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*Review*

# Molecular and cellular mechanisms for microbial entry into the CNS

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**A number of pathogenic microbes including neuroinvasive viruses, bacteria and parasites are capable of entry into the central nervous system (CNS) and cause a variety of clinical manifestations. The cellular and molecular mechanisms for the CNS invasion have been extensively studied in the last two decades. Viruses invade neurons and thereby cause encephalitis or peripheral neuritis, while bacteria enter the cerebrospinal fluid (CSF) and cause meningitis. In contrast, the mechanisms for parasitic neuroinvasion are much more complex and less clear. The capabilities that enable these elite subsets of pathogens to engineer uptake into the CNS will be the subject of this review.**

**Keywords:** neuroinvasion; blood-brain barrier; pathogenesis

## Protection of the CNS across the blood-brain barrier

To understand the CNS invasion process by neuroinvasive microbes, it is necessary to describe one of the defensive structures in the CNS that prevent microbial invasion. The CNS is sequestered from the systemic circulation by the blood-brain barrier (BBB). At the anatomic level, the BBB refers to two different but connected structures: a barrier between blood and brain in cerebral capillaries and a barrier between blood and CSF in choroid plexus (Brightman, 1989). The former is formed by intercellular tight junctions between brain microvascular endothelial cells (BMEC). The BMEC layer is supported by astrocytes, pericytes and the basement membrane (Figure 1A).

The BMEC differs from the fenestrated peripheral endothelium in two important aspects. First, tight junctions between the BMEC possess extremely strong electrical resistance (Crone and Olesen, 1982), which restricts the amount of paracellular flux. Second, the BMEC has a relatively low number of pinocytotic vesicles and thus undergoes a slow rate of fluid-phase endocytosis (Reese and Karnovsky, 1968), which restricts the amount of transcellular flux. In combination, the cerebral capillaries are highly resistant to passage of ions and small molecules such as dyes and antibiotics. Instead, specific transport systems are utilized to provide essential substances such as glucose, ions and amino acids across the barrier to support neuronal function. The energy cost of the active transport system is accompanied by a relatively high number of mitochondria.

In localized areas of choroid plexus within each of the four cerebral ventricles, the permeability of the cerebral capillaries is dramatically increased due to fenestration of the BMEC layer. A highly vascularized epithelium serves as a barrier function between blood and CSF (Figure 1B). Although the polarized choroid plexus epithelium is able to form tight junctions, the epithelial tight junctions have lower electric resistance than those of the BMEC (Zeuthen and Wright, 1981). This allows passage of some blood components across the BBB to form CSF, but exposes a weak area for microbial penetration into the CSF space. The site of microbial entry into the subarachoroid space has not been definitely identified, but choroid plexus is a leading candidate.

Neuroinvasive microbes can infect numerous brain tissues and cause a variety of clinical manifestations from viral encephalitis to bacterial meningitis, suggesting broad penetration capability across the BBB. We have selected some of the

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typical cases to illustrate the principal cellular mechanisms by which viral and bacterial pathogens invade the CNS.

## Strategies of CNS invasion by viruses

Viral pathogens may invade the CNS through either the blood circulation or the peripheral nerve route (Johnson, 1982; Tyler and Gonzalez-Scarano, 1997). There are at least four different mechanisms by which viruses traverse the BBB into the CNS. First, blood-borne viruses may gain access to the CNS by infecting the BMEC or may be transported across the BMEC (Johnson, 1982). Infection of the BMEC may provide a portal for viral entry into the CNS and disrupt the BBB function. A number of viruses such as cytomegalovirus (Lathey *et al*, 1990), human immunodeficiency virus (HIV) (Moses *et al*, 1993, 1996), and arboviruses (Dropulic and Masters, 1990) are able to infect the BMEC *in vitro*. Infection of the BMEC has also been demonstrated *in vivo* by detecting viral nucleic acid (Bagasra *et al*, 1996; Zurbriggen and Fujinami, 1988) or viral antigen (Mankowski *et al*, 1994) in cerebral capillaries of the infected individuals. Evidence suggests that canine distemper virus (Coffin and Liu, 1957) and Semiliki Forest virus (Pathak and Webb, 1974) can be directly transported to the CNS through the BBB.

