Mechanisms of Blood Brain Barrier Disruption by Different Types of Bacteria, and Bacterial–Host Interactions Facilitate the Bacterial Pathogen Invading the Brain

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Abstract

This review aims to elucidate the different mechanisms of blood brain barrier (BBB) disruption that may occur due to invasion by different types of bacteria, as well as to show the bacteria–host interactions that assist the bacterial pathogen in invading the brain. For example, platelet-activating factor receptor (PAFR) is responsible for brain invasion during the adhesion of pneumococci to brain endothelial cells, which might lead to brain invasion. Additionally, the major adhesin of the pneumococcal pilus-1, RrgA is able to bind the BBB endothelial receptors: polymeric immunoglobulin receptor (pIgR) and platelet endothelial cell adhesion molecule (PECAM-1), thus leading to invasion of the brain. Moreover, *Streptococcus pneumoniae* choline binding protein A (CbpA) targets the common carboxy-terminal domain of the laminin receptor (LR) establishing initial contact with brain endothelium that might result in BBB invasion. Furthermore, BBB disruption may occur by *S. pneumoniae* penetration through increasing in pro-inflammatory markers and endothelial permeability. In contrast, adhesion, invasion, and translocation through or between endothelial cells can be done by *S. pneumoniae* without any disruption to the vascular endothelium, upon BBB penetration. Internalins (InlA and InlB) of *Listeria monocytogenes* interact with its cellular receptors E-cadherin and mesenchymal-epithelial transition (MET) to facilitate invading the brain. *L. monocytogenes* species activate NF- κ B in endothelial cells, encouraging the expression of P- and E-selectin, intercellular adhesion molecule 1 (ICAM-1), and Vascular cell adhesion protein 1 (VCAM-1), as well as IL-6 and IL-8 and monocyte chemoattractant protein-1 (MCP-1), all these markers assist in BBB disruption. *Bacillus anthracis* species interrupt both adherens junctions (AJs) and tight junctions (TJs), leading to BBB disruption. Brain microvascular endothelial cells (BMECs) permeability and BBB disruption are induced via interendothelial junction proteins reduction as well as up-regulation of IL-1 α , IL-1 β , IL-6, TNF- α , MCP-1, macrophage inflammatory proteins-1 alpha (MIP1 α) markers in *Staphylococcus aureus* species. *Streptococcus agalactiae* or Group B *Streptococcus* toxins (GBS) enhance IL-8 and ICAM-1 as well as nitric oxide (NO) production from endothelial cells via the expression of inducible nitric oxide synthase (iNOS) enhancement, resulting in BBB disruption. While Gram-negative bacteria, *Haemophilus influenza* OmpP2 is able to target the common carboxy-terminal domain of LR to start initial interaction with brain endothelium, then invade the brain. *H. influenza* type b (HiB), can induce BBB permeability through TJ disruption. LR and PAFR binding sites have been recognized as common routes of CNS entrance by *Neisseria meningitidis*. *N. meningitidis* species also initiate binding to BMECs and induces AJs deformation, as well as inducing specific cleavage of the TJ component occludin through the release of host MMP-8. *Escherichia coli* bind to BMECs through LR, resulting in IL-6 and IL-8 release and iNOS production, as well as resulting in disassembly of TJs between endothelial cells, facilitating BBB disruption. Therefore, obtaining knowledge of BBB disruption by different types of bacterial species will provide a picture of how the bacteria enter the central nervous system (CNS) which might support the discovery of therapeutic strategies for each bacteria to control and manage infection.

Keywords Blood brain barrier · Bacterial infection · Meningitis · Therapeutic strategies

Introduction

The specialized micro-environment of the central nervous system (CNS) is maintained by the blood–brain barrier (BBB), which enables communication activities with the systemic compartment. The state of brain capillaries and their polarized microvascular endothelial cells are responsible for BBB structure and functional integrity, by possessing tight junctions (TJs) (Kniesel and Wolburg 2000). Occludin, claudin, junctional adhesion molecules (JAMs), and zonula occludens (ZO)-1 are the main elements of intercellular TJ proteins (Hawkins and Davis 2005). Control paracellular passage of substrates across the BBB is the main function of these proteins. However, changes may occur during several CNS pathological events involving bacterial infection.

Neurological disorders such as bacterial meningitis, sepsis, and brain abscess formation are mostly linked to bacterial pathogens (Join-Lambert et al. 2010; Iovino et al. 2013b). Scientifically, the commencement of bacterial meningitis takes place when blood-borne bacteria infiltrate into the BBB, gaining entrance into the CNS. The hallmark events within the pathophysiology of bacterial meningitis are; increased cytokines/chemokine levels in infected patients (Møller et al. 2005), deteriorating endothelium barrier integrity which can be caused by many meningeal pathogens through adherens junction (AJ)/TJ deformation, and BBB disruption (van Sorge and Doran 2012). For example, brain invasion has been occurred during the adhesion of pneumococcal pilus-1, RrgA to brain endothelium receptors such as platelet endothelial cell adhesion molecule-1 (PECAM-1) and polymeric immunoglobulin receptor (pIgR), together with platelet-activating factor receptor (PAFR) (Radin et al. 2005; Iovino et al. 2013a, 2016, 2017). In terms of pneumococcal meningitis, TNF- α , IL-1 β , IL-6, and IL-10 increase in order to enhance the immune response for pathogen elimination (Kornelisse et al. 1996; Paul et al. 2003; Østergaard et al. 2004). A previous report has described that BBB integrity can be affected due to microorganisms releasing and expressing cytokines, chemokines, and cell-adhesion molecules, resulting in BBB disruption (Kim 2003). In contrast to the studies mentioned above, it has been reported that *Streptococcus pneumoniae* invade the endothelial cells without any disruption to the BBB and the vascular endothelium, suggesting an intracellular or paracellular path for BBB translocation (Iovino et al. 2013b). Listeriolysin O (LLO) is the pore-forming toxin of *Listeria monocytogenes* which facilitates and enhances the expression of the surface adhesion molecules P- and E-selectin, intercellular adhesion molecule 1 (ICAM-1), and Vascular cell adhesion protein 1 (VCAM-1), as well as IL-6 and

IL-8 and monocyte chemoattractant protein-1 (MCP-1), allowing neutrophil and monocyte adhesion to the endothelial cells (Kayal et al. 2002), which might encourage BBB disruption. InhA and BslA *Bacillus anthracis* invade the endothelial cells by breaking down the TJ protein (ZO-1), and thus contributes to hemorrhaging in the CNS via BBB disruption in vitro and in vivo (Ebrahimi et al. 2009). McLoughlin et al. (2017) demonstrated that BMEC permeability was induced due to *Staphylococcus aureus* infection via the reduction of vascular endothelial cadherin (VEC), claudin-5, and ZO-1. Recent data have demonstrated that the levels of myeloperoxidase (MPO), cytokine-induced cytokine-induced neutrophil chemoattractant-1 (CINC-1), IL-1 β , IL-6, IL-10, and TNF- α were increased after Group B *Streptococcus* (GBS) infection in the hippocampus (Barichello et al. 2011a). Surprisingly, previous studies showed that GBS crosses the BBB without any evidence of intracellular TJ disruption or detection of micro-organisms between cells (Kim 2008). Also, it has been revealed that *B. anthracis* degrades endothelial cells accompanied by ZO-1 degradation, leading to bacterial adherence to the endothelium via an S-layer adhesin (BslA) (Ebrahimi et al. 2009).

