Editorial

Possible effects of *Porphyromonas gingivalis* on the blood–brain barrier in Alzheimer's disease

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1. Introduction

The blood–brain barrier (BBB) is formed by brain capillary endothelial cells covered by membranes (Figure 1). It is surrounded by pericytes and astrocyte end-feet in a neurovascular unit (NVU) (Figure 2). The function of BBB is to regulate the molecular exchange between the blood flow and the brain parenchyma thereby maintaining the homeostasis of the central nervous system (CNS) [1]. The BBB also represents the interphase between neural and circulating cells of the immune system [2]. It is a highly selective semipermeable barrier specialized to prevent pathogens and circulating cells from reaching the brain and causing brain damage.

Figure 1. The blood–brain barrier (BBB) and the neurovascular unit (NVU). Pial arteries divide into smaller arteries, so-called penetrating arteries, which branch into capillaries. Pial and penetrating arteries are covered by vascular smooth cells and are separated from brain tissues through the parenchymal basement membrane (glia limitans). One layer of smooth muscle cells covers the parenchymal arterioles. The BBB is formed by endothelial cells in capillaries. BBB properties in these cells are further maintained and regulated through communications with the basement membranes and neighboring cells in the NVU such as pericytes, astrocytes and interneurons. Adopted from Ref. [1]