Second, viruses may transmigrate across the BBB within virally infected leukocytes. Lymphocytes have been implicated to carry canine distemper virus across the BBB (Summer *et al*, 1978). Studies also suggest that HIV enters the CNS by shedding from infected $CD4^+$ T cells, macrophages, and microglia during migration through the BBB (Nottet *et al*, 1996; Peluso *et al*, 1985; Persidsky *et al*, 1997; Schmidtmayerova *et al*, 1996). A variety of host adhesion molecules have been shown to enhance entry of the virally infected leukocytes into the CNS (Brankin *et al*, 1995; Soilu-Hanninen *et al*, 1997). These include intercellular adhesion molecule 1 (ICAM-1) (Adamson *et al*, 1999; Shrikant *et al*, 1996), vascular cell adhesion molecule 1 (VCAM-1) (Sasseville *et al*, 1994, 1995) and leukocyte function antigen 1 (LFA-1) (Attibele *et al*, 1993; Hildreth and Orentas, 1989). Related to this mechanism, leukocytes may facilitate viral entry into the CNS by producing inflammatory substances, which can in turn affect permeability of the BBB. For example, TNF$\alpha$ has been demonstrated to promote HIV entry into the CNS by disrupting paracellular tight junctions of the BBB (Fiala *et al*, 1997). Consistent with these findings, bacterial lipopolysaccharide (LPS), a potent inducer of cytokines, has been found to enhance penetration of Sindbis virus into the CNS (Lustig *et al*, 1992).

Third, viruses can also penetrate the CNS by taking advantage of incomplete closure of the BBB (Johnson, 1982). Despite the intercellular tight junctions between the capillary endothelial cells in most regions of the BBB, certain areas of the CNS such as the choroid plexus, posterior pituitary, and circumventricular organs are not completely protected by the BBB due to a fenestrated endothelial cell layer and sparse basement membrane. A number of blood-borne viruses including mumps virus (Herndon *et al*, 1974), HIV (Bagasra *et al*, 1996; Falangola *et al*, 1995; Harouse *et al*, 1989), and rat parvovirus (Lipton and Johnson, 1972) have been suggested to penetrate across the choroid plexus microvessels and infect the epithelium, suggesting that these viruses may enter the CSF space. In the CSF space, viruses can subsequently infect the ependymal cells and surrounding brain tissue.

Finally, viruses can spread to the CNS through peripheral intraneuronal routes (Tyler and Gonzalez-Scarano, 1997). The motor neurons of the spinal chord and some primary sensory neurons are directly connected to the CNS, thus providing a convenient route for neurotropic viruses (Johnson, 1982). Viruses including herpes simplex virus (Johnson, 1964), pseudorabies virus (Rziha *et al*, 1986), and rabies virus (Murphy, 1977) are able to replicate within peripheral nerves and are trans-

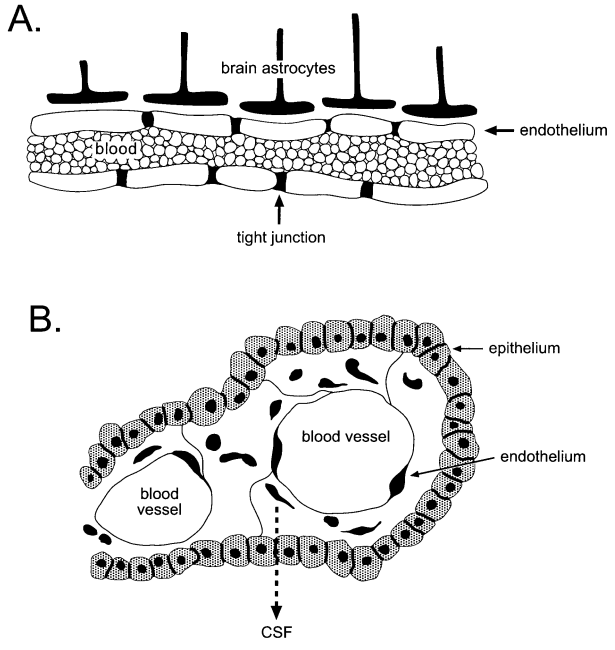


**Figure 1** Schematic illustration of the BBB structures at (**A**) the cerebral capillary endothelium and (**B**) the choroid plexus. Tight junctions of the cerebral capillary endothelium prevent the blood elements from penetration into the CNS. The endothelial barrier is supported in part by brain astrocytes. At the choroid plexus, the endothelial layer of the blood vessels is fenestrated to allow penetration of the blood contents, but the epithelium surrounding the blood vessels serves as a barrier between blood and CSF.

ported into the CNS through the axonal transport system of neurons. Certain enteroviruses can even spread to the CNS by infecting enteric neurons (Morrison and Fields, 1991; Morrison *et al*, 1991).

