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Review

The blood-brain barrier in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by the pathological accumulation of amyloid beta (Aβ) peptides and neurofibrillary tangles containing hyperphosphorylated neuronal tau protein. AD pathology is also characterized by chronic brain inflammation, which promotes disease pathogenesis. In this context, the blood-brain barrier (BBB), a highly specialized endothelial cell membrane that lines cerebral microvessels, represents the interface between neural cells and circulating cells of the immune system. The BBB thus plays a key role in the generation and maintenance of chronic inflammation during AD. The BBB operates within the neurovascular unit (NVU), which includes clusters of glial cells, neurons and pericytes. The NVU becomes dysfunctional during AD, and each of its components may undergo functional changes that contribute to neuronal injury and cognitive deficit. In transgenic animals with AD-like pathology, recent studies have shown that circulating leukocytes migrate through the activated brain endothelium when certain adhesion molecules are expressed, penetrating into the brain parenchyma, interacting with the NVU components and potentially affecting their structural integrity and functionality. Therefore, migrating immune system cells in cerebral vessels act in concert with the modified BBB and may be integrated into the dysfunctional NVU. Notably, blocking the adhesion mechanisms controlling leukocyte–endothelial interactions inhibits both Aβ deposition and tau hyperphosphorylation, and reduces memory loss in AD models. The characterization of molecular mechanisms controlling vascular inflammation and leukocyte trafficking could therefore help to determine the basis of BBB dysfunction during AD and may lead to the development of new therapeutic approaches.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with typical clinical characteristics including amnesic-type memory impairment, language deterioration, and visuospatial deficits (Cumming, 2004). AD cognitive and behavioral deficits correlate with neuronal loss and atrophy, mainly in the hippocampus and neocortex (Caselli et al., 2006). The central neuropathological hallmarks of AD are neuronal degeneration, loss of synapses, neurofibrillary tangles, gliosis and amyloid beta (Aβ) accumulation in senile plaques (Kidd, 1963; Wisniewski and Frangione, 1992; Querfurth and LaFerla, 2010). Aβ deposition is also observed in the cerebrovasculature, and is usually described as cerebral amyloid angiopathy (CAA) (Jellinger, 2002; Viswanathan and Greenberg, 2011). AD pathology is also characterized by chronic inflammation fueled by resident microglial cells and macrophages, with the contribution of circulating immune system cells (Heneka et al., 2015; Zenaro et al., 2015).

Numerous studies suggest that neurovascular dysfunction contributes to the onset and progression of AD, and propose a link between cerebrovascular changes and neurodegeneration (Kalaria, 2000; Farkas and Luiten, 2001; de la Torre, 2004; Viswanathan and Greenberg, 2011; Zlokovic, 2011; Sagare et al., 2012). Accordingly, recent data confirm age-dependent deterioration of the blood-brain barrier (BBB) during normal aging in the human hippocampus, a region involved in learning and memory, but more accelerated degradation in patients with mild cognitive impairment (MCI) compared to age-matched neurologically intact controls, suggesting this phenomenon contributes to early cognitive impairment (Montagne et al., 2015).

Aβ deposition in the vasculature leads to pro-inflammatory and cytotoxic events that contribute to the greater BBB permeability in the AD brain (Roher et al., 2003; Carrano et al., 2011; Erickson and Banks, 2013). Furthermore, CAA is associated with the degeneration of smooth muscle cells, pericytes and endothelial cells, contributing to the disruption of the BBB (Erickson and Banks, 2013). Evidence from *in vitro* studies and transgenic mouse tauopathy models suggests that tau may also promote BBB deterioration (Vidal et al., 2000; Forman et al., 2005; Kovac et al., 2009; Blair et al., 2015). BBB dysfunction correlates with the appearance of perivascular tau around major hippocampal blood vessels (Blair et al., 2015). Notably, when tau expression was suppressed, the integrity of the BBB was preserved, suggesting that the BBB can be stabilized in tauopathic brains by reducing tau levels (Blair et al., 2015). Both tau and Aβ may therefore promote the loss of BBB integrity, exacerbating the neurodegenerative process and associated inflammatory responses. Circulating neutrophils, which migrate in the brain of AD patients and accumulate in the central nervous system (CNS) of transgenic mice with AD-like pathology, may also contribute to vascular dysfunction by adhering and spreading on the brain endothelium and releasing inflammatory mediators and neutrophil extracellular traps (NETs) (Zenaro et al., 2015).