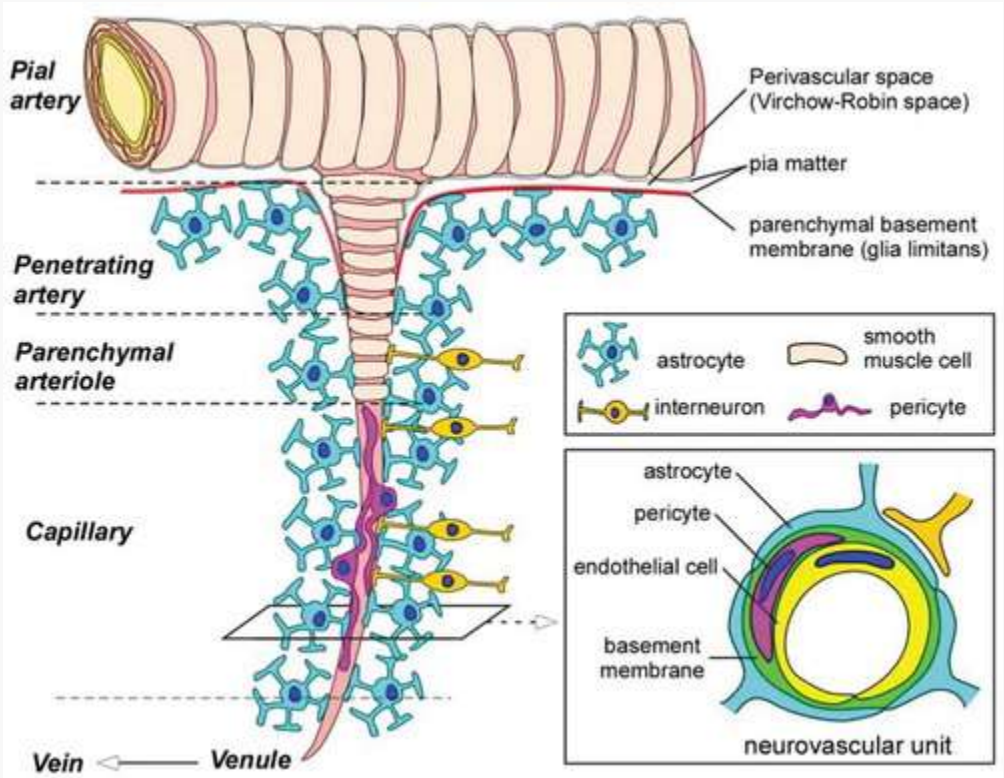

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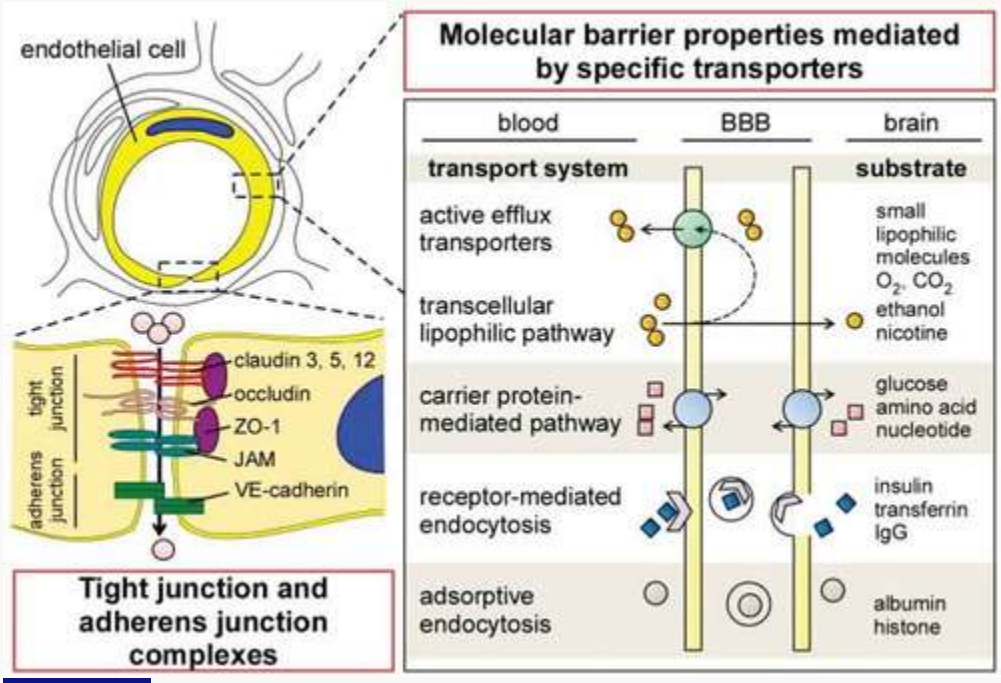
Figure 2. Physical and molecular properties of endothelial cells contributing to BBB integrity and function. Paracellular flux across the BBB is restricted by tight junction and adherens junction complexes. Some nutrients and essential molecules are selectively transported from luminal to abluminal membranes by specific influx systems. Most small lipophilic molecules passively diffused across the lipid layer are returned to the blood by ATP-dependent efflux transporters. *P. gingivalis* may cause vascular endothelial barrier disruption and increased permeability destroying intercellular junctions. This could promote the passage of this bacterium through the BBB to the AD brain where it has been found. ZO-1 = zonula occludens-1, JAM = junctional adhesion molecule, VE = cadherin (vascular endothelial-cadherin), IgG = immunoglobulin G. Adopted from Ref. [1]



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Changes in the BBB may be an early step and consequence in Alzheimer's disease (AD) [3]. During neurological diseases the NVU becomes dysfunctional, and each of its components can undergo functional changes, contributing to neuronal injury and cognitive deficit [2]. The BBB integrity and migration of immune cells into the brain are affected by pro-inflammatory molecules, such as cytokines, chemokines, adhesion molecules by glial cells, neurons, and endothelial cells [4]. The inflammatory process established promotes capillary changes such as fragmentation, thickening, atrophy of pericytes, accumulation of laminin in the basement membrane, and increased permeability of blood vessels to plasma proteins [4]. This editorial will discuss how the periodontopathogenic bacterium *Porphyromonas gingivalis*, recently associated with AD, may affect the BBB.

2. Neuroinflammation and periodontitis

Neuroinflammation is increasingly being recognized as a hallmark together with accumulated amyloid beta (Aβ) and hyperphosphorylated tau in AD. BBB dysfunction triggers neuroinflammation and oxidative stress, increases the activity of β- and γ-secretases, and promotes Aβ generation [5]. Another important cause of neuroinflammation may be peripheral infection such as periodontitis, which affects a large part of the elderly all over the world.

