

Commentary: “Age-Associated Physiological and Pathological Changes at the Blood-Brain Barrier: A Review”

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Introduction

This review article published by JCBFM in January 2017 gives an overview of the recent literature on the alterations of the Blood Brain Barrier (BBB) during normal and pathological process of aging. In the introductory section of the paper the role of blood brain barrier in the maintenance of brain homeostasis and the main cellular and molecular elements of this system are presented. The most important cellular constituents are the classical three cell type of endothelial cells, astrocytes and pericytes. However, in the last decade a close connection and complex interactions were revealed with additional cell types of neurovascular unit, like neurons and microglial cells, and further cellular elements were also included in the terminology of BBB in the scientific literature as supportive cells in displaying the blood-brain barrier function.

Having a closer view at the molecular level of BBB, we can see that the tight junctional and adherens junctional proteins [1] and also the different membrane transporter proteins [2] play an important role in the protection of the brain against the continuous changes in the concentrations of plasma constituents, harmful xenobiotic and microbial components originating from the circulation.

During embryonic development the permeability and the paracellular transport through the brain capillary endothelial cell layer change dramatically [3]. Transendothelial Electrical Resistance (TEER) has been used to study ion permeability in many epithelia [4-7], and in cerebral blood vessels [8-11], and is a measure of both the cellular and paracellular ion transport. Electrical resistance of pial vessels in 17-20 day fetuses is 300 Ω cm², lower than the 2000 Ω cm² typical for tight blood vessels [8], but considerably higher than the 2 Ω cm² observed in leaky mesenteric blood vessels [5], or the 20-30 Ω cm² as in muscle vessels and choroid plexus epithelium [4]. There is an acute increase in resistance of cerebral microvasculature to 1200 Ω cm² in 21 day fetuses, and there is no remarkable further increase in resistance after birth. The increase in electrical resistance and the onset of brain interstitial ion regulation occur immediately prior to birth over a relatively short period of time [3]. The mean electrical resistance across the wall of blood vessels on the pial surface of the brain in 28-33 day old rats is about 1500 Ω cm². The *in situ* determination of TEER values can be performed in newborn and young adult rats but seems to be technically challenging in aged animals. *In vitro* studies in endothelial cell cultures show similar permeability data to the *in vivo* observations for newborn and adult individuals [12], but the investigation of cells from aged animals is still missing.

The morphological observations of brain microvasculature have shown that the capillary wall thickness is increased in humans [13], the number of endothelial cells, mitochondria and tight junction protein expression are decreased in association with aging [14,15]. Thickness

of basal lamina, the number and size of astrocyte endfeet, glial fibrillary acidic protein expression, collagen IV and argin concentrations increase with age. Microglia turns to an amoeboid phenotype and produces pro-inflammatory cytokines while the number of pericytes is decreased in aged subjects [16-18].

In the second part of the paper the different neurodegenerative diseases are analyzed and presented in connection with the age-dependent changes in the blood-brain barrier function. The most important neurodegenerative disorders like Alzheimer's disease, multiple sclerosis, Parkinson's disease and pharmaco-resistant epilepsy and their pathomechanisms are summarized together with the neurodegenerative processes (gene defects, oxidative stress, protein misfolding and accumulation, cell death) in the supplementary file.

Alzheimer's Disease

Alteration of the BBB plays an important role in pathology of Alzheimer's disease. BBB breakdown is an early event in the aging human brain that begins in the hippocampus and may contribute to cognitive impairment. Tight junction proteins include occludin and claudins. Occludin is vulnerable to being attacked by Matrix Metalloproteinases (MMPs) and MMPs seem to have implications in Alzheimer's disease. The membrane transporters at the BBB and defected elimination mechanisms playing a role in the formation of Amyloid β plaques in the brain parenchyma in Alzheimer's patients are shown in details. The processes in the astrocytes and pericytes involved in this neurodegenerative disorder are also summarized [19].

Multiple Sclerosis

Formation of multiple sclerosis focal lesions follows the extravasation of activated leukocytes from blood through the BBB into the central nervous system (CNS). Once the activated leukocytes enter the CNS environment, they propagate massive destruction to finally result in the loss of both the myelin/oligodendrocyte complex and neurodegeneration. Also, the activated leukocytes locally release inflammatory cytokines and chemokines leading to focal immune activation of the brain endothelial cells, and loss of the normal functioning of the BBB. Tight junctions, MMPs and transporters are also involved in multiple sclerosis; their role is presented in an article [20].

Parkinson's Disease

Using histologic markers of serum protein, iron, and erythrocyte extravasation, a significantly increased permeability of the BBB in a part of the caudate putamen of Parkinson's disease patients has been shown. As in Alzheimer's disease and multiple sclerosis, MMPs seem

to have implications in Parkinson's disease and are associated with the neurodegeneration of dopaminergic neurons. Concerning the role of active transporters and tight junctions it is concluded that there is much controversy in the literature on the role of the BBB in Parkinson's disease [21,22].

Pharmacoresistant Epilepsy

Earlier studies have already indicated that seizures induce BBB transport changes; furthermore, focal epilepsies are often associated with BBB leakage. A role for ABC transporters in the pathogenesis and treatment of pharmacoresistant epilepsy has been proposed. A positive association between the polymorphism in the MDR1 gene encoding P-gp (/ABCB1) and pharmacoresistant epilepsy has been reported in a subset of epilepsy patient. Furthermore, an increased expression of P-gp at the BBB has been reported, which was determined in epileptogenic brain tissue of patients with pharmacoresistant epilepsy as well as in rodent models of temporal lobe epilepsy [23,24].

The recognition of the role of efflux and uptake transporters in the pathology of Alzheimer's [25] and Parkinson's diseases [26] and many other CNS disorders might offer new avenues for therapeutic intervention strategies for the experimental and clinical drug research focusing on the chronic neurodegenerative disorders with unmet needs. This paper and the follow up book chapter which will be published in the near future at Taylor and Francis/CRC Press (in Aging: Exploring A Complex Phenomenon" edited by Shamim Ahmad), give a comprehensive overview on the literature of aging and the role of BBB leakage and present a possible causality of BBB disruption in age-associated pathological processes.

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