In this review, we discuss BBB dysfunction during AD in the context of the neurovascular unit (NVU), highlighting vascular inflammation mechanisms that contribute to disease pathogenesis. We describe the roles of the junctional complex, endothelial cells, basal lamina, pericytes and glial cells in the context of AD pathology. We also emphasize the role of cell adhesion molecules as markers of endothelial dysfunction and vascular inflammation, and discuss recent data revealing the emerging role of leukocyte trafficking in BBB and NVU dysfunction during AD.

2. Overview of the BBB and NVU

The BBB is a highly specialized endothelial cell membrane lining cerebral microvessels, which regulates the entry of plasma components, red blood cells and leukocytes into the CNS, and ensures the export of potentially neurotoxic molecules from the brain to the blood (Abbott et al., 2006; Zlokovic, 2008; Abbott et al., 2010; Zlokovic, 2011). There are two further sites in the CNS that form a barrier between the blood and cerebrospinal fluid (CSF): the arachnoid epithelium forming the middle layer of the meninges, and the choroid plexus epithelium (Abbott et al., 2006). At each site, the physical barrier is mainly determined by tight junctions that reduce the permeability of the intercellular adhesion areas (Abbott et al., 2006). These unique biological barrier structures comprise a combination of physical, transport and metabolic barriers that separate the neural milieu from the blood (Abbott et al., 2006; Zlokovic, 2008).

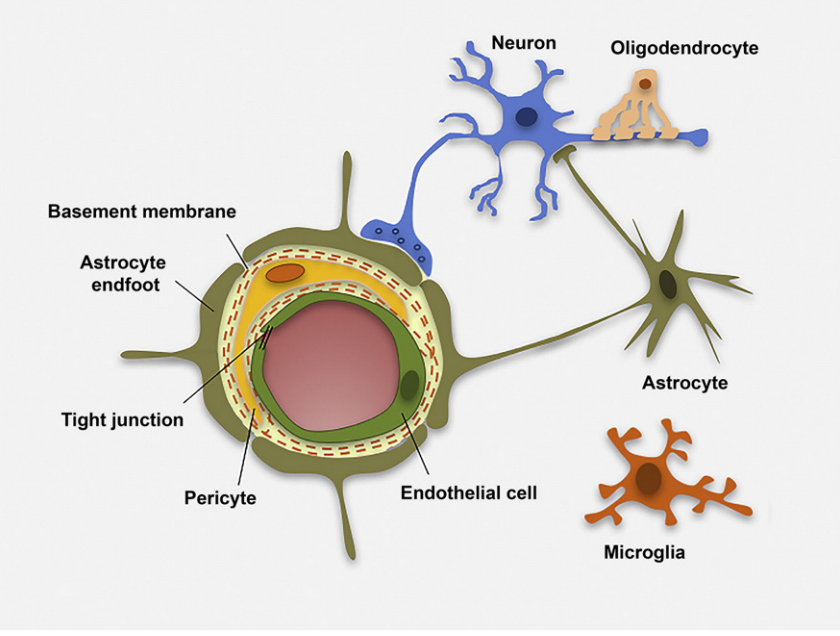

Fig. 1. Schematic cross-sectional representation of a cerebral capillary. Brain microvascular endothelial cells are the first barrier between blood vessels and brain parenchyma. Endothelial cells are linked by tight junctions (TJs), closely surrounded by pericytes and encircled by the basal lamina, which is contiguous with the plasma membranes of astrocyte endfeet and endothelial cells. Astrocyte endfeet processes support endothelial functions and provide the cellular link to neuronal cells. Ramified microglia can sense neuronal injury and release signals that are detrimental to the BBB.

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