Neurochemistry International 56 (2010) 727–735

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Review

Neurons under viral attack: Victims or warriors?

Swarupa Chakraborty, Arshed Nazmi, Kallol Dutta, Anirban Basu *

National Brain Research Centre, Manesar, Haryana 122050, India

ARTICLE INFO

Article history:
Received 11 January 2010
Received in revised form 22 February 2010
Accepted 24 February 2010
Available online 4 March 2010

Keywords:
Neurotropic virus
Major histocompatibility complex (MHC)
Lymphocytes
Toll-like receptors
Cytokines
Chemokines
Interferons

ABSTRACT

When the central nervous system (CNS) is under viral attack, defensive antiviral responses must necessarily arise from the CNS itself to rapidly and efficiently curb infections with minimal collateral damage to the sensitive, specialized and non-regenerating neural tissue. This presents a unique challenge because an intact blood–brain barrier (BBB) and lack of proper lymphatic drainage keeps the CNS virtually outside the radar of circulating immune cells that are at constant vigilance for antigens in peripheral tissues. Limited antigen presentation skills of CNS cells in comparison to peripheral tissues is because of a total lack of dendritic cells and feeble expression of major histocompatibility complex (MHC) proteins in neurons and glia. However, research over the past two decades has identified immune effector mechanisms intrinsic to the CNS for immediate tackling, attenuating and clearing of viral infections, with assistance pouring in from peripheral circulation in the form of neutralizing antibodies and cytotoxic T cells at a later stage. Specialized CNS cells, microglia and astrocytes, were regarded as sole sentinels of the brain for containing a viral onslaught but neurons held little recognition as a potential candidate for protecting itself from the proliferation and pathogenesis of neurotropic viruses. Accumulating evidence however indicates that extracellular insult causes neurons to express immune factors characteristic of lymphoid tissues. This article aims to comprehensively analyze current research on this conditional alteration in the protein expression repertoire of neurons and the role it plays in CNS innate immune response to counter viral infections.

1. Introduction

There are about 10^{11} neurons in the human brain comprising the major cell type involved in the vital motor and cognitive functions in the body (Williams and Herrup, 1988). Neurotropic viruses have been characterized by their propensity for infecting central nervous system (CNS) cells. The co-evolution of such viruses with the mammalian nervous system has witnessed a constant dueling struggle for survival. Interactions between the immune system and the central nervous system constitute the most complex and interactive regulatory network in mammals. Several features of the CNS cells have evolved unique defensive mechanisms to keep infections at bay, some of which have ironically left neurotropic viruses at a selective advantage for sustaining their life-cycle within the very same cells. While the blood–brain barrier (BBB) is an efficient mechanical check-point for filtering out blood-borne infections from entering the CNS, at the same time, it also cordons off the key cellular and molecular components which are active in immune surveillance in the peripheral organs; for instance "professional" antigen presenting cells called dendritic cells roving in the circulation are not allowed entry into the CNS. The major histocompatibility complex (MHC) class I molecules, important for antigen presentation to cytotoxic T lymphocytes (CTLs) are expressed on most nucleated cells outside the CNS in an uninfected state. Until recently constitutive expression of these MHC proteins in normal neuronal cell cultures or brain slices (Lampson, 1995) were not detected. This apparent absence of MHC on CNS cells was looked upon as a benefit to the sensitive organ system as a robust immune

Abbreviations: BBB, blood–brain barrier; BDV, borna disease virus; CCL, chemokine (C-C motif) ligand; CD, cluster of differentiation; CNS, central nervous system; CMV, cytomegalovirus; CTL, cytotoxic T lymphocytes; CXCL, chemokine (C-X-C motif) ligand; DEN, dengue fever virus; EBV, Epstein-Barr virus; EMCV, encephalomyocarditis virus; HCMV, human cytomegalovirus; HIV, human immunodeficiency virus; HSV, Herpes simplex virus; HTLV 1, human T-lymphotropic virus 1; IFN, interferon; IL, interleukin; IRF, interferon regulatory factors; ISGs, interferon stimulated genes; JEV, Japanese encephalitis virus; LMV, lymphocytic choriomeningitis virus; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; MHV, mouse hepatitis virus; MMPs, matrix metalloproteinases; NFκB, nuclear factor κB; NO, nitric oxide; PAMP, pathogen-associated molecular patterns; PI3-K, phosphatidyl inositol-3 kinase; PKR, dsRNA-dependent protein kinase; PRR, pattern recognition receptors; RABV, Rabies virus; RIG, retinoic acid-inducible gene; RLR, RIG-like receptors; SINV, Sindbis virus; SIV, Simian immunodeficiency virus; SLE, St Louis encephalitis virus; SSPE, subacute sclerosing panencephalitis; STAT, signal transducers and activator of transcription; TCR, T cell receptor; TIMP, tissue inhibitor of MMPs; TLR, Toll-like receptor; TMEV, Theiler's murine encephalomyelitis virus; TNF-α, tumor necrosis factor alpha; VSV, vescicular stomatitis virus; WNV, West Nile virus; YFV, yellow fever virus.

* Corresponding author. Tel.: +91 124 2338921x225; fax: +91 124 2338910/28.
E-mail addresses: anirban@nbrc.ac.in, anirban@nbrc.res.in (A. Basu).

