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Review

Neuroinvasion by Chandipura virus

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ABSTRACT

Chandipura virus (CHPV) is an arthropod borne rhabdovirus associated with acute encephalitis in children below the age of 15 years in the tropical states of India. Although the entry of the virus into the nervous system is among the crucial events in the pathogenesis of CHPV, the exact mechanism allowing CHPV to invade the central nervous system (CNS) is currently poorly understood. In the present review, based on the knowledge of host interactors previously predicted for CHPV, along with the support from experimental data available for other encephalitic viruses, the authors have speculated the various plausible modes by which CHPV could surpass the blood–brain barrier and invade the CNS to cause encephalitis whilst evading the host immune surveillance. Collectively, this review provides a conservative set of potential interactions that can be employed for future experimental validation with a view to better understand the neuropathogenesis of CHPV.

Contents

1. Introduction

Chandipura virus (CHPV), a member of the genus *Vesiculovirus* and family *Rhabdoviridae*, is an emerging pediatric encephalitic virus associated with a number of acute and fatal epidemic outbreaks in the central states of India (Chadha et al., 2005; Rao et al., 2004). Following natural infection, only children below the age of 15 yrs have been observed to be vulnerable to encephalitis, while the adults are refractory. Although age dependent susceptibility is noticed in several neurotropic viruses (Griffin et al., 1994; Oliver et al., 1997), the mechanisms involving age dependent resistance to fatal viral encephalitis have remained largely inconclusive. Even though the exact route of pathogenesis by which the virus reaches the brain is still unknown, the virus replication in the brain has been found to be responsible for neurological symptoms and subsequent mortality (Balakrishnan and Mishra, 2008). Vesicular Stomatitis Virus (VSV), the closest relative to CHPV, takes the olfactory route and travels in an anterograde manner to reach the brain (van den Pol, 2006), while Rabies Virus (RV), the only other known human pathogen in the *Rhabdoviridae* family, enters the motor neurons from the muscles and travels in a retrograde manner to reach the brain (Raux et al., 2000). Studies conducted on murine models have revealed that the intravenous route of CHPV infection in young

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mice resulted in viremia and the virus was observed to cross the blood–brain barrier (BBB) to replicate in the central nervous system (CNS, Balakrishnan and Mishra, 2008). Although viruses were effectively cleared from circulation by virus specific IgM antibody within 48 h, the inability of the antibodies to cross the BBB together with the lack of proper immune surveillance in the CNS, might have made it possible for the virus to continue replication in the brain causing encephalitis and subsequent death of the host within 72 h (Balakrishnan and Mishra, 2008). The absence of a window period is evident from the short duration of the viral pathogenesis (72 h). Considering the more time taken to reach the brain via the neurogenic mode (transport through the nerves as observed in Herpesvirus [Smith et al., 2000]), the contrasting short duration of CHPV pathogenesis (enters brain in <24 h; Balakrishnan and Mishra, 2008) and the high viral titer levels in blood within 24 h post infection; it can be suggested that CHPV invades the CNS through the haematogenous route.

In the present review, information of host interactors previously predicted for CHPV has been correlated with the experimental data available for other encephalitic viruses to speculate the various modes by which CHPV invade the CNS to cause encephalitis.

2. CHPV invasion of CNS

The haematogenous route of CNS invasion is most likely the primary route for majority of neurotropic viruses. After being inoculated into blood stream, these viruses generally infect monocytes, macrophages, dendritic and langerhans cells and then get transported to second cell types including epithelial, endothelial, fibroblast and/or muscle cells (Chambers and Diamond, 2003; Lindenbach et al., 2007). On the basis of the functions and cellular localization of the host proteins previously reported by the authors (Rajasekharan et al., 2013), together with the limited knowledge of CHPV pathogenesis available from literature, the authors suggest that, following inoculation into the blood stream, CHPV might initiate a biphasic disease like Venezuelan equine encephalitis virus (VEEV; Schafer et al., 2011). Initially during the peripheral phase, the virus infects leukocytes (most likely monocytes) and undergoes replication within these cells, followed by a neurotropic phase during which the virus infects CNS neurons, causing fatal encephalitis. Earlier research has shown that within 24 h post infection, CHPV invades the brain surpassing the BBB (Balakrishnan and Mishra, 2008). Based on the host interactors previously predicted for CHPV (Rajasekharan et al., 2013), the authors suggest that the virus might invade the BBB probably hidden in 'Trojan Horse' monocytes like those reported in case of West Nile Virus (WNV, family *Flaviviridae*; Getts et al., 2008), Human Immunodeficiency Virus (HIV, family *Retroviridae*; Gras and Kaul, 2010) and Japanese Encephalitis Virus (JEV, family *Flaviviridae*; Thongtan et al., 2012) and/or infect endothelial cells and subsequently cross the blood–brain barrier like Hepatitis C Virus (HCV, family *Flaviviridae*; Fletcher et al., 2012).

