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VIRUS SIGNALING AND APOPTOSIS IN THE CENTRAL NERVOUS SYSTEM INFECTION

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1. ABSTRACT

Viruses target the central nervous system (CNS) incidentally, due to complications of systemic infection, or specifically, by ascending via the axons of peripheral and cranial nerves. In the CNS, viruses cause acute disease (viz. encephalitis), latent infections or neurodegenerative pathology. Causation of acute disease or immune-mediated pathology, and virus involvement in the etiology of chronic neurodegenerative diseases depends, at least in part, on the ability to commandeer signaling pathways. Better understanding of these virus-host cell interactions will help identify molecular targets for the development of improved therapeutic strategies.

2. INTRODUCTION

Common clinical syndromes associated with acute virus infection of the CNS are encephalitis and meningitis. Many viruses cause encephalitis (Table 1), but the two most common in the US are herpes simplex (HSV) and rabies viruses (1). Members of the *Picornaviridae* family are the most common cause of meningitis in US (2). Persistent infection of the CNS is commonly associated with immune-mediated disease (3). Multiple sclerosis (MS), a disease of young adults, is characterized by the progressive accumulation of demyelination plaques within the white matter of the CNS, predominantly in the periventricular white matter, optic nerve, brainstem, spinal cord, and cerebellum. Its viral etiology is supported by studies of animal models and by the abnormal immune response of MS patients to measles virus and human herpesvirus-6 (HHV-6) (4).

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the progressive and irreversible deafferentation of the limbic system, association neocortex, and basal forebrain, accompanied by amyloid-beta (A-beta) plaque formation and neurofibrillary tangles. Spread of neurodegeneration to the intrahippocampal circuitry results in disconnection between the dentate granular cells and the CA3 region, the CA1 region and the subiculum, and impairment of learning and memory processes (5). Neuronal degeneration and cell death are common features of virus induced encephalitis as well as AD. Virus infection could lead to neuronal stress and contribute to the formation of AD plaques and neurofibrillary tangles *via* inflammatory responses or through the direct contribution of viral proteins. HSV-1 was implicated in the etiology of AD based on: (i) its ubiquitous nature (most people are infected before adulthood), (ii) overlapping HSV and AD affected brain areas, (iii) the ability of the virus to establish latent infections and reactivate spontaneously, and (iv) the

Table 1. Viruses that cause encephalitis in humans

Family	Members
Herpesviridae	• Herpes Simplex Virus Type 1 (HSV-1) • Herpes Simplex Virus Type 2 (HSV-2) • Varicella-zoster virus • Cytomegalovirus • Human Herpes Virus-6 • Epstein Barr virus
Picornaviridae	• Echoviruses 7,9,11 and 30 • Coxsackievirus B5 • Enterovirus 71
Rhabdoviridae	• Rabies
Paramyxoviridae	• Measles • Mumps
Myxoviridae	• Influenza A and B
Adenoviridae	• Adenovirus
Reoviridae	• Reovirus • Colorado tick fever virus
Retroviridae	• Human immunodeficiency virus-1 (HIV-1)
Togaviridae	• Eastern equine encephalitis virus • Western equine encephalitis virus • Venezuelan equine encephalitis virus
Flaviviridae	• Japanese encephalitis virus • St. Louis encephalitis virus • Murray Valley encephalitis virus • West Nile virus • Rocio encephalitis • Semliki Forest • Louping-ill encephalitis virus • Powassan encephalitis virus • European and Far Eastern (Russian) encephalitis
Bunyaviridae	• La Crosse virus

partial homology of HSV-1 glycoprotein B to Aβ peptide, providing a potential "seed" for Aβ plaque formation in AD (6).

Virus infection of the CNS usually occurs as a complication of systemic infection. HIV is transported to the brain by infected lymphocytes and macrophages that, after adhesion to endothelial cells, traverse the blood-brain barrier. CNS involvement, ranging from aseptic meningitis to AIDS dementia complex, has been demonstrated in 90 % of HIV patients with neurological manifestations. Alphaviruses, invade the CNS *via* direct infection of the choroid plexus, passive transport into the cerebrospinal fluid across cerebral capillary endothelial cell/ astrocyte complex (blood-brain barrier), or by retrograde transport by olfactory routes (8). Other viruses (viz. HSV and rabies) gain access to the CNS by retrograde transport from a peripheral site by ascending the axons of peripheral and cranial nerves.