Moreover, the main portals to let *Haemophilus influenzae* type b (HiB) enter the CNS are laminin receptor (LR) and PAFR, which subsequently might cause meningitis (Swords et al. 2001). It has been also revealed that BBB permeability might be facilitated by HiB lipopolysaccharide (Patrick et al. 1992) via TJ deformation (Quagliarello et al. 1986; Schubert-Unkmeir et al. 2010) and this damages the brain cells in vivo (Doran et al. 2003). Additionally, the first mechanism of BBB disruption in the presence of *Neisseria meningitidis* bacterium is that the bacterial adhesins (PilQ, an outer membrane protein involved in secretion of type IV pili in *N. meningitidis*) targets a common carboxy-terminal domain of LR to establish initial contact with the brain endothelium that might lead to bacterial pathogen invasion into the brain (Orihuela et al. 2009). *N. meningitidis* prompts the specific cleavage of occludin protein by secretion of host matrix metalloproteinase-8 (MMP-8), subsequently, this might lead to endothelial cell detachment and increased paracellular permeability (Schubert-Unkmeir et al. 2010). Pili type IV of *N. meningitidis* was shown as the main factor which disturbs functional proteins, resulting in anatomical gaps that were used by the bacteria to penetrate into the CNS (Coureuil et al. 2009, 2010). Similarly, *Escherichia coli* K1 is able to disrupt BBB integrity by a signaling process that facilitates detachment of β -catenins from cadherins (Sukumaran and Prasadarao 2003). Another study has described that brain microvascular endothelial cells (BMECs) monolayer leakage is increased upon *E. coli* interaction with Ec-gp96 (a receptor on human BMEC), via OmpA during invasion (Prasadarao 2002), which might lead to a disruption of BBB

integrity. Therefore, this review aims to elucidate the different mechanisms of BBB disruption that may occur by different types of bacterial pathogen, as well as to show the bacteria–host interactions that assist the bacterial pathogen in invading the brain. The role of some medically common bacteria on BBB disruption and the mechanisms which are responsible for the interactions between the cerebral host cell and the bacteria contributing to CNS entry are elucidated on. Therefore, obtaining knowledge of BBB disruption by bacterial infection will therefore provide a picture of how bacteria enter the CNS and could develop novel therapeutic strategies to combat these bacteria, particularly those responsible for meningitis.

BBB Structure

Preserving the homeostatic neural micro-environment of the brain is vital for normal neuronal activity and function, which is the role of the BBB. The BBB is a structural and functional barrier that controls the passage of any substances that can be transferred by blood cells into the brain (Abbott et al. 2006). Selective permeability is the main feature of BBB, where some substances are selected upon entering CNS. For examples, lipophilic molecules may pass the endothelial cells membranes and enter CNS, while, hydrophilic molecules encounter difficulties penetration into the brain (Levin 1980). The brain and neural function should be protected from any agents circulating such as neurotransmitters and xenobiotics by BBB function (Abbott et al. 2006). Additionally, BBB inhibits the entrance of pathogens and severely controls the entry of molecules into the brain parenchyma while promoting the efflux of several molecules (Brito et al. 2014). It is well known that CNS barriers including the BBB are able to provide a stable fluid microenvironment that is essential for neural function and protects the CNS tissue from any damage (Abbott et al. 2010). Thus, BBB is vital for restricting the access some of xenobiotics and metabolites to the CNS via taking out from the brain or blocking their entrance into the brain (De Lange 2004). BMECs that line cerebral microvessels are the main component of the BBB. Pericytes, astrocytes, and a basal membrane are the main periendothelial structures of the BBB (Moura et al. 2017). Pericytes and smooth muscle cells, which are surround and stabilize the endothelium, acting to reduce endothelial apoptosis, whereas astrocyte tasks include the support of CNS tissue. Scientifically, researchers utilize BMECs instead of the peripheral endothelial cells due to the fact that these types of cells have unique features including; many intercellular TJs that retains high transendothelial electrical resistance and hinder paracellular flux; fenestrae albescent and a decreased level of fluid-phase

endocytosis; and asymmetrically localized enzymes and carrier-mediated transport systems (Biegel et al. 1995).

Tight Junctions and its Adhesion Molecules in Cerebral Endothelial Cells

The apical end of the basolateral membrane is the main place of TJs, which play a major role in forming endothelial polarity. High transendothelial electrical resistance values of up to $2000 \Omega \text{ cm}^2$ due to TJs presence are existed, resulting in lesser paracellular permeability, as compared with other peripheral tissues ($3\text{--}33 \Omega \text{ cm}^2$) (Crone and Olesen 1982). TJs also aid to separate the apical and basolateral domains of the plasma membranes in epithelial cells, leading to inhibit the dispersion of integral proteins and lipids from one to the other (Tsukita et al. 2001). Occludin and claudins (Furuse et al. 1998), JAMs (Martin-Padura et al. 1998), and the endothelial cell-selective adhesion molecule (AM) are the essential membrane proteins of the cerebral microvasculature TJs (Nasdala et al. 2002). For example, PECAM-1 plays a main role in endothelial integrity and endothelial–leukocyte interactions (Privratsky and Newman 2014). A former study revealed that adhesion of *S. pneumoniae* to the BBB endothelium was intermediated by adhesion molecule expression of brain endothelial cells (Iovino et al. 2014). These four components are linked through cytoplasmic proteins (e.g., ZO-1, -2, -3, cingulin) to the actin cytoskeleton (Wolburg and Lippoldt 2002). ZO-1 is associated with TJ proteins and the actin cytoskeleton, which is essential for the steadiness, organization and signaling of TJ proteins. Any damage to or detachment of this protein from its counterparts may result in barrier permeability enhancement (Mukherjee et al. 2011).

Pathogenesis of Bacteria Correlated with Meningitis

The most common route for bacterial entrance into the meninges is through the hematogenous route and then through the BBB. It has been stated that meningeal pathogens can be disseminated via hematogenous pathogenesis into the cerebrospinal fluid (CSF) (Ferrieri et al. 1980; Huang et al. 1995; Heninger and Collins 2013). Former studies have described bacterial dispersal strategies, whereby bacteria successfully colonize the host respiratory mucosal epithelium, then invade the bloodstream and multiply, cross the BBB, and proliferate in the CSF (Kim 2003), such as in the case of *N. meningitidis* (Melican and Dumenil 2012). Additionally, adjacent sources such as otitis or sinusitis are another route which allows the bacteria to enter the CNS by CSF inoculation from several experimental models (Heninger and Collins 2013). Several species of bacteria,

including *S. pneumoniae* and *N. meningitidis*, secrete IgA1 proteases that cleave in the hinge region of IgA (Koedel et al. 2002), resulting in evasion of the immune response. Moreover, the epithelial and endothelial cells of the nasopharynx may be destroyed through bacterial adherence and colonization (Doran et al. 2016). For instance, during pneumococcal colonization, IgA1 protease, which exists in several pathogenic species of *Streptococcus*, is able to protect the pneumococcus from type-specific antibodies. On the other hand, IgA is the best effector element of the mucosal immune system. Once this component has been cleaved, the host defence is weakened (Janoff et al. 1999), leading to uncontrolled bacterial replication due to local immunodeficiency, that is the most probable cause of BBB penetration and disruption (Koedel et al. 2002).

On the other hand, it has been postulated that complex bacteria–host interaction was the main causative for neuronal injury. Once the bacteria proliferate in the CSF, the permeability of the BBB is enhanced, causing a penetration of inflammatory cells and the release of several pro-inflammatory substances. Consequently, this leads to damage of the neurons, edema, and secondary neuronal damage (Koedel et al. 2002). On the contrary, it has recently been found that BBB dysfunction is related to CNS diseases due to neuro-inflammation (Weiss et al. 2009). Remarkably, IL-17 is able to disrupt brain endothelium TJs, because of CD4 + IL-17-producing T lymphocytes (Th17) which were recently recognized as the main factor in disease progression (Miller et al. 2007). Moreover, penetration of Th17 lymphocytes across the BBB may occur by discharging chemokines, and acquiring dendritic cells in the infection sites (Kebir et al. 2007). Thus, BBB permeability is linked with leukocyte infiltration in the brain, leading to CNS neuro-inflammation.