## Strategies of CNS invasion by bacteria

A number of bacteria are capable of invading the CNS and cause bacterial meningitis (Overturf, 1994). However, the majority of bacterial meningitis cases are caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*, and in the newborn *Escherichia coli* and Group B *streptococcus*. The ability to cause true neuritis or encephalitis is much more rare in bacteria as exemplified by leprosy, Lyme disease and syphilis. In contrast to the advanced knowledge in cellular and molecular mechanisms of viral neuroinvasion (Tyler and Gonzalez-Scarano, 1997), current understanding of bacterial counterparts is still sketchy. Except for special conditions such as brain injuries due to trauma or neurosurgery, neuroinvasive bacteria enter the CNS by blood-borne infection (Ring and Tuomanen, 1997). These pathogens multiply to high densities in the blood, with the level of bacteremia correlating with the risk of CNS penetration. When bacteria reach the luminal side of the cerebral capillaries, there are several possible routes to enter the CNS (Tuomanen, 1996).

*Site of transversal*
The specific entry sites into the CNS are not known for most bacteria. *H. influenzae* appears to enter the CNS at the choroid plexus. In monkeys infected with *H. influenzae*, Daum *et al* (1978) found higher bacterial densities in the CSF of the ventricles compared to the lumbar space. Given the fact that the CSF flows unidirectionally from the ventricles down to the lumbar space, this finding suggests bacterial entry at the choroid plexus. This is consistent with the observation that plexitis is frequently observed in early meningitis. On the other hand, a recent study suggests that *N. meningitidis* cross the BBB at both the choroid plexus and the BMEC (Pron *et al*, 1997). *N. meningitidis* was found to attach to the endothelium of the choroid plexus and the meninges in a patient with meningitis. Pilus-mediated adhesion appears to be required for bacterial attachment to the BMEC (Pron *et al*, 1997). Other bacteria including *E. coli* (Huang *et al*, 1995), *Listeria monocytogenes* (Parida *et al*, 1998; Wilson and Drevets, 1998), Group B *streptococcus* (Nizet *et al*, 1997), and *S. pneumoniae* (Ring *et al*, 1998) have been demonstrated to adhere to and invade the BMEC *in vitro*. This suggests that these bacteria may transverse the BBB at the choroid plexus to infect CSF and may infect and transverse the BMEC.

*Pathway of transversal*
Current knowledge suggests that bacteria transmigrate the BBB by at least two pathways: paracellular penetration and transcellular migration (Figure 2). *E. coli* (Huang *et al*, 1995), *L. monocytogenes* (Parida *et al*, 1998; Wilson and Drevets, 1998), and Group B *streptococcus* (Nizet *et al*, 1997) invade the BMEC *in vitro*, suggesting that transendothelial migration serves as an invasion mechanism for these pathogens. Consistent with this notion, Ring *et al* (1998) have recently demonstrated that *S. pneumoniae* is able to transmigrate across human BMEC. Evidence has suggested that host receptors are required to mediate the transendothelial migration process. Platelet-activating factor (PAF) receptor can promote transendothelial migration by *S. pneumoniae* by interacting with pneumococcal phosphorylcholine (Cundell *et al*, 1995; Ring *et al*, 1998). In a similar fashion, E-cadherin is required for invasion of epithelial cells by *L. monocytogenes* (Mengaud *et al*, 1996), although its role in endothelial transmigration is unclear. In contrast, Lyme disease agent *Borrelia burgdorferi* (Szczepanski *et al*, 1990) and syphilis bacterium *Treponema pallidum* (Haake and Lovett, 1994; Thomas *et al*, 1988) appear to cross the endothelial barrier by travelling between the endothelial cells.