0197-0186/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuint.2010.02.016

attack on non-replicating virus-infected neurons may cause much greater injury than the infection itself; a fatal risk that such a vital organ system cannot afford to take under any circumstance. Thus deficient antigen presentation to infiltrating T cells along with the lack of a conventional lymphatic drainage system in the CNS are key factors responsible for keeping the CNS in an immunologically resting state, a unique harbor conducive to viral persistence. Additionally, interactions between neurons and the glial cells as well as constitutive neurotrophins and transforming growth factor-β secretion, might help in maintaining this immunological quiescence (Dorries, 2001; Neumann et al., 1998). However, some activated/memory $CD4^+$ and $CD8^+$ T cells patrol the CNS at random even in the absence of pathogenic signals, and these either flow away into the peripheral circulation or die in the brain in the absence of antigen recognition (Ransohoff et al., 2003). Thus, vertebrate antiviral mechanisms in the CNS are not constitutively active.

Sophisticated modes of intracellular transport in the physiologically complex neural tissue are favorable for viral sustenance and replication. Neurons, with their extensive cellular processes and interconnections, allow a natural freeway for disseminating viral particles and spread of infection. Understandably, CNS immune response to a viral infection must necessarily be a rapid, stringently controlled process that effectively curtails viral spread with minimal bystander damage to specialized, non-regenerating neural tissue, and preventing an autoimmune response. Extensive studies have focused on the active participation of glial cells (Farina et al., 2007; Hanisch and Kettenmann, 2007) in resisting viral attack while neurons have been interpreted to play more passive secondary roles in viral immune resistance. Recent research however indicates neurons to employ more direct mechanisms to fight a viral attack by hosting and regulating innate and adaptive immune responses in the CNS (Biber et al., 2007; Levite, 2008). Thus the long-held idea of the neuron being a mute victim to a viral infection seems no longer tenable. The main focus of this article is to delineate hitherto reported fundamental mechanisms of antiviral responses elicited by neurons.

Neurotropic viruses causing acute infection in humans include Japanese encephalitis virus (JEV) (Ghosh and Basu, 2009), West Nile virus (WNV), Venezuelan equine, and California encephalitis viruses, dengue fever virus (DEN), yellow fever virus (YFV), St Louis encephalitis virus (SLE), Murray Valley encephalitis virus (MVE), Tick-borne encephalitis (Ghosh and Basu, 2008) and Kunjin virus, polio, coxsackievirus, echovirus, paramyxoviruses (causing mumps and measles), influenza, and rabies viruses as well as members of the family *Herpesviridae* such as herpes simplex, varicella-zoster, cytomegalo and Epstein-Barr viruses (Griffin, 2003). Viruses causing latent infection include herpes simplex and varicella-zoster viruses and those causing slow virus infection include JC polyomaviruses, and retroviruses such as human T-lymphotropic virus 1(HTLV-1) and human immunodeficiency virus (HIV) (Fazakerley and Walker, 2003; Lepoutre et al., 2009; Petito et al., 1999). In case of HIV, the transactivator viral protein, Tat, that is implicated in neuronal death responsible for neurological deficits, has been shown to differ in their neurotoxic properties depending upon the clades in which the virus belong (Mishra et al., 2008). Many viruses that result in chronic infections in the rodent CNS have proven useful models for examining various mechanisms in participation and regulation of immune processes in the brain. Neurons are main targets in the murine CNS for many kinds of viruses, including JEV, Sindbis virus (SINV), WNV, vesicular stomatitis virus and lymphocytic choriomeningitis virus. Viruses causing chronic infection along with myelin loss include two well studied RNA virus models—Theiler's murine encephalomyelitis virus (TMEV), belonging to the non-enveloped *Picornaviridae* family (Brahic and Roussarie, 2009), and mouse hepatitis virus (MHV), belonging to the enveloped *Coronaviridae* family (Bergmann et al., 2006). Table 1 shows a list of major neurotropic viruses infecting humans.

Neurotropic viruses follow the general routes of virus entry into the body. Herpes virus and HIV may break mucous membranes of mouth and genital tracts, while Coxsackie, polio, entero- and echoviruses may take the gastrointestinal route. The bite of a vector organism – most often mosquitoes – can transmit arboviruses like Flavivirus, toga and bunya viruses transdermally into subcutaneous tissues. The bite of a rabid animal or an infected monkey can transmit rabies virus or herpes virus simiae from the skin into muscles transdermally. Infected blood or blood products is probably the only portal of entry for neurotropic viruses such as HIV, HTLV-I, HTLV-II, CMV, EBV and WNV to directly enter the blood. Respiratory tract infections such as mumps, measles, rubella

Table 1
Major neurotropic viruses causing human infections.

Virus Name	Family	Genus	Genome
Human immunodeficiency virus	*Retroviridae*	*Lentivirus*	ss (+) RNA-RT
Human T-lymphotropic virus-I		*Deltaretrovirus*	
Japanese encephalitis virus	*Flaviviridae*	*Flavivirus*	ss (+) RNA
West Nile virus			
Kunjin virus			
St. Louis Encephalitis			
Murray Valley encephalitis virus			
Dengue virus			
Yellow fever virus			
Tick borne encephalitis			
Sindbis virus	*Togaviridae*	*Alphavirus*	
Polio virus	*Picornaviridae*	*Enterovirus*	
Coxsackie virus			
Echovirus			
Rabies virus	*Rhabdoviridae*	*Lyssavirus*	ss (-) RNA
Vesicular stomatitis virus		*Vesiculovirus*	
Herpes simplex virus	*Herpesviridae*	*Simplexvirus*	ds DNA
Varicella zoster virus		*Varicellovirus*	
Cytomegalovirus		*Cytomegalovirus*	
Epstein-Barr virus		*Lymphocryptovirus*	

Neurotropic viruses that are commonly known to cause infections in humans are depicted in the table. These viruses have been shown to be associated with CNS inflammation and neurodegeneration in humans. Apart from the ones categorized in the table, there are some other neurotropic viruses that have been shown to infect other vertebrate animals. Similarly, these viruses may also infect non-human hosts.