The Correlation Between Inflammatory Response and BBB Disruption in Meningitis

Several brain cells such as glial cells, astrocytes, endothelial cells, ependymal cells, and resident macrophages are the main source for cytokines and pro-inflammatory molecules (TNF- α , IL-1 β , IL-6, IFN- γ , and chemokines) secretion in response to bacterial reproduction (Moreillon and Majcherczyk 2003). For example, TNF- α is considered to be a pro-inflammatory molecule which acts to enhance the immune response for pathogen elimination (Kronfol 2000). This inflammatory molecule aids to activate nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) in the brain cells, which controls the expression of several pro-inflammatory mediators (Ichiyama et al. 2002). An earlier report has shown that TNF- α was increased in the first 6 h of pneumococcal meningitis in animal models (Barichello

et al. 2010), this might lead to BBB disruption (Rosenberg et al. 1995). Additionally, Dinarello (2005) has reported that neutrophil and monocyte adhesion in endothelial cells is encouraged by IL-1 β to eliminate the bacterial pathogen. A previous study revealed that IL-1 β was increased in the CSF of patients with bacterial meningitis (Østergaard et al. 2004), as well as in animal models where it was raised in the first 24 h after pneumococcal meningitis induction (Barichello et al. 2010) by increasing the endothelium permeability. Furthermore, monocytes, endothelial cells, and astrocytes also produce IL-6 in response to IL-1 β (Parizzi et al. 1991). IL-1 β has pro-inflammatory effects, as a potent inducer of acute-phase proteins, fever and leukocytes (Gruol and Nelson 1997) and it also has a second function as an anti-inflammatory cytokine. Indeed, vascular permeability was declined and inflammatory response was increased upon IL-6 deficiency in bacterial meningitis (Paul et al. 2003). In contrast, it has been shown that defence against bacterial pneumonia was compromised in mice which lack IL-6 (van der Poll et al. 1997). B and T lymphocytes, macrophages, monocytes, and brain cells (neurons and microglia) are able to produce IL-10, which is considered as a potent immunosuppressive cytokine (Howard and O'Garra 1992). Elevated levels of this cytokine have been found in the CSF of patients with bacterial meningitis (Kornelisse et al. 1996), resulting in deactivation of macrophages and monocytes, which subsequently inhibits the production of cytokines such as TNF- α and IL-6 and then enhances reactive oxygen species (ROS) formation (Koedel et al. 1996). A lack of IL-10 in mice was linked with higher levels of TNF- α and IL-6 in animal models of pneumococcal meningitis (Zwijnenburg et al. 2003). Therefore, we understand from these previous studies that all these cytokines and pro-inflammatory molecules contribute to an increase in endothelial cell permeability, subsequently disrupting the BBB, particularly in meningitis infected by bacterial pathogens (Rosenberg et al. 1995).

Cell Movement Across the BBB

For any pathological condition in CNS, mononuclear leukocytes, monocytes, and macrophages are recruited, playing complementary roles to those of the resident microglia (Davoust et al. 2008). During BBB inflammation, mononuclear cells and circulating neutrophils are attracted to the site of infection, leading to penetration of the barrier and production of cuffs in the perivascular space around small vessels particularly venules; where immune response can be coordinated by this perivascular space (Konsman et al. 2007). Additionally, cytokines and other agents and mononuclear cells are also recruited upon BBB inflammation to open the TJs between endothelial cells, then it may enter by transcellular and paracellular routes (Konsman et al. 2007).

Nevertheless, in normal BBB, the diapedesis process may occur, by which mononuclear cells penetrate through the cytoplasm of the endothelial cells directly, but not via the paracellular route, which involves TJ opening (Wolburg et al. 2005).

Gram-Positive Bacteria and BBB Disruption

Endothelium barrier integrity may be affected by several meningeal pathogens, including Gram-positive bacteria. Several factors may contribute in endothelium barrier integrity including direct toxic effects; interfering specifically with AJs, which are an element of cell–cell junctions between neighboring cells, and TJ formation or by a high expression of inflammatory cytokines, chemokines, and molecules (Fig. 1). For instance, *S. pneumoniae* and GBS stimulate barrier disruption through secreting a pore-forming toxin in infected BMECs (Nizet et al. 1997; Zysk et al. 2001; Lembo et al. 2010). Based on previous studies, meningitis is initiated by GBS, which is associated with higher toxin production through a process involving IL-8 and ICAM-1 enhancement (Doran et al. 2003). Moreover, as mentioned earlier, the host response to infection can harmfully affect BBB function via a high expression of inflammatory cytokines, chemokines and molecules. Previous studies have shown that a higher level of TNF- α is associated with BBB permeability in infant rats infected with *S. pneumoniae* (Barichello et al. 2011b). It is reported that BBB invasion has occurred during the pneumococcal adhesion into the brain endothelial cells receptors such as PECAM-1 and pIgR, together with PAFR (Iovino et al. 2016, 2017). Moreover, *S. pneumoniae* and GBS enhance nitric oxide (NO) production from endothelial cells via expression of inducible nitric oxide synthase (iNOS) enhancement (Leib et al. 1998; Winkler et al. 2001), this might lead to disruption of BBB integrity (Mittal and Prasadaraio 2010). Additionally, *B. anthracis* has the ability to affect both AJs and TJs via secreted non-pore-forming factors including lethal

toxin complexes, proteases, and edema (van Sorge and Doran 2012). Similarly, former studies have revealed that immune inhibitor A (InhA), a metalloprotease that exists in specific types of bacteria as a toxin agent, disrupts ZO-1, a TJ component (Ebrahimi et al. 2009, 2011; Mukherjee et al. 2011), indicating BBB disruption. Thus, in the following paragraphs below, specific Gram-positive bacteria related to BBB disruption mechanisms and bacterial–host interactions that facilitate brain invasion are reviewed in details.

Streptococcus pneumoniae

Genus *Streptococcus* consists of several species, *S. pneumoniae* is one of them. It is alpha-hemolytic or beta-hemolytic and facultative anaerobic (Kenneth and Ray 2004). *S. pneumoniae* is identified as the main cause of pneumonia in several humoral immunity studies. Respiratory tract, sinuses, and nasal cavity are the most colonized parts by *S. pneumoniae* asymptotically in healthy subjects. However, individuals with compromised immune systems, especially young children and the elderly, are more susceptible to this bacterium, as the bacteria may become more pathogenic and spread to other sites to cause disease, and can be a cause of neonatal infections (Baucells and Hally et al. 2016). Infants and adults are diagnosed with pneumococcus by 40% and 15% respectively, where human nasopharynx mucosa is considered the main habitat of pneumococcus (Barichello et al. 2012a). Coughing and sneezing are the two main ways where the bacteria is transferred to people. The main *S. pneumoniae*-related diseases are community-acquired pneumonia and meningitis in children and elderly (van de Beek et al. 2006). Polysaccharide capsule is one of the main component of this bacterium, functioning as a virulence factor for the microorganism. There are approximately more than 90 various serotypes identified within this species, which differ in virulence, prevalence, as well as level of drug resistance. This bacterium can also induce meningitis, which shows signs and symptoms including vomiting, headache, photophobia, stiff neck, fever nausea, and mental status changes

Fig. 1 Mechanisms of BBB disruption, and bacterial–host interactions upon Gram-positive bacterial infection

including lethargy and confusion (Heninger and Collins 2013). According to Cundell et al. who is the first author confirmed that PAFR serves as a ligand for *S. pneumoniae* that has surface-exposed phosphorylcholine on their surface, where PAFR mediates pneumococcal infection in respiratory cells (Cundell et al. 1995). Former studies have found that several receptors are responsible for brain invasion during the adhesion of pneumococci to brain endothelial cells such as PECAM-1 and pIgR, together with PAFR (Radin et al. 2005; Iovino et al. 2013a, 2016). Similarly, another study has been conducted by Iovino et al. (2017), who stated that pneumococcal pilus-1, RrgA, bound into the two BBB endothelial receptors: (pIgR) and PECAM-1, contributing to brain invasion. In the same study, pneumococcal entry was prevented into the brain and meningitis improvement by using a bacteremia-derived meningitis model and mutant mice, as well as antibodies against those two receptors. Likewise, *S. pneumoniae* CbpA targets the common carboxy-terminal domain of the LR establishing initial contact with brain endothelium in experimental meningitis models (Orihuela et al. 2009) that might result in BBB penetration. Similarly, CbpA enables pneumococci to adhere and colonize the nasopharyngeal through binding to pIgR (Zhang et al. 2000). Moreover, previous study proved that CbpA is responsible in adherence activity by recruiting a vacuole targeted for transcytosis upon pneumococci, proposing CbpA interacts with the PAFR and serve as a pneumococcal element driving the transcytotic mechanism, consequently, BBB might be invaded and crossed (Ring et al. 1998). Additionally, Neuraminidase A (NanA) which is a surface protein, is expressed by *S. pneumoniae*, which promoted infiltration of the BBB by inducing chemokine discharge from brain endothelial cells (Uchiyama et al. 2009; Banerjee et al. 2010). Moreover, pneumolysin of pneumococci has able to breach endothelial cells, then enter CNS (Zysk et al. 2001). It is proposed that pneumolysin neutralization might be a potential approach for new therapeutic intervention for pneumococcal diseases treatment (Hirst et al. 2004). Therefore, the disruption or modulation of the interaction between *S. pneumoniae* bacterial adhesins and LR, PECAM-1, pIgR and PAFR and pneumolysin might encourage a researchers to explore effective therapeutic agent treating pneumococcal bacterial meningitis, as shown in (Fig. 1) (Orihuela et al. 2009; Iovino et al. 2016).