3. Disruption of blood–brain barrier during CHPV infection

BBB with increased permeability is a pathological hallmark during various neurotropic viral infections. The CHPV–human host protein interactions identified by the authors in their previous study (Rajasekharan et al., 2013) are highlighted in the present review on the basis of their functional relevance during CHPV neuroinvasion and prioritized based on the known pathogenesis of other neurotropic viruses like VSV, RV, JEV, WNV, VEEV, Influenza A virus and Alpha herpesviruses.

3.1. 'Trojan Horse' crossing

During infection, the activated endothelial cells over express cellular adhesion molecules like VCAM-1, Inter Cellular Adhesion Molecule 1 (ICAM-1) and E-selectin, which enhances the transmigration of immune cells into the cerebral parenchyma (Shen et al., 1997; Verna et al., 2009). Integrin beta-1 (ITGB1) and Lymphocyte function-associated antigen 1 (LFA-1) expressed on the surface of infected leukocytes recognize these over expressed VCAM-1 and ICAM-1, respectively, and thereby enables the leukocyte-endothelial cell binding (Yang et al., 2005). ITGB1 is a subunit of Very Late Antigen 4 (VLA-4) which is normally expressed on monocytes along with LFA1. These proteins only adhere to VCAM-1 or ICAM-1 (expressed on endothelial cells), when activated by chemotactic agents or some other stimuli like viral infection (Gordon et al., 1995). The association among these proteins rapidly activates the endothelial cell derived Reactive Oxygen Species (ROS) through the activation of endothelial cell associated metalloproteinases (MMPs; Deem and Cook-Mils, 2004). Activated MMPs degrade extracellular matrix, tight junction proteins and cell surface receptors in cell–cell junctions (Alexander and Elrod, 2002; Lohmann et al., 2004; Seiki, 2002). The degradation disrupts the integrity of BBB leading to invasion of neural tissue by blood derived immune cells and direct cellular damages (Haorah et al., 2008; Kim et al., 2003). The viral infection and signaling pathways induced during infection can activate macrophages and microglial cells which in turn could lead to the production of pro- and anti- inflammatory molecules such as IL-6, IL-8, type I and II interferons and further promote the disruption of BBB and thus lead to enhanced leukocyte infiltration (Ghoshal et al., 2007; Munoz-Fernandez and Fresno, 1998). The interactions among these proteins thus play a critical role in infiltration of BBB (Baron et al., 1993) and migration of monocytes to CNS (Getts et al., 2012; Henderson et al., 2003). CHPV glycoprotein (G) was predicted to associate with ITGB1, VCAM1, LFA1 and ICAM1 by the authors in an earlier study, suggesting a similar mode of BBB infiltration by CHPV (graphical abstract).

3.2. Direct blood–brain barrier (BBB) crossing

Another aspect through which encephalitic viruses can also disrupt the BBB and invade CNS is the infection of brain microvascular endothelial cells (BMECs; Avirutnan et al., 1998). Various neuropathogenic viruses like WNV (Verma et al., 2010), HCV (Fletcher et al., 2012), Human T cell leukemia virus (HTLV-1; Afonso et al., 2008) are known to directly infect BMECs. The infection stimulates the loss of tight junctions and production of metalloproteinases which disrupts the intergrity of BBB leading to uncontrolled migration of immune cells into brain parenchyma (Xu et al., 2012). The proteins expressed on the surface of the endothelial cells - ICAM1, N-methyl-D-aspartate Receptor 1 (NMDAR1), C-X-C chemokine receptor type 4 (CXCR4), Low density lipoprotein receptor-related protein 1 (LRP1) and insulin-like growth factor 1 receptor (IGF1R) proteins are reported to act as a receptor(s) and/or co-receptor(s) for several viruses for entry into the brain endothelial cells. Cell line studies have reported that the activation of NMDAR1 through exposure of HIV-1 gp120 protein decreases the tightness of BBB and increases the permeability to monocytes causing the BBB to dysfunction (Kanmogne et al., 2007). ICAM-1 acts as receptor for Coxsackie viruses and Echoviruses that cause meningitis in humans (Schneider-Schaulies, 2000). LRP1 acts as viral receptor and mediates the entry of flaviviruses into cells through endocytosis (Agnello et al., 1999). Moreover, both animal and cell line studies have shown that the proteins like VCAM1, ICAM1, NMDAR1, CXCR4, ITGB1 and L-selectin (SELL) are upregulated during HIV-1 brain infection (Kanmogne et al., 2007; Toneatto et al., 1999) and JEV infection