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CROSSING THE BLOOD-BRAIN BARRIER BY NEUROINVASIVE PATHOGENS

**Tkáčová, Z.[1], Káňová, E.[1], Jiménez-Munguía, I.[1]
Čomor, Ľ.[1], Širochmanová, I.[1], Bhide, K.[1], Bhide, M.[1, 2]**

1Laboratory of Biomedical Microbiology and Immunology
University of Veterinary Medicine and Pharmacy, Kosice
[2]Institute of Neuroimmunology, Slovak Academy of Sciences, Bratislava
Slovakia

zuzana.tkacova17@gmail.com

ABSTRACT

The penetration of the blood-brain barrier (BBB) and invasion of the central nervous system (CNS) are important steps for all neuroinvasive pathogens. All of the ways of pathogens passing through the BBB are still unclear. Among known pathways, pathogen traversal can occur paracellularly, transcellularly or using a "Trojan horse" mechanism. The first step of translocation across the BBB is the interactions of the pathogen's ligands with the receptors of the host brain cells. Lyme disease, the most common vector-borne disease in the temperate zones of Europe and North America, are caused by *Borreliella* species (former *Borrelia burgdorferi* sensu lato) that affects the peripheral and the CNS. In this review, we have presented various pathogen interactions with endothelial cells, which allow the disruption of the BBB so that the pathogens can pass across the BBB.

Key words: blood-brain barrier; *Borreliella*; paracellular and transcellular passage; "Trojan horse" mechanism

INTRODUCTION

Infections of the CNS, with associated high morbidity often cause serious permanent damage to the CNS [20]. Despite the availability of antimicrobial treatment, in the last two decades, an increase in the incidence of bacterial neuroinfections has been recorded. A large number of bacterial pathogenic species have the potential to infect the CNS. Nevertheless, it is not clear why a relatively small number of pathogens are responsible for infections of the CNS. Among various bacterial pathogens which cause infections of the CNS, *Neisseria meningitidis, Borreliella, Streptococcus pneumoniae* and *Listeria monocytogenes* are the most important ones in central Europe [30]. These pathogens are capable of crossing the BBB, where they invade the CNS, which further leads to damaged cells of the neurovascular unit (NVU). The neurovascular unit includes the brain microvascular endothelial cells (BMEC), glial cells, astrocytes and neurons [13] (Fig. 1).

Blood-brain barrier

The BBB is a regulatory interface between the peripheral circulation and the CNS [30]. The BBB regulates the passage of blood-borne substances and cells into the brain and thus maintains the homeostasis of the neural microenvironment that is crucial for normal neuronal activity and function [1]. It is a specialized system which has a unique role in the protection of the brain from toxic substances in blood and filters harmful compounds from the brain back to the bloodstream. The BBB allows the passage of water, some gases, and lipid-soluble molecules by passive diffusion, as well as the selective transport of molecules such as glucose and amino acids [1]. The unique property of the BBB is primarily determined by the presence of endothelial junctional complexes made up of adherens junctions (AJs) and highly specialized tight junctions (TJs). Apart from the presence of specialized TJs, other unique properties of the BBB are the absence of fenestrae, reduced level of fluid-phase endocytosis and asymmetrically localized enzymes [2]. An intact BBB prevents the transfer of macromolecules to the brain tissue. The penetration of substances into the brain, also avoids enzymatic barriers, which are composed of enzyme systems located in the walls of the cerebral blood vessels (e. g. aminopeptidase or monoaminooxidase).

Cells of blood-brain barrier

The BBB is formed by the brain microvascular endothelial cells (BMECs) that line the cerebral microvessels. The periendothelial structures of the BBB include pericytes (related to smooth muscle cells, surrounding the endothelium, reduced endothelial apoptosis and the stabilization of the endothelium), astrocytes (induce many BBB features and support the tissue of the CNS) and a basal membrane (Fig. 1). Astrocytes are glial cells that vastly outnumber the neurons in the brain. Astrocytes are involved in metabolic interactions with neurons, and also form close associations with endothelia and fibroblasts [52]. Less is known about the role of the pericytes in the BBB. The characteristic shape of astrocytes is a stellate appearance with long cytoplasmic processes. They are specialized cells within the capillary basement membrane, which help to maintain structural integrity and the function of the blood vessels [13]. The basal lamina of cerebral microvessels provides a scaffold upon which the endothelial and the glial compartments interact [2]. The BMECs interact dynamically with neighboring cells, astroglia, pericytes, and microglia that contribute to their unique characteristics. Despite the fact that astrocytes envelop more than 99 % of the BBB endothelium, they are not directly involved in the physical properties of the BBB [23]. Interaction of astrocytes with the BMECs induces and modulates the development of the unique properties of the BBB which is the reduction in the adhesional and tight junctional gap areas [52].