As mentioned before, former study reported that cytokines and pro-inflammatory molecules (TNF- α , IL-1 β , IL-6, and IL-10) can be produced in response to bacterial replication in several brain cells (Moreillon and Majcherzyk 2003). In term of pneumococcal meningitis, TNF- α , IL-1 β , IL-6, and IL-10 are increased to enhance the immune response for pathogen elimination (Kornelisse et al. 1996; Paul et al. 2003; Østergaard et al. 2004). A previous report has described that BBB integrity can be affected due to

micro-organisms releasing and expressing cytokines, chemokines, and cell-adhesion molecules, resulting in a developing BBB disruption (Kim 2003). Thus, the increase of pro-inflammatory markers may have an adverse effect; disrupting the BBB and increasing endothelial permeability (Barichello et al. 2010) for this bacterium. Additionally, it has been revealed that CINC-1 levels were also augmented, related with BBB breakdown between 12 and 24 h in the hippocampus and at 12 and 18 h in the cortex, in wistar rats infected with *S. pneumoniae* (Barichello et al. 2012b). CINC-1 is a neutrophil chemoattractant and may be associated to events in pneumococcal meningitis pathophysiology, due to its ability to promote leukocyte migration (Barichello et al. 2012b). TNF- α plays an essential role in bacterial meningitis related to brain damage (Sellner et al. 2010). Besides, IL-1 β also encourages BBB injury and meningitis in the animal model (Quagliarello et al. 1991); thus, chemokine secretion is normally persuaded by pro-inflammatory cytokines (Baggiolini et al. 1993). In contrast to the studies mentioned above, it has been reported that adhesion, invasion and translocation through or between endothelial cells can be done by *S. pneumoniae* without any disruption to the vascular endothelium, upon BBB penetration, suggesting that an intracellular or paracellular path is used for BBB translocation (Iovino et al. 2013b). The pneumococcal pathogens cross the BBB by several ways: for example pneumococcal pneumolysin destruct the endothelial cell layers (Marriott et al. 2008). While in another study, BBB can be crosses between the cells via TJs disruption, in *S. pneumoniae* (Attali et al. 2008). Additionally, BBB might be transversed by transcytosis process, where an intracellular transport route designed to transport molecules and vesicles through cells from the apical to basolateral side (Ring et al. 1998).

Listeria monocytogenes

Listeria monocytogenes is facultative intracellular bacterium, which causes invasive diseases in humans and animals, such as CNS infections (Vázquez-Boland et al. 2001). Contaminated food is the main source of *L. monocytogenes* infection in humans. An epidemiological study of bacterial meningitis in the United States in 1995, showed that *L. monocytogenes* is approximately tenfold more effective at invading the CNS than other neuroinvasive Gram-positive bacteria, including *S. pneumoniae* and GBS (Schuchat et al. 1997). Bacterial meningitis are mostly caused by *L. monocytogenes* in Western Europe and North America (Kyaw et al. 2002). There are increasingly more studies concerning CNS infections caused by *L. monocytogenes*, which report the mechanisms of how the bacteria enter the CNS and disrupt the BBB. *L. monocytogenes* is distinctive among neuro-invasive bacteria where in vitro and in vivo data propose that it has the possibility to enter the CNS by several various mechanisms (Drevets et al.

2004). These mechanisms include (1) transportation across the BBB within parasitized leukocytes, (2) direct invasion of endothelial cells by extracellular hematogenous spread, or (3) retrograde (centripetal) migration into the brain within the axons of cranial nerves (Drevets et al. 2004). Internatins (InlA and InlB) are the main pathogenic proteins of *L. monocytogenes* that interact with its cellular receptors E-cadherin and mesenchymal-epithelial transition (MET), respectively, for intestinal and placental barriers crossing purposes. Therefore, there is one potential explanation stating that *L. monocytogenes* might cross BBB, due to these receptors are expressed at the surface of choroid plexus epithelial cells, and MET which is also expressed at the brain endothelial level, leading these mechanisms might to occur for blood-CSF and BBB crossing purposes (Gründler et al. 2013). In vitro studies showed that *L. monocytogenes* can enter and reproduce inside a wide variety of endothelial cells such as the umbilical vein and BMECs (Drevets et al. 2004), and might lead to an increase in the permeability and disruption of the BBB. Similarly, previous analysis has also revealed that the invasion protein InlB of *L. monocytogenes* mediates invasion of BMECs and human umbilical vein endothelial cells (HUVEC) in vitro (Greiffenberg et al. 1998, 2000; Parida et al. 1998). Additionally, listeriolysin O (LLO) is the pore-forming toxin that allows *L. monocytogenes* to activate NF- κ B cultured endothelial cells. In brain microvessels, LLO facilitates and enhances the expression of the surface adhesion molecules P- and E-selectin, ICAM-1 and Vascular cell adhesion protein 1 (VCAM-1), as well as IL-6 and IL-8 and MCP-1, allowing neutrophil and monocyte adhesion to the endothelial cells (Kayal et al. 2002). These effects may disrupt BBB function and lets *L. monocytogenes* access the CNS. Nine humans who died of brainstem encephalitis revealed that the inflammatory profiles infiltrate inside nuclei, tracts, and intra-parenchymal parts of cranial nerves in different areas of the oropharynx after a careful analysis of autopsy (Antal et al. 2005). Therefore, it is clear that adherence molecules, as well as inflammatory markers, are the main factors stimulating endothelium permeability, which then leads to BBB disruption.

In terms of therapeutic purposes, as mentioned earlier, it has been suggested that NF- κ B activation in endothelial cells plays a main role in *L. monocytogenes* crossing the BBB (Kayal and Charbit 2006). There are two pathways to activate NF- κ B. First, LLO stimulates I κ B kinase β -dependent phosphorylation of the physiological NF- κ B inhibitor I κ B α , followed by proteasomal degradation of the latter, subsequently allowing nuclear translocation of NF- κ B (Kayal et al. 2002). InlC directly binds with IKK α , a subunit of the I κ B kinase complex critical for the phosphorylation of I κ B and NF- κ B activation (Gouin et al. 2010). Second, *L. monocytogenes* has been demonstrated to activate mitogen-activated protein kinase (MAPK) through LLO early in infection

(Tang et al. 1994) upon escape from the phagosome (Opitz et al. 2006). The MAPK cascade has been involved both in bacterial entry into endothelial cells (Tang et al. 1998) and in the induction of cytokine expression in vitro (Schmeck et al. 2005) and in vivo (Lehner et al. 2002). As a result, all these markers for NF- κ B, MAPK, InlA and InlB activations are responsible for *L. monocytogenes* spreading into the brain; however, targeting them will facilitate the reduction of the pathogenesis and may be considered as a potential therapeutic agent against meningitis.