Periodontitis is mainly regarded as an infection. Although a number of bacteria can be recovered from this disease, the keystone pathogen is believed to be *P. gingivalis* [6–8]. The ulcerated epithelium in periodontal pockets, typical of periodontitis, enables easy access for this bacterium and its lipopolysaccharide (LPS), proteases (gingipains) and other virulence factors [9], as well as inflammatory products to the blood circulation. In

periodontitis, bacteriemias can occur repeatedly during the day [10]. Interestingly, positive blood cultures were significantly higher ($p = 0.05$) for tooth extraction cases with periodontitis (79.40%) than for tooth extraction cases without periodontitis (56.50%) [11]. The periodontal microbiota may also reach the brain through the trigeminal nerve, circumventricular organs, perivascular spaces and olfactory unsheathing cells acting as Trojan horses [12]. Although combined antibiotic therapy has been found effective in animal models of AD, antibacterial drugs are not being widely investigated in AD patients [13]. However, inhibition of gingipain reduced established *P. gingivalis* brain infection, blocked $A\beta_{1-42}$ production, diminished neuroinflammation, and rescued hippocampal neurons [14]. Therefore, gingipain inhibitors may be valuable for treating *P. gingivalis* brain colonization and neurodegeneration in AD.

3. LRP-1 and RAGE

BBB dysfunction can cause accumulation of Aβ leading to alterations and disruption of the NVU (reviewed by [15]). The main transporter for efflux of accumulated Aβ at the BBB is low-density lipoprotein receptor-ligated protein 1 (LRP-1), while receptor for advanced glycation end product (RAGE) prevents Aβ from entering the brain [16,17]. With disability in LRP-1, BBB clearance is reduced, brain levels of Aβ are increased, and cognition is impaired [18]. Recently, LRP-1 was also found to regulate the uptake and spread of tau [19]. Increased levels of RAGE at the BBB can cause failing BBB function, which has been implicated as a main factor mediating Aβ cytotoxicity in AD [20]. Attenuation of RAGE may prevent Aβ from accumulating in the cerebral blood vessels and causing neurotoxicity [20].

P. gingivalis caused increased Aβ influx by directly affecting RAGE in brain endothelial cells [21]. The increased influx was significantly reduced by the RAGE-specific inhibitor (FPS-ZM1). Parallel with the increase in RAGE expression there was a significant decline in memory after 3 weeks of chronic systemic *P. gingivalis* infection in middle-aged mice [21]. This was the first study demonstrating cerebrovascular-related amyloid genesis caused by systemic *P. gingivalis* infection. Aβ is not exclusively generated in the brain but also peripherally by platelets, skeletal muscle cells, fibroblasts and monocytes/macrophages [21–24]. Systemic infection with *P. gingivalis* can enhance the peripheral pools of Aβ in the body [23], and there could be a synergetic interplay between cerebral RAGE expression and peripheral generation of Aβ during chronic *P. gingivalis* infection [21]. In mice, oral *P. gingivalis* infection caused brain colonization and increased production of $A\beta_{1-42}$, which is a component of amyloid plaques [14].

P. gingivalis has also some effect on LRP-1. Thus, salvianolic acid B (SalB) (20 and 40 mg/kg) reduced cognitive impairment by inhibiting neuroinflammation and decreasing Aβ levels in *P. gingivalis*-infected mice [25]. Of note was that the protein expression of LRP-1 was increased and that of RANGE decreased in the mice brains.