Polarized cells have functions such as: the transport of ions and nutrients; secretion of protein products; and protection of the interior of the organism from pathogens. Cell polarity is observed in the functionally distinct portions of the plasma membrane known as the apical domain and the basolateral domain [35]. The apical domain contains anion channels, H^+/K^{+-} ATPase and transporters, whereas the lateral portion of the basolateral domain contains proteins involved in attachment to neighboring cells and cell-

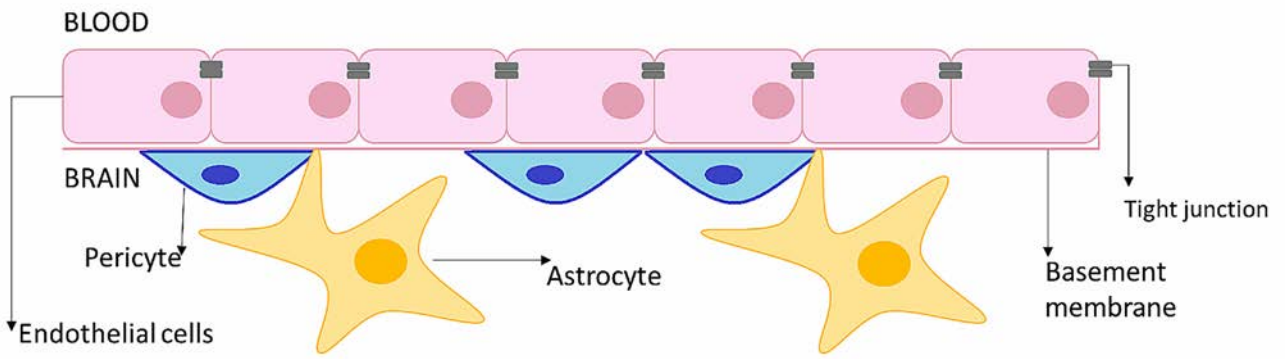

Fig. 1. Structure of the blood brain barrier
BBB consists mainly of brain microvascular endothelial cells (BMEC), pericytes, astrocytes and basement membrane. An original drawing

cell communication. The basal portion of the basolateral domain contains the binding sites for constituents of the basal lamina, receptors for hormones and other signaling molecules that regulate the function of the cell [35]. The TJs, which are localized in the apical end of the basolateral membrane, play a key role in establishing endothelial polarity. The TJs of the cerebral microvasculature are composed of four integral membrane proteins — occludin [17], claudins [18], junctional adhesion molecules (JAM) [34] and the recently discovered endothelial cell-selective adhesion molecule [36] (Fig. 2).

Traversal of the BBB by pathogens

One of the basic steps in the invasion of a pathogen into the CNS is crossing through the BBB. Several pathogens are able to penetrate physiologically impermeable barriers such as the BBB. There are two main types of passing through the BBB, paracellular and transcellular [30] (Fig. 3). Crossing through the BBB is associated with protein-protein interactions between the pathogen and cells of the BBB. Some pathogens have developed an array of complex types of BBB disruptions. One of the most perfect mechanism of translocation, without mechanical damage to the BBB is the "Trojan horse" mechanism or mimicry of surface ligands on the host cells. Some neuroinvasive pathogens express the ligand of the surface receptors of the host proteases, which break down the extracellular matrix or components of the basal membrane.