Bacillus anthracis

Rod-shaped and spore-forming are the main traits of *Bacillus anthracis*. The main disease related to *B. anthracis* infection is anthrax, which has three different clinical forms depending on the major routes of infection: cutaneous, inhalational, and gastrointestinal (Inglesby et al. 2002). All types of anthrax can be fatal if left untreated as it leads to the systemic spreading of this lethal bacteria through lymphatic and hematogenous routes. A previous clinical case report has shown that this type of bacteria disperses to the brain, subsequently resulting in haemorrhagic meningitis (Inglesby et al. 2002). In Sverdlovsk-Russia, 50% of fatal haemorrhagic meningitis infected with *B. anthracis* was recorded during the epidemic of anthrax inhalation (Inglesby et al. 2002). In another study, anthrax histological analysis was shown that the secreted pathogenic factors such as InhA induces BBB destruction, by making it leaky and permeable (Inglesby et al. 2002; Ramarao and Lereclus 2005). Numerous mechanisms are involved for pathogenicity by this factor (InhA) upon *B. anthracis* infection, such as escape of bacteria from macrophages, cleavage of antibacterial proteins, control of blood coagulation, and degradation of matrix-associated proteins (Ramarao and Lereclus 2005; Chung et al. 2008, 2009; Kastrop et al. 2008; Guillemet et al. 2010). A previous study has shown that InhA and BsIA invade the endothelial cells by breaking down the TJ protein (ZO-1), thus contributes to hemorrhaging in the CNS via BBB disruption in vitro and in vivo (Ebrahimi et al. 2009). Similarly, purified anthrax lethal toxin-induced human lung microvascular endothelial cells permeability occurred through TJ disruption (Warfel et al. 2005). Additionally, BsIA of *B. anthracis* acts as a global adherence factor for anthrax disease pathogenesis, where the adherence to BMEC was reduced by the BsIA-deficient mutant in vitro, related with a decreased risk for development of CNS infection in vivo (Kern and Schneewind 2010). Moreover, anthrax lethal toxin also enhances endothelial barrier dysfunction, leading to vascular leakage following intraperitoneal injection (Gozes et al. 2006). There is one explanation shows how this bacterium penetrate the brain described by van Sorge et al. (2008). van Sorge et al. (2008) reported that *B. anthracis* infected-BMEC enhanced

the neutrophil recruitment response into the infection sites. Nevertheless, the innate defence pathway was down-regulated upon the presence of the toxin-encoding pXO1 plasmid of *B. anthracis* (van Sorge et al. 2008). This result leads to inhibition of the neutrophil chemotaxis, allowing the dissemination of the bacteria into the CNS (van Sorge et al. 2008).

Therefore, it is clarified that *B. anthracis* surface-associated adhesin may encourages BMEC binding and BBB infiltration, contributing to the pathogenesis of *B. anthracis*-caused meningitis. As a result, pXO1, InhA, and BslA may serve as an attractive new target for drug or vaccine development, aiming to inhibit development of the disease upon systemic anthrax infection.

Staphylococcus aureus

Staphylococcus aureus is a facultative anaerobe and round-shaped bacterium which is often found in the nose, on the skin, and in respiratory tract. Although *S. aureus* is not always pathogenic, skin infections including abscesses (Esen et al. 2010), respiratory infections such as sinusitis (Manarey et al. 2004; Huang and Hung 2006), and food poisoning are common causes of it (Chiang et al. 2008). Virulence factors of pathogenic strains such as potent protein toxins and expression of a cell-surface protein that interacts and inactivates antibodies, may stimulate infections (Bebington and Yarranton 2008). Although many studies have been conducted on various aspects biologically and epidemiologically, there has yet to be any approved vaccine for *S. aureus*. Additionally, it is considered the most prevalent opportunistic bacterial pathogen responsible for community- and hospital-acquired infections worldwide. The mortality rate associated with *S. aureus*-mediated sepsis and meningitis is 36% (Aguilar et al. 2010). The varied range of proteins on its surface, act as virulence factors that assist the bacterium to adhere and invade host cells, including vascular endothelial cells (Foster et al. 2014). McLoughlin et al. (2017) have demonstrated that BMEC permeability was induced due to *S. aureus* infection via the reduction of VEC, claudin-5 and ZO-1 in a dose-dependent manner. The main mechanism of BBB disruption due to junctional protein disruption is related to pro-inflammatory cytokine signaling, which is associated with ROS generation (Rochfort and Cummins 2015; Rochfort et al. 2016). There is a strong correlation between ZO-1 levels and ROS signaling. It is found that the ZO-1 was disrupted in murine cells upon exposure to hypoxia with reoxygenation (MHR) due to Nicotinamide adenine dinucleotide phosphate (NADPH) activation. Additionally, ZO-1 was also disrupted in murine BMECs treated with oxidized low-density lipoprotein (ox-LDL) (Wang et al. 2012) and Amyloid β Protein Fragment 1–42 (A β 1–42) (Carrano et al. 2011) approved by NADPH

oxidase enhancement. It is shown that high mRNA expression levels of several cytokines: IL-1 α , IL-1 β , IL-6, TNF- α , MCP-1, and macrophage inflammatory proteins-1 alpha (MIP1 α) in *S. aureus* infected rat brain abscess models, have led to BBB disruption (Kielian and Hickey 2000). In addition, *S. aureus* infection induced IL-6 production in HUVEC (Park et al. 2007). ROS generation has also been observed in *S. aureus* infection especially in neutrophils, monocytes, macrophages, and resident bone marrow stem cells (Nandi et al. 2015), resulting in enhancement of the inflammatory response. Furthermore, it has been shown that the expression of adhesin protein (SpA) protein is also able to increase BMEC permeability, accompanied by VEC protein reduction and NF- κ B/p65 activation by this pathogenic bacteria (McLoughlin et al. 2017). As a result, barrier integrity maybe disrupted due to *S. aureus* infection of BMECs through induction of pro-inflammatory cytokines, oxidative stress, and NF- κ B activation, in parallel with the reduction of TJ protein expression. For therapeutic purposes, a previous study has demonstrated a role for membrane-anchored lipoteichoic acid (LTA), mediating *S. aureus* adhesion and cellular invasion into immortalized human BMECs, resulting in BBB penetration (Sheen et al. 2010). A previous report has also shown that IL-17 enchantment of the host defence circuit may offer a basis for innovative therapeutic approaches to treat *S. aureus* infectious diseases (Cho et al. 2010). Accordingly, to prevent the disease development during this bacterial infection, it is speculated that LTA, IL-17 and SpA may serve as an attractive new target for drug or vaccine development.

Streptococcus agalactiae

Catalase-negative, beta-hemolytic, and facultative anaerobe are the characteristics of *Streptococcus agalactiae*, or group B *Streptococcus* (GBS). GBS is a harmless human microbiota colonizing the genitourinary and gastrointestinal tracts of up to 30% of healthy adults, asymptotically. Nevertheless, severe invasive infection might occur due to GBS (Edwards and Baker 2005). Polysaccharides (exopolysaccharide) is the main component of GBS which surrounds the bacterial capsule. Based on the GBS capsular polysaccharide immunologic reactivity, 10 GBS serotypes have been identified (Ia, Ib, II, III, IV, V, VI, VII, VIII, IX) (Rosa-Fraile et al. 2014). It is found that serotype III of GBS has been related to meningitis (Edmond et al. 2012) and other types of diseases (Whidbey et al. 2013, 2015; Leclercq et al. 2016). Meningitis is the most common disease related to GBS in neonates (Brouwer et al. 2010). Although intensive care management and antibiotic treatment are applied, the mortality rate is still 10%, while 25–50% of survivors show neurological sequelae, such as seizures, mental retardation, deafness, blindness, and cerebral palsy (Edwards and Baker

2005). Several virulence factors exist in GBS contributing to the interaction with brain endothelium, such as LTA (Doran et al. 2005), β -hemolysin / cytotoxin (β -H/C) (Doran et al. 2003), pili (Maisey et al. 2007; Banerjee et al. 2011a), serine-rich repeat (Srr) proteins (van Sorge et al. 2009; Seo et al. 2012), and hypervirulent GBS adhesion (HvgA) (Tazi et al. 2010). Surprisingly, GBS crosses the BBB without any evidence of intracellular TJ disruption or detection of microorganisms between cells (Kim 2008). Lately, it has been proved that the GBS pilus protein PilA and Srr-1 bind with host extracellular matrix (ECM) components, stimulating BBB disruption and the enhancement of meningitis (Banerjee et al. 2011a; Seo et al. 2012). Specific microorganisms can proliferate within the CSF, resulting in release of bacterial components, which encourage the release of neuro-inflammatory molecules (Yadav et al. 2009). Cytokines and other pro-inflammatory molecules such as TNF- α , IL-1 β , and IL-6 can be induced by various brain cells, in response to bacterial stimuli (Moreillon and Majcherzyk 2003), subsequently, other cascade of inflammatory mediators are triggered such as MMP, MPO and ROS. As mentioned earlier, cytokines themselves may contribute to impairment of the BBB and brain damage (Miric et al. 2010). A previous study has measured the levels of cytokine, chemokine, MPO, and oxidative stress in the hippocampus and cortex of neonatal wistar rats in a meningitis model induced by GBS (Barichello et al. 2011a). The data demonstrated that the levels of MPO, cytokine-induced CINC-1, IL-1 β , IL-6, IL-10, and TNF- α were increased after GBS infection in the hippocampus (Barichello et al. 2011a). It is speculated that neonatal bacterial infections of the CNS are severe, where complex network of cytokines and chemokines, other inflammatory mediators and oxidants tend to amplify the disease and might lead to BBB destruction (Barichello et al. 2011a). Neutrophilic penetration during acute bacterial meningitis was noticed, where pilus protein (PilA) mediates GBS attachment to the brain endothelium (Banerjee et al. 2011b). In vivo study has shown higher levels of bacterial

CNS penetration and BBB permeability are associated with increased neutrophilic infiltrate (Banerjee et al. 2011a). Thus, we may speculate from previous studies that the pro-inflammatory cytokines and chemokines are the main causative agent of BBB integrity in GBS infection.