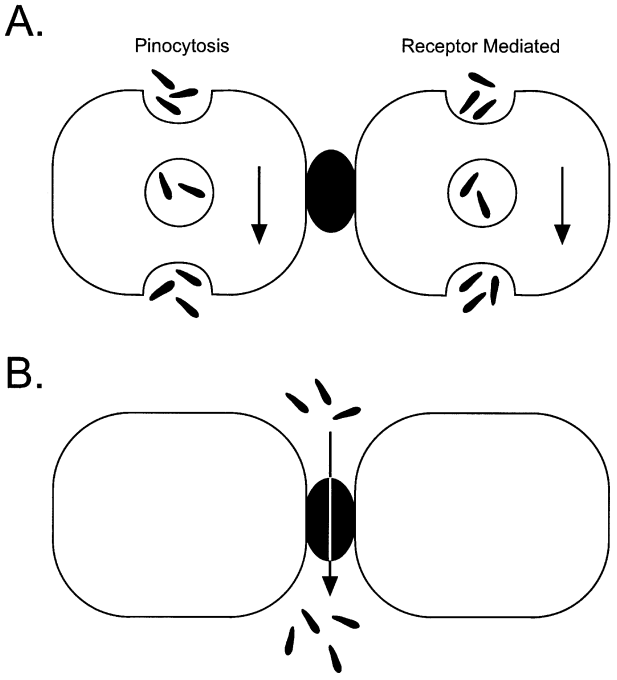


**Figure 2** Bacterial passage across the BBB via (**A**) intracellular or (**B**) paracellular routes. Intracellular penetration is initiated by bacterial adherence to the blood vessels followed by bacterial entry into the capillary endothelium through pinocytotic or receptor-mediated mechanisms. In contrast, other bacteria may cross the BBB through tight junctions. Factors loosening or interrupting the tight junctions may facilitate paracellular penetration by bacteria.

*Bacterial products and the CNS invasion*
BBB permeability can be modulated by bacterial components such as LPS (Patrick *et al*, 1992; Temesvari *et al*, 1993; Wispelwey *et al*, 1988), cell wall (Burroughs *et al*, 1992), and proteins (Spellerberg *et al*, 1995; Wispelwey *et al*, 1989). In a bacterial meningitis model, inoculation of animals with live *H. Influenzae* or bacterial LPS caused functional and ultrastructural changes of the BBB (Wispelwey *et al*, 1988, 1989). Release of these bacterial products during bacteremia could compromise the integrity of the BBB, which may facilitate bacterial entry into the CNS. Consistent with these findings, Lustig *et al* (1992) have shown that bacterial LPS facilitates viral neuroinvasion in a mouse model. Increased BBB permeability could be a direct effect of these bacterial products on the BBB or an indirect effect of host inflammatory mediators such as nitric oxide (Jaworowicz *et al*, 1998), TNF$\alpha$ and IL-1 (Mun-Bryce and Rosenberg, 1998).

## Strategies of CNS invasion by fungi and parasites

A number of fungal and parasitic pathogens can infect the CNS and cause a variety of neurological complications. Several examples are discussed here to illustrate the principles of CNS invasion by these pathogens. *Candida albicans* and *Cryptococcus neoforman* are the leading causes of neuroinvasive fungal infections, particularly in immunocompromised hosts (Casadevall and Perfect, 1998; Odds, 1988). Although, the routes of CNS infections by fungal pathogens appear to be similar to viral and bacterial blood-borne infections, it is not clear how fungi overcome the BBB to enter the CNS. *C. albicans* is able to bind to a variety of brain cell types including the BMEC, microglia, and neurons (Blasi *et al*, 1991; Denaro *et al*, 1995). Similarly, studies have shown that *C. neoforman* can invade vascular endothelium (Ibrahim *et al*, 1995) and a variety of brain cells (Gomes *et al*, 1997; Lee *et al*, 1995). Available evidence suggests that neuroinvasive fungi are capable of entry into the CNS by invasion of the BMEC.

Neuroinvasive parasites gain access to the CNS via blood circulation. The mechanisms for subsequent entry of parasite pathogens across the BBB are poorly understood. *Toxoplasma gondii*, causing severe encephalitis in immunocompromised hosts, is able to attach to and invade a wide range of vertebrate nucleated cells (Sibley, 1995). The ability of *T. gondii* to invade microglia (Fischer *et al*, 1997) and BMEC (Gay-Andrieu *et al*, 1999) suggest that *T. gondii* may enter the CNS by transmigrating the BBB. In sharp contrast to *T. gondii*, malaria *Plasmodium* parasites primarily invade reticulocytes, particularly erythrocytes. Thus, cerebral malaria does not appear to be caused by parasitic invasion in the CNS. However, *Plasmodium* parasites are evolved to modify the surface of the infected erythrocytes (Howard, 1988; Smith *et al*, 1995). The modified erythrocytes acquire ability to adhere to the BMEC and uninfected erythrocytes (Dobbie *et al*, 1999; Ockenhouse *et al*, 1992b), which has been postulated to contribute to the pathogenesis of cerebral malaria (Aikawa, 1988; Miller *et al*, 1994). *Plasmodium*-infected erythrocytes adhering to the BMEC lead to increased permeability, progressive deterioration and breakdown of the BBB (Hermsen *et al*, 1998; Polder *et al*, 1992; Thumwood *et al*, 1988).