1. Transcellular passage involves penetration of the pathogens through the BMECs. This crossing is initiated by adherence of the pathogen to the ECs leading to the entry of the bacterium into the CNS across the BBB using pinocytosis or receptor-mediated mechanisms. Transcellular traversal of the BBB has been demonstrated for *Escherichia coli* [30], Group B *Streptococcus* [40], *Listeria monocytogenes* [21], *Mycobacterium tuberculosis* [27], *Citrobacter freundii* [3], *Haemophilus influenzae* [41], *Streptococcus pneumoniae* [45] and *Candida albicans* [28].
2. The paracellular route is defined as microbial infiltration between the cells. This traversal involves loosening of the TJs or disturbing the supporting components of TJs, i.e. basement membrane and glial cells [55]. The paracellular transmigration of the BBB has been suggested for the *Trypanosoma* [24] and T*reponema pallidum* [22].

   Both routes have also been suggested for *Cryptococcus neoformans* [11, 12], *Neisseria meningitidis* [38, 10], and the Lyme disease pathogen *Borrelia burgdorferi* [9].
3. In the case of the "Trojan horse" mechanism, the first step is infection of leukocytes, primary lymphocytes, and/or mononuclear leukocytes by pathogens. Then these infected immune cells carry the pathogen through the BBB. This way of crossing is mainly used by bacteria that are able to survive in the host immune cells [30]. Passing the BBB by the "Trojan horse" mechanism has been suggested for bacteria such as *Listeria monocytogenes* and *Mycobacterium tuberculosis* [15].

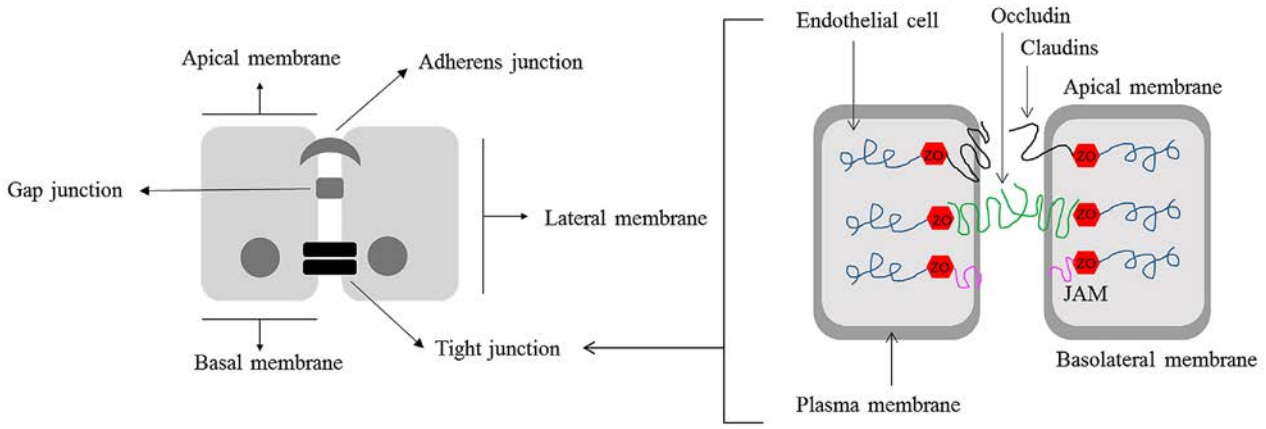

Fig. 2. Organization of intracellular junctions

BMEC attached to each other via adherens junctions, tight junctions and gap junctions. The TJs are composed of integral proteins: occludin, claudins, junctional adhesion molecules (JAM) and the recently discovered endothelial cell-selective adhesion molecule. Edited according to [35]