In terms of therapy strategies, a previous study has demonstrated that Srr-1, which are glycoproteins responsible for adhesion function, mediating the interaction of GBS to fibrinogen, the major protein in human blood. This interaction probably takes place through a DLL-like mechanism, involving the C-terminus of the fibrinogen A α chain. It is shown that this adhesion marker binds to fibrinogen by DDL as a general mechanism for attachment by Gram-positive organisms to the host cell. The most important point is that this binding of Srr-1 to fibrinogen seems to be vital for the bacterium adherence to brain endothelium and then meningitis development. Additionally, PilA interacts with the extracellular matrix component collagen, which then involves α 2 β 1 integrins on brain endothelium to stimulate bacterial attachment and pro-inflammatory chemokine release. As a result, Srr-1 and PilA appear to be expressed by most clinical isolates of GBS, therefore this bindings might confirm to be a favorable candidate for innovative therapies targeting bacterial pathogen (Banerjee et al. 2011a; Seo et al. 2012).

Gram-Negative Bacteria and BBB Disruption

In terms of meningeal pathogens, Gram-negative bacteria have also able to target AJ protein and VEC, by using their surface adhesion molecules to exploit brain endothelial cell signaling to enhance paracellular translocation (Coureuil et al. 2009, 2010). Brief mechanisms have been shown in Fig. 2, illustrating the main markers which are responsible for BBB disruption upon Gram-negative bacterial infection. For example, attachment of meningococci (type IV pili) to brain endothelial cells acts to disrupt AJ formation, subsequently opening up the paracellular route for

Fig. 2 Mechanisms of BBB disruption, and bacterial-host interactions upon Gram-negative bacterial infection

the translocation into the CNS, leading to meningococcal meningitis (Coureuil et al. 2009). In addition, this category of bacteria might stimulate specific cleavage of the TJ component occludin through the release of host MMP-8, causing endothelial cell detachment and developed paracellular permeability (Schubert-Unkmeir et al. 2010). In addition, IL-6 levels were increased significantly in Gram-negative bacteria infection (Abe et al. 2010). Therefore, this group of bacteria may disrupt the BBB via TJ and AJ deformation and also enhance pro-inflammatory parameters in the case of meningitis. Therefore, in the following paragraphs below, specific Gram-negative bacteria related to BBB disruption mechanisms and bacterial-host interactions that facilitate brain invasion are reviewed in detail.

Haemophilus influenzae

Haemophilus influenzae is a Gram-negative, facultative anaerobic, and pathogenic bacterium belonging to the Pasteurellaceae family. Globally, HiB is one of the most common types of this bacterium that causes meningitis in infants and adults. In the 1980s, half of the cases of meningitis which lead to death in infants were due to HiB alone, before the conjugate HiB vaccine was introduced. However, the cases decreased dramatically (78%) following routine vaccination (Peltola 2000). Nevertheless, lack of HiB vaccination programs in developing countries (Peltola 2000), 173,000 cases of meningitis are recorded globally (Watt et al. 2009). Basically, vaginal tracts, skin and upper respiratory tracts of healthy people could be colonized by HiB. In addition, HiB carriage (transient or intermittent) is able to remain asymptotically (Stephens 1999). The main portals that let HiB enter the CNS are LR and PAFR, subsequently *H. influenzae* pathogens might cause meningitis (Swords et al. 2001). Similarly, *H. influenzae* OmpP2 has the ability to target the common carboxy-terminal domain of LR to start initial interaction with brain endothelium (Orihuela et al. 2009). According to several studies, it was stated that *Haemophilus* species pili probably interacted with PAFR on brain endothelial cells (Kolberg et al. 1997; Weiser et al. 1998). Thus, it is suggested that LR and OmpP2 (See Fig. 2) are a potential therapeutic target to block BBB infiltration upon *H. influenzae* infection (Orihuela et al. 2009).

It has been shown that pili of HiB or fibrils can interact with BMEC (St. Geme and Cutter 1995, St Geme 3rd and, 1996). Additionally, it has also been revealed that BBB permeability might occur by HiB lipopolysaccharide (Patrick et al. 1992) through damaging the brain cells in vivo (Wellmer et al. 2002; Doran et al. 2003). Furthermore, disruption of intercellular TJs was also observed upon *H. influenzae* infection by alterations of the BBB functionally and morphologically in animal models (Quagliarello et al. 1986; Schubert-Unkmeir et al. 2010). As previously described,

neutrophil infiltration also encourages BBB permeability (Banerjee et al. 2011a). Interestingly, HiB meningitis outcomes have been improved after the prevention of leukocyte infiltration into the CNS using anti-CD18 antibody (Tuomanen et al. 1989; Saez-Llorens et al. 1991). Thus, it can be suggested that the TJ deformation that occurs upon *H. influenzae* dissemination is the sole mechanism responsible for BBB disruption.

Neisseria meningitidis

Meningitis and other forms of meningococcal disease such as meningococemia, a life-threatening sepsis can be caused by Gram-negative bacteria, where *Neisseria meningitidis* is one of them. Nasopharynx is the main reservoir of this bacterium carried by 10% of adults (Stephens 2007). In addition, skin, upper respiratory, and vaginal tract are the other places for *N. meningitidis* colonization in healthy individuals. Death in 10% children and youth adults have been estimated due to this type of bacteria. Saliva and respiratory secretions are the main factors for *N. meningitidis* dissemination during such activities such as chewing, kissing and coughing (Er et al. 2009). Notable, several serotypes which belong to *N. meningitidis* are limiting the vaccination strategies against it (Gray et al. 2006). Therefore, the possible way to treat meningococcal meningitis infected by *N. meningitidis* is a vaccine that includes all serotypes, or when there is preserved antigen that exists in all disease isolates. Although, this bacterium is sometimes stable, transient (Stephens 1999) and often remain asymptomatic in the carriage, however, the bacteria may penetrate host cellular barriers to start local infection leading to systemic spreading. The adherence of *N. meningitidis* to cell host can be occurred by pili and other virulence factors such as surface-exposed Opa and Opc proteins. Similar to *S. pneumoniae*, pili or fibrils are the main organelles that can be utilized by *N. meningitidis* to initiate binding to BMECs. The first mechanism of BBB penetration in the presence of this bacterium is that the bacterial adhesins (PilQ), targets a common carboxy-terminal domain of LR to establish initial contact with the brain endothelium that might lead to bacterial pathogen invasion into the brain (Orihuela et al. 2009). The other determinants of host cell binding are existed upon this bacterium infection are complex protein (ACP) as well as the autotransporter meningococcal serine protease A (MspA) (Virji 2009). Thus, all these markers are mentioned above might be considered as the main target for therapeutic purposes in *N. meningitidis* meningitis.

To show the similarities and differences between three types of bacteria (*S. pneumoniae*, *S. agalactiae*, and *N. meningitidis*), Table 1 has illustrated the mechanisms of BBB disruption and bacterial-host interaction sites that enabling brain invasion among these types of bacteria.

