Journal of Neuroimmunology 308 (2017) 43–49

Contents lists available at ScienceDirect

Journal of Neuroimmunology

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

Review article

Defining nervous system susceptibility during acute and latent herpes simplex virus-1 infection

Chandra M. Menendez [a], Daniel J.J. Carr [a,b,*]

[a] Department of Microbiology, Immunology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
[b] Department of Ophthalmology, University of Oklahoma Health Sciences Center, Oklahoma City, OK. USA

ARTICLE INFO

Article history:
Received 23 December 2016
Received in revised form 13 February 2017
Accepted 13 February 2017

Keywords:
HSV-1 neural tropism
Acute infection
Latent infection

ABSTRACT

Herpes simplex viruses are neurotropic human pathogens that infect and establish latency in peripheral sensory neurons of the host. Herpes Simplex Virus-1 (HSV-1) readily infects the facial mucosa that can result in the establishment of a latent infection in the sensory neurons of the trigeminal ganglia (TG). From latency, HSV-1 can reactivate and cause peripheral pathology following anterograde trafficking from sensory neurons. Under rare circumstances, HSV-1 can migrate into the central nervous system (CNS) and cause Herpes Simplex Encephalitis (HSE), a devastating disease of the CNS. It is unclear whether HSE is the result of viral reactivation within the TG, from direct primary infection of the olfactory mucosa, or from other infected CNS neurons. Areas of the brain that are susceptible to HSV-1 during acute infection are ill-defined. Furthermore, whether the CNS is a true reservoir of viral latency following clearance of virus during acute infection is unknown. In this context, this review will identify sites within the brain that are susceptible to acute infection and harbor latent virus. In addition, we will also address findings of HSV-1 lytic gene expression during latency and comment on the pathophysiological consequences HSV-1 infection may have on long-term neurologic performance in animal models and humans.

Contents

1. Introduction . . . 44
2. Acute infection of herpes simplex virus-1 in the nervous system . . . 44
   2.1. Herpes simplex induced encephalitis in humans . . . 44
   2.2. Evidence of HSV-1 in the central nervous system of human patients and correlation with neurological disease . . . 44
   2.3. HSV-1 dissemination to and from peripheral nerves . . . 45
   2.4. Brain susceptibility during acute HSV-1 infection in mouse models . . . 45
   2.5. Viral tropism for the lateral ventricles and hippocampus . . . 45
   2.6. HSV-1 genes involved in neurovirulence . . . 46
3. Defining HSV-1 latency . . . 46
   3.1. HSV-1 latency in the peripheral ganglia . . . 46
   3.2. Evidence of sporadic activation during latency in the peripheral ganglia . . . 46
   3.3. HSV-1 latency in the CNS . . . 47
   3.4. Evidence of persistent HSV-1 replication in the CNS during latency . . . 47
4. Conclusions . . . 47
Acknowledgments . . . 47
References . . . 48

Abbreviations: CNS, central nervous system; DPI, days post infection; FACS, Fluorescence-activated cell sorting; HSV-1, herpes simplex virus-1; HSE, Herpes Simplex Encephalitis; NPCs, neural progenitor cells; TG, trigeminal ganglia.

* Corresponding author at: Department of Microbiology, Immunology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.
E-mail address: dan-carr@ouhsc.edu (D.J.J. Carr).

http://dx.doi.org/10.1016/j.jneuroim.2017.02.020
0165-5728/

1. Introduction

The *Herpesviridae* family consists of a subfamily, the Alphaherpesvirinae, that contains a subset of neurotropic viruses including the common human pathogens, herpes simplex viruses types 1 and 2 (HSV-1, HSV-2) and varicella zoster virus (Smith, 2012). Humans are the natural host of herpes simplex viruses. HSV-1 resides in greater than 60% of the world's population and can reactivate to cause peripheral disease, such as cold sores, or ocular infection that can lead to recurrent herpes keratitis (Farooq and Shukla, 2012, Looker et al., 2015). HSV-1 is more frequently found in the oral mucosa and ocular areas than HSV-2 and is one of the leading etiological agents of sporadic encephalitis, known as Herpes Simplex Encephalitis (HSE) (Kollias et al., 2015). In the United States alone, there is an estimated 1500 cases of HSE per year (Knipe and Cliffe, 2008).

HSV-1 infection is initiated in epithelial cells at mucosal surfaces upon initial binding of viral glycoproteins gB and gC with host cell surface heparan sulfate proteoglycans. This allows attachment of the viral glycoproteins gB, gD, and gL to host cellular receptors such as Nectin-1, herpes virus entry mediator, or 3-O-sulfated HS for membrane fusion and viral entry (Agelidis and Shukla, 2015). Following membrane fusion, viral tegument proteins are released in the cytosol such that the viral nucleocapsid is directed to the nucleus along microtubules to release the viral genome (Smith, 2012). In the nucleus, viral DNA circularizes to transcribe immediate-early (IE), early (E) and late (L) viral gene products sequentially (Knipe and Cliffe, 2008). Once viral DNA has replicated, progeny nucleocapsids are assembled, acquire tegument proteins, and are enveloped during budding with the inner nuclear membrane (Knipe and Cliffe, 2008). The resulting capsids then bud again with the cytoplasmic membranes of the trans-golgi network for secretion outside of the cell (Johnson and Baines, 2011, Mettenleiter et al., 2009). Once released, virus gains access to the sensory nerve fibers of the peripheral nervous system (PNS) by direct fusion of the axonal membrane and are transported by retrograde microtubule-associated transport to the cell body of the neuron (Cunningham et al., 2006, Mingo et al., 2012). Acute infection is suppressed to a lifelong latent infection that can result in intermittent reactivation.