Rabies virus infects the cells at the neuromuscular junction and is transported to the CNS *via* peripheral (sensory and motor) nerves by retrograde axoplasmic flow (9). HSV is transported by axonal retrograde movement from the site of primary infection (mucosal membranes or abraded skin) to the sensory ganglia, where latency is established. Both HSV serotypes (HSV-1/2) exhibit a centripetal spread to the CNS under conditions that are not yet elucidated. However, HSV-2 infection of the CNS affects mainly neonates, and the route of transmission is believed to be hematogenous, following systemic infection. The outcome is primarily a diffuse encephalitic process that results in generalized encephalomalacia. In adults, HSV transmission is believed to occur primarily by a neuronal route *via* the olfactory nerves or tracts, or along the branches of the trigeminal nerve innervating the basal meninges. In adults, HSV-2 causes aseptic meningitis. By contrast, HSV-1 infection of the adult CNS results in encephalitis, involving the limbic system (10). Whatever the pathway by which it gains access to the CNS, disease causation is at least partially dependent on the ability of the virus to commandeer cell signaling pathways in a complex network of cross talk. Various strategies are used towards this goal and some of these are briefly reviewed here. Focus is on potential targets for therapeutic approaches based on the modulation of apoptosis, a common aspect in the pathogenesis of neurological disorders.

3. VIRAL MODULATION OF SIGNALING PATHWAYS IN CNS PATHOGENESIS

In virus infections of the CNS, neurotoxicity is due to the cellular effects of virus replication or to the action of resident or infiltrating immune/inflammatory cells that respond to newly expressed viral antigens. Direct effects involve modulation of signal transduction pathways and are designed to maximize virus replication/progeny production, evasion of host defenses, and the control of cellular fate. In some cases, the virus inhibits apoptosis, in order to enable completion of its replicative cycle before the cell's demise. In other cases, specific cellular proteins (viz. Bcl-2) inhibit virus-induced apoptosis, leading to virus persistence in neurons. The apoptotic cascade and signaling pathways targeted by viruses include the major neurotrophin-activated ERK and PI3-K, the stress-induced JNK and p38MAPK, apoptotic cascades, inducible nitric oxide synthase (iNOS), and immune/inflammatory responses. These pathways are schematically represented in the preceding article (Aurelian).

3.1. *Retroviridae*

Lentiviruses belong to the Retroviridae family and include HIV-1. They cause aseptic meningitis, subcortical dementia and myelopathy. The incidence of HIV-associated dementia (HAD) has decreased since virus replication in the blood has begun to be controlled by the administration of antiretroviral therapy. However, a less severe form of HAD, comprising a milder cognitive and motor disorder, is a potentially serious problem at this time (11). Approximately 25 % of AIDS patients have HIV-induced encephalitis (HIVE), characterized by severe neuronal damage (reactive gliosis, demyelination, microglial nodules, multinucleate giant cells, brain atrophy) and neuronal loss in the absence of significant neuronal infection. HIV enters the brain, primarily within infected monocytes that cross the blood–brain barrier. Most of the virus produced in the brain is from infected macrophages and microglia, suggesting that immune deregulation may play an important role in neurotoxicity. The HIV proteins

gp120 and Tat exert neurotoxicity by increasing neuronal Ca^{2+} concentrations and activating the NMDA receptors (12). gp120 can also activate the ERK, JNK, and p38MAPK pathways and trigger apoptosis (13). Moreover, neuronal chemokine receptors (viz. CXCR4, CCR3, and CCR5), which are co-receptors for HIV-1 entry into lymphocytes and macrophages, are involved in Ca^{2+} influx into the cell, resulting in the activation of signaling pathways. As such, they link neuronal and inflammatory responses. Indeed, gp120 and Tat induce inflammatory cytokines (viz. IL-1 and TNF-alpha) that, in turn, trigger cytokine (viz. IL-6, TGF-beta) and prostaglandins production providing an autocrine feedback loop that results in neuronal damage. The chemokines macrophage inflammatory protein-1α (MIP-1α), MIP-1β, normal T cell expressed and secreted (RANTES) and IFN-inducible protein of 10 kDa (IP-10) are upregulated in the brains of patients with HIV encephalitis, presumably resulting from increased numbers of CD40+ microglia and their interaction with CD40L. Monocyte chemoattractant protein-1 (MCP-1) and IP-10 are also induced via signaling pathways, viz. ERK and p38MAPK, respectively (14).