Table 1 Illustration of the BBB disruption mechanisms and the bacterial–host interaction sites among 3 different types of bacteria (*S. pneumoniae*, *S. agalactiae* and *N. meningitidis*)

<i>S. pneumoniae</i>	<i>N. meningitidis</i>	<i>S. agalactiae</i>
<p>The main <i>S. pneumoniae</i>-related disease in children and elderly is meningitis</p> <p>TNF-α, IL-1β, IL-6 and IL-10, and CINC-1 are usually increased after <i>S. pneumoniae</i> infection in order to enhance the immune response for pathogen elimination (Kornelisse et al. 1996; Paul et al. 2003; Østergaard et al. 2004; Barichello et al. 2012b), which most probably leads to BBB disruption</p> <p>Adhesion, invasion and translocation through or between endothelial cells occurs after <i>S. pneumoniae</i> infection without any disruption to the vascular endothelium, upon BBB penetration, suggesting that an intracellular or paracellular path is used for BBB translocation (Iovino et al. 2013b)</p> <p>The disruption or modulation of the interaction between <i>S. pneumoniae</i> bacterial adhesins and LR, IPECAM-1, pIgR, PAFR might encourage pneumococcal bacterial meningitis (Orihuela et al. 2009; Iovino et al. 2016)</p> <p><i>S. pneumoniae</i> bacterial adhesins and LR, IPECAM-1, pIgR, PAFR and pneumolysin can be an effective therapeutic agent in treating pneumococcal bacterial meningitis (Orihuela et al. 2009; Iovino et al. 2016)</p>	<p>Meningitis can be caused by <i>N. meningitidis</i> in children and young adults</p> <p><i>N. meningitidis</i> triggers IL-6 and IL-8 production in BMECs by activating MAPK pathways (Sokolova et al. 2004; Banerjee et al. 2010, 2011a)</p> <p>Meningococci species induces AJ deformation (VE-cadherin), subsequently, the bacterial pathogen penetration into the CNS occurs, due to the opening up of the paracellular route (Coureuil et al. 2009)</p> <p><i>N. meningitidis</i> is able to disrupt TJ components (occluding) via MMP-8 production, leading to endothelial cell detachment and developed paracellular permeability (Schubert-Unkmeir et al. 2010)</p> <p>PilQ targets a common carboxy-terminal domain of LR PAFR to establish initial contact with the brain endothelium that might lead to bacterial pathogen invasion into the brain (Orihuela et al. 2009)</p> <p>PilQ, LR and PAFR, might be considered as the main targets for therapeutic purposes in <i>N. meningitidis</i> meningitis (Orihuela et al. 2009)</p>	<p>Meningitis is the most common disease related to GBS in neonates</p> <p>MPO, CINC-1, IL-1β, IL-6, IL-10 and TNF-α are also increased in the hippocampus after GBS infection (Barichello et al. 2012b), which might lead to BBB disruption</p> <p>GBS is also able to cross the BBB without any evidence of intracellular TJ disruption or detection of microorganisms between cells (Kim 2008)</p> <p>GBS pilus proteins PilA and Srr-1 bind to host ECM components, stimulating BBB disruption and penetration (Banerjee et al. 2011a; Seo et al. 2012)</p> <p>Srr-1 and PilA appear to be a favourable candidates for innovative therapies targeting bacterial virulence (Banerjee et al. 2011a; Seo et al. 2012)</p>

The mechanism for BBB disruption is via inflammatory activation of brain endothelial cells by cytokines, which are typically elevated in meningitis patients (Fida et al. 2006; Nagesh Babu et al. 2008), where it can stimulate host receptor expression, resulting in an enhanced bacterial invasion. A former study has revealed that *N. meningitidis* triggers IL-6 and IL-8 production in BMECs by activating MAPK pathways (Sokolova et al. 2004; Banerjee et al. 2010, 2011a), that most probably resulted in BBB disruption. The other mechanism of BBB disruption in this bacterium is through AJ and TJ deformation. A former study has shown that pili (Type IV) bind to BMECs in meningococci species inducing AJ deformation, by reducing one of its components (VEC), subsequently, the bacterial pathogen penetrates into the CNS, due to the opening up of the paracellular route (Coureuil et al. 2009). Similarly, *N. meningitidis* has able to disrupt TJ component (occluding) via MMP-8 production, leading to endothelial cell detachment and developed paracellular permeability (Schubert-Unkmeir et al. 2010). Overall, all these studies, it is found that *N. meningitidis* may disrupt the BBB via accelerated cytokine expression and cause a defect in TJ components resulting in expression of MMP-8, subsequently enhancing paracellular permeability.

Escherichia coli

The lower intestine of warm-blooded organisms is the main place of *Escherichia coli*. *E. coli* is facultatively anaerobic and coliform bacterium (Tenaillon et al. 2010). Most of *E. coli* strains are harmless, which produce vitamin K2, and in the same time prevent any colonization of the intestine with pathogenic bacteria, as these strains are considered part of the normal flora (Hudault et al. 2001). However, some serotypes of *E. coli* are intermittently responsible for product recalls due to food contamination, and can cause severe food poisoning in their hosts (Vogt and Dipold 2005). An correlation between high-level bacteremia and enhancement of meningitis was observed in *E. coli*, in experimental models of hematogenous meningitis (Bell et al. 1985). It is stated that Pili (or fimbriae) or the fibrils (Danne and Dramsi 2012), is responsible for initiating binding to BMECs in *E. coli* K1 (Teng et al. 2005). According to Khan et al. (2002), cytotoxic necrotizing factor-1 (CNF-1) activates Ras homolog gene family, member A (RhoA), which leads to *E. coli* K1 invasion of BMECs in vitro and increased penetration of BBB in vivo. The LR is known as the main internalization receptor for *E. coli* K1 to BMECs (Kim et al. 2005), that might facilitates brain invasion. Additionally, another way for penetration to CNS is through *E. coli* OmpA binds to C4-binding protein (C4 bp), a classical complement pathway regulator to block the complement cascade reaction, thus avoids bacteriolysis and recognition by immune cells (Prasadarao et al. 2002). Therefore, these

mechanisms highlight that the pharmacological inhibition of the host receptor and host cell signaling molecules, which contributes to *E. coli* invasion of BMEC, is a good indicator to prevent meningitis occurred by *E. coli*. Table 2 illustrates the mechanisms of BBB disruption and the bacterial-host interaction sites that enabling brain invasion among Gram-positive and -negative bacteria.

As mentioned above, once the host responds to infection, inflammatory cytokine and chemokine molecules are elevated by the host, resulting in BBB dysfunction and disease. Previous studies have demonstrated that *E. coli* binds to BMECs, resulting in IL-6 and IL-8 release in vitro (Zhou et al. 2012). Furthermore, through the predominant cell-surface antigen OmpA, *E. coli* K1 increases NO production from brain endothelial cells by inducing expression of iNOS, subsequently weakening BBB integrity and stimulating bacterial invasion (Mittal and Prasadarao 2010). A higher level of NO has been detected in animal models of bacterial meningitis and also in human patients with the meningeal disease (Murawska-Cialowicz et al. 2000). There is a growing indication that NO is an important modulator of cerebral vascular permeability (Mayhan 2000), confirming that this marker induces vascular permeability, which then leads to BBB disruption. Another study has described that BMEC monolayers leakage are increased upon *E. coli* interaction with Ec-gp96 (a receptor on human BMEC), via OmpA during invasion (Prasadarao 2002), which might lead to an disruption of BBB integrity. Another mechanism of BBB disruption by *E. coli* is the separation of VEC from other molecules of the TJs in endothelial cells (Sukumaran and Prasadarao 2003), that most probably lead to BBB disruption.

Conclusion

It can be concluded from this review that each bacteria has a different mechanism for BBB disruption, as well as a different mechanism for antigen-host cell interaction to invade the brain.