## Molecular and genetic determinants of microbial neuroinvasion

To invade the CNS, pathogens need to replicate in the peripheral organs and/or blood and then specifically interact with the host CNS cells. A number of microbial molecules have been demonstrated to enhance neuroinvasion in animal models or cell cultures (Ring and Tuomanen, 1997; Tyler and Gonzalez-Scarano, 1997). A few examples are selected here to illustrate the potential roles played by these microbial molecules.

*Viral envelope proteins*
Viral envelope proteins have been shown to play an important role in neuroinvasion of some viral pathogens as exemplified by HIV-1 glycoprotein gp120 (Turner and Summers, 1999). AIDS dementia complex is caused by HIV-1 infection of the CNS (Kolson *et al*, 1998). Numerous studies have shown that the HIV-1 gp120 is essential for the CNS entry of HIV-1 (Kolson *et al*, 1998). gp120 has been clearly shown to bind to the CD4 receptor and other coreceptors in non-endothelial cells (Berger, 1998), but this protein has not been well described in terms of its interaction with BMEC receptors. Glycosylated recombinant gp120 can be taken up by the BMEC and transported across the BBB into brain tissue (Banks *et al*, 1997). Based on available information, gp120 may mediate HIV-1 transversal across the BBB by enhancing the migration of infected leukocytes across the BMEC (Hurwitz *et al*, 1994), modulating the BBB permeability (Annunziata *et al*, 1998), or enabling viruses to invade and infect the BMEC (Kolson *et al*, 1998). Since the BMEC does not express the principal CD4 receptor (Moses *et al*, 1993), it is postulated that gp120 interacts with the chemokine receptors and/or other unknown receptor(s) expressed on the BMEC.

Mosquito-borne infection by bunyaviruses causes pediatric encephalitis (Griot *et al*, 1994). The middle segment of the bunyavirus genome encodes two surface glycoproteins that determine the ability of the viruses to invade the CNS in a mouse model

(Janssen *et al*, 1984, 1986). Another example is the E2 glycoprotein of Sindbis virus. E2 is required for neuroinvasion in infected mice, since single amino acid substitutions can abolish neuroinvasiveness (Davis *et al*, 1986; Dubuisson *et al*, 1997). Although the exact roles played by these viral envelope proteins in neuroinvasion are not clear, it is possible that these proteins are involved directly or indirectly in receptor binding (Pekosz *et al*, 1995; Tucker *et al*, 1993) and/or cellular penetration (Davis *et al*, 1986).

*Other viral components*

Viral polymerase has been shown to be associated with neuroinvasiveness in bunyaviruses (Griot *et al*, 1993, 1994). Mutations in viral polymerase resulted in an avirulent phenotype (Griot *et al*, 1993). It is not clear how the viral polymerase enhances neuroinvasion. Finally, neuroinvasiveness has been mapped to unexpected regions of viral genomes, including non-coding sequences in poliovirus (Macadam *et al*, 1994) and Sindbis virus (Dubuisson *et al*, 1997). It has been suggested that sequences in these regions are critical for formation of stem-loop structures, which are required for efficient translation of viral genes (Skinner *et al*, 1989; Strauss and Strauss, 1994).

*Bacterial molecules*

The molecular determinants of neuroinvasive bacteria are not well understood. Two examples with molecular information are *E. coli* and *S. pneumoniae*. Several surface structures of *E. coli* K1 have been extensively studied in terms of BMEC invasion. The filamentous S-fimbrae appears to be a key virulence factor involved in neonatal meningitis (Korhonen *et al*, 1985; Parkkinen *et al*, 1988). Two S-fimbrae proteins, SfaA and SfaS, have been shown to enhance *E. coli* K1 attachment to the BMEC by binding to sulfated glycolipids (Prasadarao *et al*, 1993) and terminal sialyl-2,3-galactose epitopes of glycoproteins (Stins *et al*, 1994), respectively. A major outer membrane protein designated OmpA is able to bind to N-acetylglucosaminyl1-4N-acetylglucosamine structures expressed on BMEC glycoproteins (Prasadarao *et al*, 1996a) and thereby promote *E. coli* invasion (Prasadarao *et al*, 1996b). More recently, a small *E. coli* protein called Ibe10 has been identified to be essential for *E. coli* invasion of the BMEC (Huang *et al*, 1995). Ibe10 appears to interact with an albumin-like protein on the surface of the BMEC (Prasadarao *et al*, 1999). Unlike OmpA which is expressed by both clinical and nonclinical isolates (Prasadarao *et al*, 1996b), Ibe10 is expressed only in clinical *E. coli* K1 isolates, but not in laboratory strains of *E. coli* K12 (Huang *et al*, 1995). Therefore, the Ibe10 protein appears to be a specific determinant of the BMEC invasion. Thus, four proteins promote the interaction of *E. coli* K1 with the BMEC and their relative roles are yet to be determined.