Recent evidence suggests that injection heroin abusers are at increased risk of CNS complications from HIV infection, involving immune functions and the CNS response to HIV. Indeed, astroglia maintain the blood-brain barrier and influence inflammatory signaling in the CNS. Astrocytes can express mu-opioid receptors, and are likely targets for abused opiates, which preferentially activate mu-opioid receptors. While Tat alone disrupts astrocyte function, when combined with morphine, Tat causes synergistic increases in Ca^{2+} ions. Astrocyte cultures treated with morphine and Tat showed exaggerated increases MCP-1, RANTES, and IL-6 release. Neurological disease is due to the direct toxic effects of HIV proteins and/or to cell destruction caused by immunologically active molecules (viz. chemokines), which are secreted by infiltrating macrophages, perivascular microglia and astrocytes. Thus, opiates may increase virus access to the CNS (*via* recruited monocytes/macrophages) and enhance its ability to cause encephalitis by synergistically increasing MCP-1 and RANTES release by astrocytes (15). HIV establishes persistent infection in astrocytes, providing a virus reservoir within the CNS (16).

It is generally believed that HAD and HIVE associated apoptosis is due to the interaction of viral proteins with chemokine receptors (viz. CXCR4), independent of CD4 receptor binding. Apoptosis was linked to multiple signal transduction pathways and was reported to involve virus-mediated inhibition of cAMP and activation of IP3. Indeed, CXCR4-mediated neuronal apoptosis was blocked by HA1004, an inhibitor of calcium/calmodulin-dependent protein kinase II, PKA, and PKC. By contrast pharmacological inhibitors of ERK, JNK and p38 MAPK did not inhibit neuronal apoptosis, suggesting that MAPKs are not involved in virus-induced apoptosis (17). This is distinct from the findings in T cells, in which HIV binding to CD4 receptors results in activation of the MEK/ERK pathway independent of CXCR4 binding, and cytokines/chemokines production (18). ERK activation, resulting in AP-1 upregulation/activation and its interaction with NF-kappaB, is also responsible for virus replication in response to mitogens or other extracellular stimuli (19). The prostate apoptosis response-4 (Par-4) protein, which inhibits expression of the anti-apoptotic protein Bcl-2 and activates caspase-8, may also be involved in HIVE pathogenesis and its expression is increased in the hippocampus from HIVE patients (20).

Inducible iNOS was also implicated in HAD pathogenesis. Staining for iNOS and the HIV protein gp41 co-localized in macrophages and microglia and increased with HAD severity (21). NO generated from iNOS can contribute to neuronal dysfunction by activating apoptotic mechanisms through stimulation of NMDA receptors (22). Stimulation of NMDA receptors by astrocyte-released glutamate has also been proposed as an indirect mechanism of gp120-induced neuronal apoptosis. In this pathway, gp120 acts on the CXCR4 receptor on astrocytes and triggers Ca^{2+} increase and ERK activation, resulting in TNF-α release. TNF-α may induce the production of prostaglandin E2 in astrocytes, and it, in turn, triggers a second wave of Ca^{2+} increase as well as extracellular glutamate release (23). Studies of murine macrophages showed that in the lipopolysaccharide-stimulated iNOS expression paradigm, NO production and upregulation of iNOS expression occurs via the JNK pathway (24). However, it is not known whether JNK is also involved in iNOS/NO mediated neuronal dysfunction in HAD or HIVE. Apoptosis may also ensue from direct interaction of gp120 with neurons (25).

