago, researchers like Paul Ehrlich and Edwin Goldman discovered that when water-soluble dyes were injected into the bloodstream, they did not stain the brain [2,3]. Similarly, Max Lewandowsky observed that Prussian blue did not pass from the blood to the brain. It was Lewandowsky who coined the term BBB (Bluthirnschranke). These early observations led to the concept of a diffusion barrier that restricts the free movement of substances from the blood into the brain parenchyma, highlighting the distinct separation between the circulation and the brain. It is widely acknowledged that the Blood-Brain barrier (BBB) consists of three primary cellular components: endothelial cells, astrocyte end-feet, and pericytes. Endothelial cells line the walls of the capillaries and form tight junctions that selectively prevent the entry of most substances from the bloodstream into the brain. Astrocyte end-feet surround the vessel walls and play a crucial role in establishing and maintaining the integrity of the tight junction barrier. Pericytes, on the other hand, are contractile cells that significantly influence the regulation of capillary blood flow and the permeability of the BBB. However, their contractile nature can have detrimental effects in conditions like ischemic injury or stroke.

Apart from the BBB, there are other barriers that are vital for maintaining brain homeostasis. These include the blood-spinal cord barrier, the arachnoid blood-cerebrospinal fluid barrier, the hypothalamic blood-cerebrospinal barrier, and the choroid plexus blood-cerebrospinal fluid barrier. In this special issue, Dr. Verkhratsky and Dr. Pivoriunas provide an overview of the structure and function of these different barriers [4].

In addition to serving as a diffusion barrier between the circulation and the brain, the BBB also plays a role in the removal of metabolic waste. Dr. Wang and her colleagues delve into the molecular mechanisms that mediate the clearance function of the BBB. They specifically focus on astrocytic Aquaporin-4 and its physiological and pathological roles in various central nervous system disorders by affecting the clearance ability of the glymphatic system. The Blood-Brain Barrier (BBB) serves as a protective mechanism, both anatomically and physiologically, safeguarding brain cells by shielding neurons from toxins present in the bloodstream. It functions in conjunction with neurons, microglia, and the surrounding cellular components to form a Neurovascular Unit (NVU). The BBB plays a vital role in supplying oxygen and nutrients to meet the energy demands of neighboring neurons. In recent years, accumulating evidence has highlighted a reciprocal relationship between the vascular system and neurons, microglia, and oligodendrocytes [5].

Precise regulation of neurovascular coupling ensures that regional blood flow is increased promptly in response to local neural activation, providing a rapid supply of nutrients and oxygen while eliminating metabolic waste. An intriguing yet partially unexplored question pertains to whether changes in neuronal activity can influence BBB permeability and function. Additionally, in addition to neuronal-BBB crosstalk, NVU cells collaborate closely with oligodendrocytes.

Oligodendrocytes play a crucial role in producing myelin, a fatty substance that acts as insulation around neurons' axons, enabling faster neuronal transmission. Beyond their role in myelination, oligodendrocytes contribute to BBB maintenance by regulating the expression of proteins that control the barrier's permeability. Dysfunction in oligodendrocytes can disrupt the BBB, compromising brain function, as observed in neurological conditions like multiple sclerosis and cerebral hypoxia.

In this issue, Dr. Ji and his colleagues delve into the significance of oligodendrocytes in preserving axonal integrity within the central nervous system, as well as the susceptibility of oligodendrocytes to ischemic injury. They provide an overview of potential therapeutic strategies that target oligodendrocytes and their receptors to mitigate ischemic injury and facilitate functional recovery following a stroke. Microglia, another important cellular component of the neurovascular unit (NVU), has gained significant attention in recent years. Compelling evidence indicates that inflammation plays a critical role in the pathology of various neurological diseases, including stroke, amyotrophic lateral sclerosis, and Alzheimer's disease. Inflammation can trigger the activation and remodeling of NVU components, particularly microglia, which are the immune cells resident in the brain. As the brain ages, it undergoes a series of structural and functional changes. A transcriptomic study has revealed that microglia is among the first cells to undergo age-related alteration, which may subsequently affect their roles in maintaining the physiological processes of the NVU [6].