For brain invasion status and therapeutic purposes, several mechanisms have been described as below:

- *S. pneumoniae* CbpA targets a common carboxy-terminal domain of LR to establish initial contact with brain endothelium (Orihuela et al. 2009), that might assist to invade the brain. Additionally, other receptors were also found to be responsible for brain invasion during adhesion of pneumococci to brain endothelial cells including PECAM-1 and pIgR, together with PAFR (Radin et al. 2005; Iovino et al. 2013a, 2016).
- InlA and InlB of *L. monocytogenes* interact with its cellular receptors E-cadherin and MET, respectively,

Table 2 Illustration of mechanisms which are responsible for BBB disruption and BBB invasion in Gram-positive and -negative bacteria

The name of bacteria	The brief mechanisms which contribute to BBB penetration and enter the CNS due to the bacterial infection	The factors which contribute to BBB disruption
<i>S. pneumoniae</i>	<i>S. pneumoniae</i> CbpA targets the common carboxy-terminal domain of the laminin receptor (LR) (Orihuela et al. 2009) PECAM-1 and pIgR, together with PAFR are another key markers for BBB penetration (Radin et al. 2005; Iovino et al. 2013a, 2016, 2017)	TNF- α , IL-1 β , IL-6 and IL-10 and CINC-lupregulation (Kornelisse et al. 1996; Paul et al. 2003; Østergaard et al. 2004; Barichello et al. 2012b) <i>S. pneumoniae</i> leads to adhesion, invasion and translocation through or between endothelial cells without any disruption to the vascular endothelium (Iovino et al. 2013b)
<i>L. monocytogenes</i>	InIA and InIB of <i>L. monocytogenes</i> interact with its cellular receptors E-cadherin and MET, respectively, (Gründler et al. 2013)	High expression of the surface adhesion molecules P- and E-selectin, ICAM-1 and VCAM-1, as well as IL-6 and IL-8 and MCP-1 (Kayal et al. 2002)
<i>B. anthracis</i>	pXO1 <i>B. anthracis</i> inhibits the innate defence pathway, resulting in neutrophil chemotaxis prevention, allowing the dissemination of the bacteria into the CNS (van Sorge et al. 2008)	Down regulation the TJ protein ZO-1 (Warfel et al. 2005; Ebrahimi et al. 2009)
<i>S. aureus</i>	The role of LTA <i>S. aureus</i> is to anchor in brain endothelial cells (Sheen et al. 2010)	Increasing of IL-1 α , IL-1 β , IL-6, TNF- α , MCP-1, MIP1 α markers (Kielian and Hickey 2000) Downregulation of Claudin-5 and ZO-1 interendothelial junction protein (McLoughlin et al. 2017)
<i>S. agalactiae</i>	Srr-1 is responsible for adhesion function, mediating the interaction of GBS with fibrinogen, (Banerjee et al. 2011a; Seo et al. 2012) Additionally, Pila interacts with the extracellular matrix component collagen, which then involves $\alpha 2\beta 1$ integrins on brain endothelium to stimulate bacterial attachment and pro-inflammatory chemokine release (Banerjee et al. 2011a; Seo et al. 2012)	Levels of cytokine, chemokine, MPO and oxidative stress enhancement (Barichello et al. 2011a)
<i>H. influenzae</i>	LR and PAFr are the main portals which Hib enters the CNS, subsequently disseminating meningeal pathogens (Swords et al. 2001)	TJ deformation (Quagliarello et al. 1986; Schubert-Unkmeir et al. 2010)
<i>N. meningitidis</i>	LR and PAFr binding sites have been recognized as common routes of CNS entry by <i>N. meningitidis</i> (Orihuela et al. 2009)	Inducing AJs deformation as well as triggers IL-6 and IL-8 production in BMECs (Sokolova et al. 2004; Banerjee et al. 2010, 2011a) <i>N. meningitidis</i> also induces specific cleavage of the TJ component occluding (Courreuil et al. 2009; Schubert-Unkmeir et al. 2010)
<i>E. coli</i>	LR is known as the main internalization receptor for <i>E. coli</i> K1 on BMECs (Kim et al. 2005)	High levels of IL-6 and IL-8, and iNOS production (Zhou et al. 2012) The disassembly of TJs between endothelial cells due to the separation of VEC from other TJ molecules (Sukumaran and Prasadarao 2003)

(Gründler et al. 2013), that might facilitates BBB invasion.

- InhA and BslA may encourage BMEC binding and BBB infiltration in vivo upon *B. anthracis* infection, (Ebrahimi et al. 2009). Additionally, pXO1 *B. anthracis* inhibits the innate defence pathway, resulting in neutrophil chemotaxis prevention, allowing the dissemination of the bacteria into the CNS (van Sorge et al. 2008).
- LTA, mediating *S. aureus* adhesion and cellular invasion into immortalized human BMECs, resulting in BBB penetration (Sheen et al. 2010). LTA, IL-17 and SpA are being considered as a good indicators for *S. aureus* treatment (Cho et al. 2010; Sheen et al. 2010; McLoughlin et al. 2017).
- PilA of GBS interacts with the extracellular matrix component to stimulate bacterial attachment on brain endothelium (Banerjee et al. 2011a; Seo et al. 2012), which might enable brain invasion.
- In terms of *H. influenza* OmpP2, LR and PAFR, are the main portals to let the pathogen enter the CNS and BBB invasion (Swords et al. 2001; Orihuela et al. 2009).
- The bacterial adhesins of *N. meningitidis* (PilQ) targets a common carboxy-terminal domain of LR to establish initial contact with brain endothelium (Orihuela et al. 2009), which encourages BBB invasion.
- *E. coli* K1 encouraged BMECs invasion and increased penetration of BBB through CNF-1 activates Ras homolog gene family, member A (RhoA) (Khan et al. 2002). Additionally, another way for penetration of *E. coli* to CNS through OmpA binds to C4 bp (Prasadarao et al. 2002).

Thus, all these interactions mentioned above may prove to be promising mechanisms for novel therapies targeting bacterial virulence, where they might stimulate protection against bacterial meningitis and may provide a therapeutic target for the prevention and treatment of the disease.

The following points are the mechanisms which are responsible for BBB disruption in Gram-negative and -positive bacteria:

- *S. pneumoniae* species induced meningitis and BBB disruption through TNF- α , IL-1 β , IL-6 and IL-10, CINC-1 production (Kornelisse et al. 1996; Paul et al. 2003; Østergaard et al. 2004; Barichello et al. 2012b). In contrast, *S. pneumoniae* lead to adhesion, invasion and translocation through or between endothelial cells without any disruption to the vascular endothelium, upon BBB penetration, suggesting that an intracellular or paracellular path is used for BBB translocation (Iovino et al. 2013b).
- *L. monocytogenes* encouraged the expression of P- and E-selectin, ICAM-1 and VCAM-1, as well as IL-6

and IL-8 and MCP-1 (Kayal et al. 2002), resulting in endothelium permeability and then BBB disruption.

- Down regulation of the TJ protein (ZO-1) levels by *B. anthracis* contributing to BBB disruption (Warfel et al. 2005; Ebrahimi et al. 2009).
- BMEC permeability and BBB disruption were induced by *S. aureus* infection via VEC, claudin-5 and ZO-1 reduction and induction of pro-inflammatory cytokines (IL-1 α , IL-1 β , IL-6, TNF- α , MCP-1, MIP1 α), oxidative stress and NF- κ B activation (Kielian and Hickey 2000; McLoughlin et al. 2017).
- Levels of cytokine, chemokine, MPO and oxidative stress in a meningitis-induced model were increased during GBS infection (Barichello et al. 2011a), which might encourage to BBB dysfunction.
- *H. influenza* bacteria is able to disrupt the BBB due to TJ deformation (Quagliarello et al. 1986; Schubert-Unkmeir et al. 2010).
- *N. meningitidis* induced AJs deformation, leading to the opening up of the paracellular route for *N. meningitidis* translocation into the CNS. *N. meningitidis* also triggered IL-6 and IL-8 production in BMECs that most probably results in BBB disruption (Sokolova et al. 2004; Banerjee et al. 2010, 2011a). *N. meningitidis* also induced specific cleavage of the TJ component occluding, leading to endothelial cell detachment and increased paracellular permeability (Coureuil et al. 2009; Schubert-Unkmeir et al. 2010).
- *E. coli* infection encouraged IL-6 and IL-8, and iNOS production (Zhou et al. 2012), that facilitates BBB disruption. The disassembly of TJs between endothelial cells was induced by *E. coli* due to the separation of VEC from other TJ molecules (Sukumaran and Prasadarao 2003).

Overall, all these studies have found that each bacteria has their own way to disrupt the BBB and enter into the CNS, which has assisted the researchers in obtaining more knowledge about bacteria pathogenicity, especially in meningitis.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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