Neurotrophins play an important role in the progression of HIV infection of the CNS by increasing the numbers of live neurons that can support virus replication. The levels of NGF and BDNF are increased in HIVE patients (26), and they may contribute to neuronal survival by upregulating Bcl-2 which protects from the neurotoxic effects of HIV-1 Tat (27). Fibroblast growth factor (FGF) also has neuroprotective activity. It regulates the expression of CXCR4 on neurons and inhibits the gp120 toxicity in a dose-dependent manner. Its neuroprotective activity may involve PI3-K/Akt dependent inactivation of glycogen synthase kinase-3β (GSK-3), which is involved in neuronal apoptosis (28) and gp120 toxicity (29). Neuroprotective therapies targeted to blunt the effects of macrophage activation and reverse their pro-apoptotic activity are likely to improve the management of HIVE and HAD patients.

3.2. Arboviruses

Human Arborviruses in North America include La Crosse virus (*Bunyaviridae*); Western, Eastern and Venezuelan equine encephalitis viruses (*Togaviridae*); St. Louis encephalitis, West Nile, and Powassan viruses (Flaviviridae) and Colorado tick fever virus (*Reoviridae*). Colorado tick fever and Powassan fever viruses are transmitted by ticks; the others by mosquitoes. Other tick borne encephalitis viruses include Russian Spring Summer encephalitis and Louping ill encephalitis viruses. Other mosquito-borne viruses include Murray Valley encephalitis virus found in Australia, New Zealand and New Guinea, and Japanese encephalitis virus which is endemic in the

Western Pacific islands and Asia (Korea, Indonesia, China and India).

3.2.1. *Bunyaviridae*

Apoptosis was described for the Hantaviruses, that cause pulmonary syndromes (30) and La Crosse virus, the causative agent of California encephalitis, a vector-borne disease of children (mostly boys aged 6 months to 16 years) (31). Focal neurological signs in the temporal lobe occur in most cases of California encephalitis and neurological sequelae were reported in 12 - 46 % of infected children (2). The virus replicates locally at the site of the mosquito bite, resulting in viremia. It reaches the CNS *via* cerebral capillary endothelial cells or the choroid plexus. Studies of a mouse model indicated that CNS toxicity is due to apoptosis, and neuroprotection was achieved by expression of the anti-apoptotic protein Bcl-2 (31). Apoptosis is caused by a non-structural viral protein known as NSs that triggers cytochrome c release from the mitochondria and induces caspase activation (32).

3.2.2. *Togaviridae*

Venezuela (VEE), Eastern (EEE) and Western (WEE) equine encephalitis viruses are enveloped, positive-strand RNA viruses of the genus *Alphavirus*. They are transmitted by mosquito bites. VEE is an emerging zoonotic disease that affects both equines and humans and is maintained enzootically in small rodents. Children are more susceptible to neurological manifestations and develop fatal encephalitis. Apoptosis is an important feature of VEE infection and it is triggered both by virus replication and the inflammatory response (such as iNOS and TNF-α) (33). CNS manifestations in EEE or WEE infected humans are preceded by a 2-10 days incubation period and a prodrome period consisting of fever, myalgia, headache, nausea, vomiting, and abdominal pain that signals virus replication in non-neural tissue (2). The viruses enter the CNS *via* cerebral capillary endothelial cells during secondary viremia. Neurons and glia are infected. An inflammatory response also occurs, with perivascular cuffing and lymphocytic and polymorphonuclear infiltration (9). Mortality from EEE infection can reach 70 % in infants and children, and survivors evidence neurological sequelae, including seizures and mental retardation (9). EEE antigens are present mainly in neurons (perikaryon and dendrites) of basal ganglia and thalamic nuclei with temporary involvement of the cortex. Apoptosis is primarily in glial and inflammatory cells, but its mechanism is still unclear (34). WEE apparently arose by recombination between EEE and Sindbis-like viruses (35). In humans, WEE causes a mild, subclinical disease except in children under 1 year of age. Inflammatory cells entering the brain parenchyma and perivascular areas presumably cause neuronal death. Neurological sequelae were reported for infants younger than 3 months of age (2).