A specific subset of microglia, known as vessel-associated microglia (VAM), has been identified as crucial in preserving the integrity of the Blood-Brain Barrier (BBB) under normal physiological conditions. However, during sustained inflammation associated with certain neurological diseases, VAM can engage in phagocytosis, targeting and engulfing components of the NVU.

The blood-brain barrier (BBB) can become more permeable to solutes and may experience infiltration by immune cells from the periphery. This can lead to damage to the tight junctions within the BBB, potentially exacerbating the progression of various diseases. Consequently, Vessel-

Associated Microglia (VAM) has emerged as a promising therapeutic target, offering new insights into the treatment of central nervous system diseases. In this issue, Dr. Gao and her colleagues provide a comprehensive overview of the roles played by VAM and Perivascular Macrophages (PVM) in regulating vasculature development and pathological progression across different diseases. Their work highlights the potential of targeting VAM as a therapeutic strategy for a wide range of brain diseases.

Given that the Neurovascular Unit (NVU) functions as a cohesive entity, it is crucial to develop novel approaches for labeling and targeting its components in vivo and in animal models. In recent years, several tools and techniques have been developed to label and target the cellular elements of the NVU, enabling the study of its functions in live organisms. These include optogenetic methods and in vivo calcium imaging, which allow for the assessment of NVU cell activity, such as pericytes, in response to neural activity. The use of genetically encoded calcium sensors, such as GCaMP6, in conjunction with pericyte-specific Cre mice has enabled the in vivo imaging of NVU components, specifically pericytes [7]. These advancements provide valuable avenues for investigating the dynamics and functionality of the NVU in living organisms. To image calcium transients and pericyte contractility with high spatiotemporal resolution, the NG2-Cre:GCaMP mice were employed. These mice offspring were utilized for visualizing cellular activity through calcium imaging. Moreover, optogenetics offers a means to manipulate the activity of neurovascular unit (NVU) elements. By exerting fast and precise control over pericytes, researchers can investigate their contractile function in regulating neurovascular coupling and cerebral blood flow modulation *in vivo* [7]. In this special issue, Dr. Xu and his colleagues provide a comprehensive review of various approaches for imaging and targeting NVU cellular elements in vivo, including widely used fluorescent dyes, genetic mouse models, and adeno-associated virus vectors.

In addition to rodent models, *Drosophila Melanogaster* (fruit flies) has been employed as an animal model to study NVU functions in brain development and diseases. *Drosophila* offers several advantages as a model organism: it has a relatively short lifespan, a readily accessible genetic mutation library, and the ability to mimic human diseases, such as Alzheimer's disease, epilepsy, and addiction, through genetic manipulation [8]. These characteristics make *Drosophila Melanogaster* a valuable model for unraveling the mechanisms underlying neurovascular disorders. In this special issue, Dr. Klambt and his colleagues present a literature review on studies utilizing *Drosophila* as a model to investigate the regulation of the Blood-Brain Barrier (BBB) during infection and inflammation, drug clearance, sleep, and neurodegenerative diseases.

The significance of the Neurovascular Unit (NVU) in maintaining Central Nervous System (CNS) homeostasis in both healthy and diseased states is increasingly recognized. It is crucial to enhance awareness of the NVU's importance and its role in various neurological disorders. By comprehending the mechanisms underlying the interplay between NVU components, we can identify potential therapeutic targets for the treatment of these disorders. Although there is still much progress to be made, the reviews and research articles featured in this issue have yielded exciting advancements. These findings inspire optimism and hold promise in advancing our understanding of the NVU and ultimately paving the way for more effective treatments for neurovascular disorders.

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