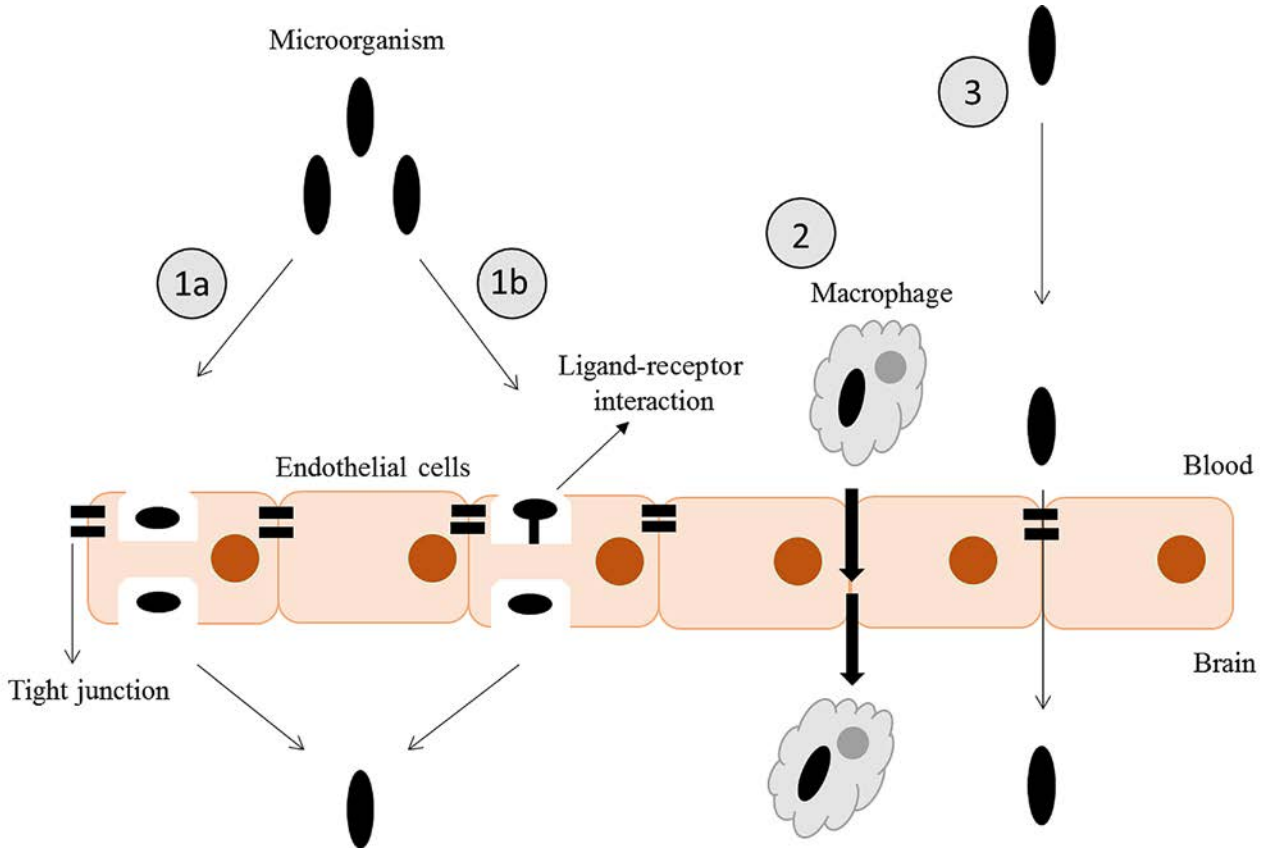

Fig. 3. Mechanisms of crossing through the BBB

1a) Transcellular penetration-pinocytosis (ligands are brought into endothelial cell, forming an invagination and they are released into brain); 1b) Transcellular penetration-ligand-receptor interaction (pathogen ligand interacts with host receptor and it allows the pathogen to cross the BBB); 2) The "Trojan horse" mechanism (Infected phagocytes to carry the pathogen through the BBB); 3) Paracellular penetration (Passage through the endothelial cells with or without disrupted tight and adherens junction). An original drawing

In recent years, the interest of researchers has been aimed at the cell signaling pathway, which is triggered after infection in the cells of the NVU. Neuroinvasive pathogens infect host cells through ligand-receptor interactions. Pathogens ligands interact with receptors, which are bound to the brain microvascular endothelial cells. These interactions are described in a variety of pathogens (Table 1).

Transversal of the BBB by Borrelia

Lyme disease is an infectious bacterial disease caused by the microaerophilic spirochete *Borreliella* species, which affects the peripheral and CNS. It is one of the most common tick-borne diseases in Europe and in North America [49]. Neurological complications, collectively termed neuroborreliosis, can occur in up to 15 % of untreated patients. Typical symptoms of the damage of the CNS are headache, flu-like symptoms, fatigue, memory loss and depression. In the case of the infection of the peripheral nervous system, typical symptoms are the malfunction of the facial nerve and muscle weakness [49].