Several pneumococcal surface molecules including phosphorylcholine and choline binding protein A (CbpA) have been identified to be important for BMEC invasion and transmigration (Ring *et al*, 1998). Endothelial cell surface oligosaccharide LnNT has been suggested to bind to pneumococcal CbpA (Rosenow *et al*, 1997). Pneumococcus strains undergo spontaneous phase variation that changes the amount of these invasive determinants on the bacteria (Weiser *et al*, 1994). In a two-chamber model, variants bearing more CbpA and phosphorylcholine were able to invade human BMEC and subsequently transmigrate across BMEC monolayer to the basolateral side, whereas counterparts without these determinants were predominantly recycled back to the apical side (Ring *et al*, 1998). Phosphorylcholine appears to participate in the BMEC invasion by directly interacting with the PAF receptor (Cundell *et al*, 1995) and anchoring a family of choline-binding proteins including CbpA to the pneumococcal surface (Tuomanen and Masure, 1997).

Bacterial cell wall components such as LPS in *E. coli* and *H. Influenzae* (Patrick *et al*, 1992; Temesvari *et al*, 1993) and glycoproteins from *S. pneumoniae* (Spellerberg *et al*, 1995) have been known to affect BBB permeability. Release of these substances during bacteremia may facilitate bacterial entry into the CNS. Meningococcal LPS and several surface proteins including pilin, Opa, Opc, and PilC have been known to bind to a variety of host cellular receptors (Jerse and Rest, 1997). A specific role in CNS invasion has been suggested for PilC (Pron *et al*, 1997). In contrast, little is known about molecular basis of CNS invasion in *L. monocytogenes*, although a number of virulence-associated proteins have been identified in this pathogen (Cossart and Lecuit, 1998).

*Fungal and parasitic factors*

Adherence and invasion of host tissues by fungi and parasites depend on cells surface structures. *C. albicans* surface proteins including integrin-like protein (Int1) and hypha-specific surface protein (Hwp1) are required for virulence and fungal adherence to epithelial and endothelial cells (Gale *et al*, 1998; Gozalbo *et al*, 1998; Staab *et al*, 1999). Other *C. albicans* proteins such as ALA1 (Gaur and Klotz, 1997) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (Gozalbo *et al*, 1998) have been reported to mediate adherence of the fungus to various extracellular matrix proteins. Another set of *C. albicans* cell wall proteins have been implicated in adherence to host tissues (Kanbe and Cutler, 1998), but these proteins require O-mannosyl modification for adhesin activity (Buurman *et al*, 1998; Timpel *et al*, 1998). Mannoproteins are also involved in cytoadherence of *C. neoformans*

(Hamilton and Goodley, 1996). Finally, *C. neoformans* capsule influences fungal invasion of vascular endothelium (Ibrahim *et al*, 1995). The specific roles of these fungal surface proteins in neuroinvasion have not been determined.

The actin cytoskeleton of *T. gondii* is necessary for host cell invasion (Dobrowolski and Sibley, 1996). Despite lack of evidence, the parasitic cytoskeleton is likely to be also involved in host invasion of other protozoan parasites. Significance of parasitic proteins in adherence has been clearly demonstrated with a *Plasmodium* protein, designated erythrocyte membrane protein 1 (PfEMP1). PfEMP1, an antigenic variant protein encoded by a family of *var* genes (Baruch *et al*, 1995; Su *et al*, 1995), is among numerous *Plasmodium* proteins exported to the membrane of the infected cells (Howard, 1988; Smith *et al*, 1995). PfEMP1 binds to multiple host receptors including CD36, thrombospondin, ICAM-I, and chondroitin sulfate A expressed on the BMEC (Baruch *et al*, 1996; McCormick *et al*, 1997; Reeder *et al*, 1999). PfEMP1 is also able to specifically interact with complement-receptor 1 (Rowe *et al*, 1997) and heparan sulfate (Chen *et al*, 1998) expressed on uninfected erythrocytes. PfEMP1-mediated adherence of the infected erythrocytes to vascular endothelium and uninfected erythrocytes leads to phenomena known as sequestration and rosetting, respectively, which are considered to contribute to manifestations of cerebral malaria (Fernandez *et al*, 1998; Miller *et al*, 1994).