Sindbis virus causes encephalitis and paralysis in animal models (viz. mice) and is widely used as a model for alphavirus-induced age-dependent human encephalitis [fatal encephalitis occurs in newborn but not mature mice (36)]. Both necrotic and apoptotic pathways are involved in neuronal cell damage. Apoptosis is triggered in the process of cell penetration or by expression of specific viral proteins (37). Excitotoxicity, mediated by excessive activation of NMDA-type glutamate receptors, and the subsequent increase in intracellular Ca^{2+} are believed to be responsible for the necrotic death of infected neurons *in vitro*. A bystander death effect was observed in uninfected nearby cells, presumably due to NMDA-mediated excitotoxicity (38). Bystander death is a common feature of several other neurovirulent viruses, such as Dengue (39) and reovirus (40). Apoptosis is an important factor in Sindbis encephalitis. It occurs in infected neurons and correlates directly with neurovirulence and mortality rates (41). Bcl-2 protects mice against fatal encephalitis, inhibits virus replication and neuronal cell death, and allows for virus persistence in cultured cells (41). The anti-viral activity of Bcl-2 was associated with its interaction with a novel 60-kDa protein named Beclin that, when overexpressed, has anti-apoptotic and antiviral activities and protects from virus-induced encephalitis (42). Beclin is a tumor suppressor that interacts with PI3-K and is involved in autophagy, a Ras-associated non-apoptotic programmed cell death (43). In non-neuronal cells, heterodimerization of Bcl-2 pro-survival proteins with pro-apoptosis family members (viz. Bad) promotes Sindbis virus-induced apoptosis (44). Apoptosis appears to be cell-type specific and it involves additional signaling proteins, such as Ras, the JNK and p38MAPK pathways (45), NF-kB, and inhibition of tyrosine-phosphorylated PKC (46). However, CNS symptoms are generally not seen in human Sindbis virus infection.

Rubella virus is the sole member of the Rubivirus genus in the Togaviridae family that uses the same replication strategy as Sindbis virus. While considered a benign childhood disease, a vertically-infected fetus exhibits a range of neurological symptoms and birth defects due to virus replication. Fetal damage occurs in 90 % of cases when infection occurs in the first 10 weeks of pregnancy but the risk declines to about 10-20 % by 16 weeks. In adults, rubella virus may cause a post-infectious encephalitis syndrome and a neurodegenerative disease called progressive rubella panencephalitis (PRP), which is characterized by demyelination and resembles MS. The mortality rate for rubella encephalitis is 0-30%, and most patients recover quickly with no neurological sequelae (47). Apoptosis was implicated in rubella virus pathogenesis and it is associated with virus replication. *In vitro,* the virus triggers caspase-dependent apoptosis of oligodendrocytes, likely explaining the demyelinating effect of infection (48). Virus replication in non-neuronal cells does not affect the expression of the Bcl-2 proteins and apoptosis is independent of p53 (49).

3.2.3. *Flaviviridae*

Encephalitic flaviviruses are a diverse group of viruses that include mosquito-borne (Japanese encephalitis, St. Louis encephalitis, Murray Valley encephalitis, Rocio encephalitis, Semliki Forest, and West Nile) and tick-borne (European and Far Eastern or Russian encephalitis, Louping-ill encephalitis, and Powassan encephalitis) human pathogens. In addition to encephalitis they cause a

wide range of diseases, from a mild febrile illness to hemorrhagic fever syndromes. The St. Louis encephalitis (SLE) syndrome affects primarily the elderly (2,9). Encephalitis is characterized by focal neuronal degeneration and inflammatory infiltrates in the gray and white matter. CNS pathogenesis may involve apoptosis and pro-apoptotic Bcl-2 family members (viz. Bax) (50). Powassan encephalitis, first reported in the U.S. in 1994, is associated with 10-15% mortality. Pathological damage primarily involves the grey matter and is characterized by inflammatory infiltrates of lymphocytes and macrophages. Molecular events involved in the CNS disease are still unknown.