4. BBB dysfunction and tau pathology

A correlation between BBB dysfunction and tau pathology has been reported [5]. BBB damage has been observed in tauopathies that lack Aβ overproduction, suggesting a role for tau in such damage [4]. *P. gingivalis* was found to induce tau hyperphosphorylation by, in part, attenuating the activity of protein phosphatase 2A (PP2A) by triggering systemic inflammation and neuroinflammation in wild-type SD rats [26]. *P. gingivalis* gingipains also cleaved tau which promoted aberrant phosphorylation and accumulation of misfolded insoluble tau. This might increase the turnover rate of tau and induce a compensatory increase in tau production to maintain homeostasis in neurons infected by *P. gingivalis* [14].

5. Leptomeninges

The leptomeninges are in front to defend the CNS against infection [27]. *P. gingivalis* LPS can activate the leptomeninges/choroid plexus, which is formed at the blood-cerebrospinal fluid barrier (BCSFB) and induce microglia-mediated neuroinflammation [28,29]. The leptomeninges also serve as an important route for transduction of inflammatory signals from macrophages to microglia by secreting proinflammatory mediators during exposure to *P. gingivalis* LPS [28]. Macrophages activated by *P. gingivalis* markedly induced production of TNF-α, IL-1β and IL-6 in leptomeningeal cells [28]. Wang et al. [30] reported that in leptomeningeal cells *P. gingivalis*-induced reactive oxygen species, activated JAK2 and regulated production of inflammatory cytokines through c-Jun. A JAK2 inhibitor (coniferyl aldehyde) suppressed the pro-inflammatory reactions exerted by *P. gingivalis*-stimulated macrophages [30]. The JAK2/STAT3 axis in hippocampal neurons has been suggested as a novel target in the therapy of patients with AD [31].

6. Immune suppression

P. gingivalis can, in addition to increase BBB permeability, prevent the entry of immune cells into the brain and inhibit the local IFN-γ response [32]. This is consistent with the scarcity of adaptive immune cells detected in AD neuropathology and supports the notion that *P. gingivalis* can induce immune suppression in the brain [33].

P. gingivalis is resistant to destruction by complement due to gingipains degrading the complement components C3 and C5. Deposition of C3b and C5a on the surface of *P. gingivalis* is thereby prevented [34]. This may give *P. gingivalis* better opportunities for direct contact with endothelial cells [21].

7. APOE-ε4

The *apolipoprotein-ε4* (*APOE-ε4*) genotype is an important risk factor for AD and vascular pathology. It can lead to BBB breakdown and degeneration of brain capillary pericytes [35–38] that sustain BBB integrity [39,40]. Riphagen et al. [41] found that the relationship between BBB dysfunction and AD pathology is modulated by IL-6 and that this association is driven by the *APOE-ε4* genotype. Human APOE-ε4 expression in mice weakened

cerebral vascularization and BBB function [42]. Of note, *APOE* has been considered as a susceptibility gene involved in the life cycle of *P. gingivalis* and other possible AD pathogens [43]. In addition, *P. gingivalis* can cleave APOE into Arg residues which may have neurotoxic effects [8,44,45].

Gene therapy may be a future tool for treating neurodegenerative diseases such as AD [46]. However, successful therapy depends on the full knowledge of the pathogenesis of the diseases and the spatial efficiency of gene expression. New, advanced techniques such as MRI-guided convection-enhanced delivery (iMRI-CED), which verifies accurate vector delivery in real time, may change this [47].

8. Concluding remarks

BBB dysfunction is an important hallmark of AD which can be caused by neuroinflammation. An important cause of neuroinflammation may be *P. gingivalis* which reaches the brain after systemic spread from its primary habitat – the periodontal pocket, established under 'chronic' periodontitis. The inflammagens of this pathogen – LPS and gingipains – have been found in the brain of animal models and humans with AD. *P. gingivalis* may even penetrate the BBB of non-AD elderly with reduced BBB stability and increased permeability and make its way to the brain by affecting LRP-1, RAGE, tau and APOE, and by exerting its high capacity to suppress immunity. Although *P. gingivalis* is not be the sole organism that can enter the brain, it has the preference to initiate dysbiosis even at low concentrations.