Several bacteria express their own proteases that digest the extracellular matrix in order to invade tissues, however, *B. burgdorferi* appear to utilize the fibrinolytic system of the host to disseminate [7]. *B. burgdorferi* does not produce any collagenase, elastase, hyaluronidase or plasminogen activators [31]. It is a well-known fact that *Borreliella* can bind plasminogen and promotes degradation of the ECM [7]. On the other hand, fibrinolytic system also initiates other proteases, including the matrix metalloproteinases (MMPs), which are predicted to be essential for borrelial invasion into the brain [16]. Plasminogen bound on the bacterial surface can be converted into plasmin by host activators [4]. Plasmin bound to the surface of the bacterial cell is stabilized and protected against inactivation by α1- and α2-antiplasmin [42]. *Borreliella* induces the expression and secretion of the urokinase-type plasminogen activa-

Table 1. Protein-protein interactions during translocation of pathogen across the BBB

Pathogen	Predicted ways of BBB penetration	Ligand (pathogen)	Receptor (host)	References
E.coli	Transcellular	CNF1 FimH OmpA IBEA	37 LRP, 67 LRP CD48 Gp96 45-kDa protein	[14], [29] [44] [26]
S. pneumoniae	Transcellular	Phosphorylcholin	Platelet-activating factor receptor	[45]
L. monocytogenes	Transcellular "Trojan horse" mechanism	Internalin B Vip ND	gC1q-R (receptor for the globular head of the complement component C1q) Met receptor tyrosine kinase gp96 ND	[21], [5], [47] [6] [15]
Neisseria meningitidis	Transcellular	Opc (outer membrane protein) Pili (Pil A and Pil B)	Fibronektin (anchoring to the integrin-α5β1 receptor) CD46	[56], [37] [43]
Group B Streptococci	Transcellular	Glycosyltransferase LTA Lmb FbsA Pili (PilA and PilB)	ND Laminin Fibrinogen ND ND	[53] [53] [33] [33]
Treponema pallidum	Paracellular	ND	ND	[54]
Borrelia burgdorferi s. l.	Transcellular Paracellular	ND Vsp1 OspA 70-kDa PBP	ND Proteoglycans Platelet integrins Glycosaminoglycans Glycosphingolipids Plasmin(ogen) proteoglycans Plasmin(ogen)	[9] [51] [12] [46] [46] [25] [25]
Mycobacterium tuberculosis	Transcellular "Trojan horse" mechanism	Upregulation of genes Rv0980c Rv0987c Rv0989c Rv1801	ND ND ND ND ND	[27] [39] [39] [39] [39]

N. D. — not detected (unknown)

tor (uPA) and the expression of the uPA receptor (uPAR; CD87) by a variety of cell types, including monocytes [8]. The protection of cell surface-bound plasmin from physiological inhibitors may allow the spirochete to traverse normal tissue barriers, to colonize organs and to propagate pathological processes within the affected tissues. *Borreliella* is able to activate and upregulate proinflammatory cells of human MMPs [19] and induce the release of MMP9 (gelatinase), and MMP1 (collagenase). These molecules are subsequently exploited for penetration through different host barrier, including the BBB [19].

Another alternative, which is used by *Borreliella* to translocate through the BBB, is the exploitation of CD40. OspA of *Borreliella* binds CD40 expressed on brain endothelial cells of the host. This binding induces the expression of various types of integrins and the expression of matrix metalloproteinases (MMP3 and MMP9). Activation of CD40 in endothelial cells mediates downstream signaling that leads to the production of pro-inflammatory cytokines [35] and enhanced expression of ICAM-1, E-selectin, VCAM-1 with the consequent increase in cell binding, vascular endothelial growth factor (VEGF) and vascular permeability factor (VPF), and finally creates fenestrations [50, 48, 32] that leads to a weakening of the barrier. OspA is undoubtedly a multifunctional protein that is absolutely necessary in the various stages of borrelial lifecycle and pathogenesis. It is also well known that *Borreliella* can bind plasminogen via OspA on their surface [12]. Plasminogen can be activated to plasmin [12, 8] leading to degradation of the extracellular matrix and translocation across the BBB.

CONCLUSIONS

Passing through the BBB is an important step in the invasion of pathogens. This summary explains different ways of passages of pathogens across the BBB. The identification of pathogenic ligands and the understanding of ligand-receptor interactions helps us to unfold the basic principles of neuroinvasion and increases the probability of creating a suitable vaccine against such neuroinfections.

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