## Host cellular receptors

A number of host factors ranging from oligosaccharides and lipids to proteins have been identified to serve as receptors for neuroinvasive pathogens. Interestingly, single host molecules can serve as receptors for different pathogens. Three examples are the CD46, α-dystroglycan, and ICAM-1 (Tables 1 and 2). CD46 binds to both lymphocytic choriomeningitis virus and *N. meningitidis* PilC; α-dystroglycan serves as a receptor for both measles virus and *M. leprae*; Human rhinovirus and *Plasmodium* PfEMP1 specifically interact with ICAM-1, although the virus and parasitic protein bind to distinct sites of ICAM-1 molecule (Ockenhouse *et al*, 1992a).

*Viral receptors*

Among numerous viral receptors (Tyler and Gonzalez-Scarano, 1997) (Table 1), HIV-1 receptors have been most extensively investigated in terms of specific receptor interactions. HIV-1 infects non-endothelial cells by receptor-mediated absorptive endocytosis in a two-step process. The gp120 glycoprotein initially binds to either the CD4 receptor (Maddon *et al*, 1986) or the galactosylceramide binding site (Fantini *et al*, 1993), which in turn facilitates gp120 binding to heparin-sulfate-bearing chemokine receptors (Feng *et al*, 1996; Pleskoff *et al*, 1997). A recent study has suggested that HIV-1 invades the BMEC by a similar endocytotic mechanism (Banks *et al*, 1998). However, the BMEC does not express either CD4 receptor or galactosylceramide binding sites and HIV-1 penetrates the BBB in a CD4/galactosylceramide-independent manner (Moses *et al*, 1993). Despite absence of these receptors, gp120 appears to be critical for HIV-1 penetration across the BBB (Banks and Kastin, 1998; Hurwitz *et al*, 1994). Several chemokine receptors including CCR3, CCR5, and CXCR4 have been identified recently in the BMEC (Lavi *et al*, 1998). The CCR5 receptor has been shown to be essential for BMEC infection by simian immunodeficiency virus (SIV) (Edinger *et al*, 1997). However, the roles of these coreceptors in the CNS entry of HIV-1 have not been determined.

*Bacterial receptors*

Several molecules expressed in the BMEC have been shown to enhance transversal of *E. coli* across the BBB (Table 1). These host molecules range from glycolipids to proteins and are able to bind to *E. coli* surface structures including S-fimbrae and outer membrane proteins. The recently identified Ibe10-binding protein (Ibe10R) is particularly interesting, since it is essential for *E. coli* invasion of the BMEC (Prasadarao *et al*, 1999). Similarly, the PAF receptor is necessary for pneumococcal invasion of the BMEC through interaction with phosphorylcholine expressed on the pneumococcal surface (Cundell *et al*, 1995; Ring *et al*, 1998). Laminin and α-

**Table 1** Host cell receptors or factors for neuroinvasive viruses

| *Virus* | *Host receptor or factor* | *Reference* |
|---|---|---|
| Echovirus | Integrin | Bergelson *et al*, 1992 |
| | CD55 | Bergleson *et al*, 1994 |
| α-herpesvirus | HveA | Montgomery *et al*, 1996 |
| | HveB | Warner *et al*, 1998 |
| | HveC | Geraghty *et al*, 1998 |
| HIV-1 | CD4 | Maddon *et al*, 1986 |
| | Orphan receptor | Edinger *et al*, 1998a,b |
| | Chemokine receptors | Berger, 1998 |
| LCMV | α-Dystroglycan | Cao *et al*, 1998 |
| Measles virus | CD46 | Dorig *et al*, 1993 |
| Poliovirus | Poliovirus receptor | Mendelsohn *et al*, 1989 |
| Rabies virus | Acetylcholine receptor | Superti *et al*, 1986 |
| | Gangliosides | Wunner *et al*, 1984 |
| | Phospholipids | Reagan and Wunner, 1985 |
| | Neural cell-adhesion molecule | Thoulouze *et al*, 1998 |
| | Nerve-growth factor receptor | Tuffereau *et al*, 1998 |
| Rhinovirus | ICAM-1 | Greve *et al*, 1989 |
| Sendai virus | Gangliosides | Haywood, 1974 |
| Sindis virus | Laminin receptor | Wang *et al*, 1992 |

HIV-1=human immunodeficiency virus 1; ICAM-1=intercellular adhesion molecule 1; LCMV=lymphocytic choriomeningitis virus.

