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Controversies in Multiple Sclerosis

Studying the blood–brain barrier will provide new insights into neurodegeneration – Yes

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Neurological disorders are the third leading cause of mortality, morbidity, and disability throughout the world and impose a significant burden on society and healthcare budgets in Western European countries. Current medication regimes of neurological disorders have disappointing results and may lead to severe side effects. Therefore, the need to develop new ways to treat or even cure and/or prevent these neurological disorders is high.

Interestingly, loss of proper brain vascular function and inflammation thereof is a common denominator of numerous neurological disorders, such as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Alzheimer's disease, and other forms of dementia, but is also ongoing in aging and memory loss, as observed in the growing elderly population. Vascular dysfunction in the brain is nowadays even proposed as a predisposition factor for a number of neurological disorders, albeit to a different extent.

Together this illustrates that identification of the pathways that counteract neurovascular failure may provide new and selective means to fight neurological diseases. However, in-depth knowledge of the underlying mechanisms of impaired neurovascular function and how this contributes to neurological disorders is lacking.

Within this issue of the controversy series of *MS Journal*, we here position the brain endothelial cells as a target organ of therapeutic importance to modify or prevent the development of neurological disorders, including MS, based on its essential role in proper functioning of the central nervous system (CNS), including cognition and neuronal performance.

Background

The brain vasculature is surrounded by pericytes, astrocytes, and neurons, together forming the so-called neurovascular unit, which together ensure optimal functioning of the specialized brain endothelium that lines the blood vessels. To maintain brain homeostasis, brain endothelial cells are sealed together through tight junction protein complexes, which limit the passive diffusion of unwanted molecules into the CNS, together forming the so-called blood–brain barrier (BBB). Endothelial cells within the CNS differ markedly from peripheral endothelial cells, with low levels of pinocytosis, absence of fenestrae, highly controlled and restricted endothelial permeability, and a high mitochondrial content, reflecting their high metabolic rate.

The BBB is more than just a barrier separating the CNS from the circulation; it actively supports the influx of essential nutrients and signal molecules and it regulates the efflux of waste product from the CNS. To actively remove compounds and metabolites from the brain, the BBB endothelium is equipped with efficient efflux pumps (ATP binding cassette (ABC) transporters), in particular P-glycoprotein (P-gp), that drive cellular efflux of their substrates, including β-amyloid and inflammatory mediators. Vice versa, the brain endothelium actively supplies the brain with essential nutrients by selective transporters and in addition produces neurotrophic factors, highlighting the importance of proper brain endothelial function for optimal neuronal performance. The BBB not only actively protects the brain from the influx of excessive and unwanted neurotoxic components and immune cells but is also adapted to promptly provide neurons with a sufficient supply of essential nutrients and oxygen depending their high and fluctuating demands.

Loss of the proper function of the neuroprotective BBB is a critical and chronic event in numerous neurological disorders. Earlier work has shown that in MS and in Alzheimer's disease, a severe and continuous loss of the protective function of the BBB is apparent throughout the disease.[1–3] Moreover, barrier dysfunction goes hand in hand with a profound inflammation of the endothelial cells, thereby promoting infiltration of auto-reactive T-cells and monocytes[4,5] and amyloid deposition[3] which further induces irreversible tissue damage. In turn, inflamed brain endothelium contributes to disease progression

by its release of pro-inflammatory factors which activates the surrounding glial cells, together reinforcing astrogliosis, microglia activation, and consequently neurodegeneration.[1]

Although less well documented, BBB dysfunction remains ongoing in the progressive phase of MS; subtle but persistent leakage can be observed by magnetic resonance imaging (MRI)[6] and tight junction molecule expression levels are persistently altered[7] in lesions of MS patients. Therefore, ways to promote BBB function and herewith dampen immune cell activation and transmigration are promising strategies to limit disease progression selectively throughout the MS.

Initial proof of concept of the causality of BBB dysfunction for MS onset and its therapeutic potential comes from animal models. In experimental allergic encephalomyelitis (EAE), brain endothelial dysfunction precedes the development of clinical symptoms, as evidenced by MRI.[8] Interestingly, transgenic animal studies indicated that restoring BBB integrity by overexpressing the tight junction protein claudin-1, limited the progression of clinical symptoms. More importantly, prevention of BBB disruption using antioxidants inhibited the onset of clinical signs.[9]

In many other neurodegenerative conditions such as PD, ALS, epilepsy and vascular dementia, BBB dysfunction has also been demonstrated both in patient derived tissue and animal models. Strikingly, BBB dysfunction almost always precedes symptom development in animal models that mimic these diseases.

An important question remains if BBB dysfunction is a cause or consequence in neurodegenerative disorders. Direct evidence for the necessity of optimal function of the BBB for proper neuronal function and prevention of neurodegeneration is difficult to obtain in patients. Animal studies, however, indicate that chemically induced BBB disruption resulted in neuronal death and epileptic seizures in a mouse model,[10] underlining the crucial role the BBB has in the maintenance of brain homeostasis. Recent work shows that BBB specific deletion of an essential tight junction protein claudin-5, results in clinical symptoms that resemble schizophrenia.[11] Together these studies provide evidence that BBB dysfunction is an interesting target for treatment to fight neurological disorders and warrants further in-depth investigation of the BBB and the mechanisms that regulate its function.

Declaration of Conflicting Interests

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