Herpes simplex viruses are thought to reside in the sensory ganglia of the PNS and share transynaptic dissemination pathways into the central nervous system (CNS). In rodent models, infection with HSV-1 and HSV-2 results in the transynaptic passage through neurons of the PNS to the CNS producing lethal encephalitis. However, it is unclear why the occurrence of HSE is low in humans relative to more common peripheral eye or skin disease. This review aims to describe the neurotropic regions in human case reports and animal models to delineate HSV-1 trafficking in the CNS and the cause(s) of the long term neurological sequelae that is often observed following HSE in human patients.

2. Acute infection of herpes simplex virus-1 in the nervous system

2.1. Herpes simplex induced encephalitis in humans

HSE typically manifests as an acute and focal necrotizing infection most generally found in the frontal and temporal lobes of the brain, yet its direct pathogenesis is largely unknown (Rozenberg et al., 2011). Even with antiviral therapy, survival rates remain at 70% and life-long neurological deficits are often reported (Aldea et al., 2003, Skelly et al., 2013). Post-HSE sequelae include but are not limited to anterograde amnesia, difficulties with executive function, and aphasia (Skelly et al., 2013). The cause of these pathologies has not been identified.

2.2. Evidence of HSV-1 in the central nervous system of human patients and correlation with neurological disease

Whereas HSV-1 rarely causes encephalitis, it is commonly associated with peripheral manifestations including “cold sores” or ocular keratitis. Nevertheless, HSV-1 DNA is found in a high percentage of PNS and CNS tissue of humans devoid of active clinical signs of disease (Fraser et al., 1981, Mori et al., 2004, Sequiera et al., 1979). Relative to the CNS, upon examination of post-mortem brains of normal and multiple sclerosis patients, 6 of 11 tested positive for HSV-1 DNA (Fraser et al., 1981). The association of HSV-1 DNA and neurological illness was noted in other small studies including patients who died of chronic psychiatric illness (Sequiera et al., 1979) and familial Alzheimer's disease (Mori et al., 2004). While incidental, these reports do raise the possibility that latent/subclinical HSV-1 infection may influence the development of neuronal deficits or neurological disorders themselves.

Clinical investigations have documented the development of HSE following neurosurgery in latently infected patients including an 8-year-old patient suffering from complex partial seizures (Bourgeois et al., 1999) and a 28-year old patient who underwent surgery to excise an oligodendroglioma (Aldea et al., 2003). The latter patient did display symptoms consistent with HSE in previous medical history but HSV-1 DNA was never detected by PCR. In fact, precision in defining appropriate conditions that can reproducibly amplify HSV-1 DNA within the cerebral spinal fluid (CSF) is critical prompting concerns that a threshold level is necessary before HSV-1 nucleic acid amplification can be detected with confidence. (Saldanha et al., 1986, Sequiera et al., 1979).

Cases have recorded the development of HSE following neurosurgery in patients without prior evidence of HSE or any indication of previous HSV-1 infection. Two separate cases reported HSE symptoms in patients following removal of a craniopharyngioma which was later (2 weeks) confirmed to be due to HSV-1 (Kwon et al., 2008, Perry et al., 1998). In both instances, it took several months for the patients to improve with blindness reported in one patient due to acute retinal necrosis. These findings are consistent with an older post-mortem study that revealed a 65-year old glioma patient displayed signs of herpetic encephalitis (Ochsner, 1981). An additional report recognized HSE symptoms and seizure development following neurosurgectomy of a parasagittal meningioma that resulted in death (Spuler et al., 1999). In a somewhat unique case, HSV-1 antigen was detected in cells of a glioblastoma removed from a 28-year old patient who later died 3 days following the surgery (Sheleg et al., 2001). Whether HSV-1 was acquired or reactivated during the development of the malignancy and may have contributed to the neuropathology associated with the neoplasia is unknown. Collectively, these studies elicit consideration in defining a casual or causal relationship between some forms of CNS disease and HSV-1 acute infection/reactivation.

Patients with HSE present primarily with edema or hemorrhage in the frontal or temporal lobes or orbital cortex (> than 75%) but can also involve other regions including the occipital and parietal lobes (Rozenberg, 2013, Skelly et al., 2013). Predilection to traffic and infect these particular brain regions is still unclear but may be related to “hard wiring” between CNS sites. It is thought that the virus directly reaches the temporal lobes *via* the olfactory neurons that innervate the nasal mucosa (Gilden et al., 2007). Alternatively, HSV-1 can disseminate into the CNS through the brainstem from the TG as trigeminal nuclei are located within all levels of the brainstem (Kruger, 1981). Experimentally, it has become evident that the dose and virulence of HSV-1 strains along with the genetic background of the host contributes to greater dissemination throughout the CNS. For example, one study found when mice were infected with a sub-lethal dose of HSV-1 (strain 2) the effects of CNS dissemination were dependent on the mouse strain. In C57BL/6 mice, virus was restricted to the brainstem. However,