Dystroglycan have been demonstrated to promote neural invasion of *Mycobacterium leprae* (Rambukkana *et al*, 1997, 1998), although the specific bacterial ligands have not been identified. Host receptors for other pathogens in CNS invasion remain to be investigated.

*Fungal and parasitic receptors*

Host receptors for fungi and parasites are poorly understood. Fibronectin, laminin, and vitronectin have been shown to mediate adherence of *C. albicans* to extracellular matrix (Forsyth *et al*, 1998; Klotz and Smith, 1991; Spreghini *et al*, 1999). Multiple host molecules expressed on the BMEC and erythrocytes bind to the *Plasmodium* PfEMP1 protein (Table 2). Interactions of PfEMP1 with CD36, thrombospondin, ICAM-I, and chondroitin sulfate A contribute to sequestration of *Plasmodium*-infected erythrocytes to the BMEC (Baruch *et al*, 1996; Reeder *et al*, 1999). Similarly, CD36, complement-receptor 1, and heparan sulfate of normal erythrocytes bind to PfEMP1 on the infected erythrocytes, leading to rosetting (Chen *et al*, 1998; Handunnetti *et al*, 1992; Rowe *et al*, 1997). Other host molecules have been implicated as receptors for *Plasmodium*-infected erythrocytes including VCAM-1, endothelial leukocyte adhesion molecule 1 (ELAM-1) (Ockenhouse *et al*, 1992b), and platelet/endothelial cell adhesion molecule 1 (PECAM-1/CD31) (Treutiger *et al*, 1997).

**Table 2** Host cell receptors or factors for neuroinvasive bacteria, fungi and parasites

| *Bacterial protein* | *Host receptor or factor* | *Reference* |
|---|---|---|
| *E. coli* | | |
| SfaA | Sulfated glycolipid | Prasadarao *et al*, 1993 |
| SfaS | NeuAc-2, 3-Gal | Stins *et al*, 1994 |
| OmpA | GlcNAc1-4GlcNAc | Prasadarao *et al*, 1996a |
| Ibe10 | Ibe10R | Prasadarao *et al*, 1999 |
| *L. monoctyogenes* | | |
| Internalin | E-cadherin | Mengaud *et al*, 1996 |
| ActA | Heparan sulfate proteoglycan | Alverez-Dominguez *et al*, 1997 |
| *M. laprae* | Laminin | Rambukkana *et al*, 1997 |
| | α-Dystroglycan | Rambukkana *et al*, 1998 |
| *N. meningitidis* | | |
| Opc | Vitronectin | Virji *et al*, 1994 |
| Opa | CD66 | Virji *et al*, 1996a,b |
| PilC | CD46 | Kallstrom *et al*, 1997 |
| *S. pneumoniae* | | |
| P-Choline | PAF receptor | Cundell *et al*, 1995; Ring *et al*, 1998 |
| CbpA | LnNT | Rosenow *et al*, 1997 |
| *C. albicans* | | |
| GAPDH | Fibronectin, laminin | Gozalbo *et al*, 1998 |
| *P. falciparum* | | |
| PfEMP1 | Heparan sulfate | Chen *et al*, 1998 |
| | Complement receptor 1 | Rowe *et al*, 1997 |
| | CD36 | Barnwell *et al*, 1989; Baruch *et al*, 1996 |
| | Thrombospondin | Baruch *et al*, 1996; Roberts *et al*, 1985 |
| | ICAM-1 | Baruch *et al*, 1996; Berendt *et al*, 1989 |
| | Chondroitin sulfate A | Reeder *et al*, 1999; Robert *et al*, 1995; Rogerson *et al*, 1995 |

P-Choline=phosphorylcholine; PAF=platelet-activating factor; GAPDH=glyceraldehyde-3-phosphate dehydrogenase.

## Conclusion

Despite the vast genetic diversity among neuroinvasive microbes, these pathogens face similar obstacles on the way into the CNS, and some share mechanisms for crossing the BBB. Most of these pathogens, however, use uniquely tailored routes, with viruses generally targeting brain parenchyma and bacteria targeting the CSF space. It is now clear that molecular interactions between the pathogens and the hosts determine the outcome of the infection. Our understanding of the molecular mechanisms of CNS diseases is still fragmentary. Increasingly, identification of microbial virulence factors and host receptors will provide solutions for this complex puzzle. Understanding these capabilities will increase our ability to interrupt neuroinvasion in disease. However, it will also teach how to use these entry routes for therapeutic benefit, for example, for gene delivery of therapy of cancer and neurodegeneration disorders.

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