Japanese encephalitis virus (JEV) is one the most common causes of arbovirus infection worldwide. Encephalitis is primarily seen in children and the elderly and it is associated with high mortality and morbidity. Severe cytopathic effects and cell death are primarily in the thalamus and brain stem, and they are due, at least in part, to apoptosis. JEV-induced apoptosis appears to involve the endoplasmic reticulum (ER) unfolded protein response (UPR) that signals malfunctioning of ER in neuronal and non-neuronal cells (52). UPR is a stress-activated ER-nucleus signaling cascade. It causes increased expression of certain proteins and inhibition of translation at the initiation step in order to curtail the accumulation of unfolded proteins in the ER lumen. Among the proteins induced by UPR is the death-related transcription factor CHOP/GADD153 that may downregulate Bcl-2 and stimulate production of reactive oxygen species (53). However, in cultured cells, Bcl-2 (but not its homolog Bcl_{XL}) inhibits virus-induced apoptosis in a cell-type dependent manner (51), leading to persistent infection (64). Virus persistence was reported in approximately 5% of JEV-induced encephalitis patients, potentially involving Bcl-2 inhibition of the ER-associated caspase-12. JEV-induced apoptosis involves activation of the p38MAPK stress signaling pathway and translocation of the activated transcription factor CHOP to the nucleus (51). It is still unclear whether p38MAPK is upstream or downstream of UPR in the apoptotic sequence of events that leads to CHOP activation. Because flaviviruses induce proliferation of ER membranes and accumulation of viral proteins in the ER lumen, it will be interesting to see whether the UPR/CHOP and/or UPR/caspase-12 constitute common apoptotic pathways for most or all the flaviviruses.

West Nile virus (WNV) is an emerging human pathogen in North America, first documented in New York City in 1999. It has become the single most common cause of arboviral disease in the US (2). WNV crosses the blood brain barrier and causes encephalitis, aseptic meningitis or meningoencephalitis (when the leptomeninges are involved). Encephalitis and/or meningoencephalitis occur in approximately 60 % of cases. In non-neuronal cells, WNV causes both necrosis and apoptosis, depending on the virus dose. Apoptosis was observed at the lower multiplicities of infection and it had classical features including cytochrome c release from the mitochondria and activation of caspases-9 and -3 (55). In cultured neuronal cells, WNV induced apoptosis was associated with upregulation of the pro-apoptotic protein Bax. The capsid protein (WNV-Cp) activates caspase-9/3 and induces inflammation *in vivo* (56).

Dengue virus, another mosquito-borne flavivirus can cause encephalitis and encephalopathy in both primary and secondary infections. Apoptosis is a crucial aspect of CNS pathogenesis. It involves sequential activation of phospholipase A2 (PLA2) and NADPH oxidase leading to production of arachidonic acid (AA) and reactive oxygen species (ROS). Mitochondrial damage-induced by oxidative stress, and activation of the transcription factor NF-kB and p53 are also involved (57). Dengue virus also infects monocytes/macrophages and T-cells, suggesting that immune mechanisms such as the cytokine response (TNF-α, IL-1, CF2 cytotoxin) may also contribute to neuronal pathology.

3.3. *Picornaviridae*

Enteroviruses (polio-, echo, and coxsackieviruses) are members of the *Picornaviridae* family. In the United States they cause 10-15 million symptomatic infections annually, affecting almost every organ in the body. They enter the body through the upper respiratory or gastrointestinal tracts and commonly target the CNS, resulting in aseptic meningitis. Meningoencephalitis or encephalitis syndromes also are known to occur. Since immunizations virtually eliminated poliovirus from the US, this review will only mention recent advances concerning non-polio serotypes. Among these, viruses which are most often associated with CNS damage include echoviruses 4, 7, 9, 11, 16, and 30 (causative agents of aseptic meningitis); enterovirus 71 (responsible for large outbreaks of acute poliomyelitis-like paralysis); and coxsackieviruses group A (cause 10-20 % of viral encephalitis cases in children and infants) and B (B2, B5, causative agents of aseptic meningitis) (58). Neonates are particularly susceptible to enterovirus (echo- and group B coxsackieviruses) infection acquired vertically from their mothers. They show a high rate of mortality, especially when combined with myocarditis (usually caused by group B coxsackieviruses serotypes 2-5).

Enterovirus 71 (EV71) causes a wide range of diseases, from hand-foot-mouth disease to encephalitis. Cytopathic effects in EV71 infected non-neuronal cells have morphological and biochemical features of apoptosis (nuclear condensation, DNA fragmentation and PARP cleavage). They are caused by the virus-encoded protease $2A^{pro}$. It cleaves the eukaryotic polypeptide chain initiation factor (eIF) 4 GI (eIF4GI), a component of the cap-binding complex involved in initiation of translation. EIF4GI cleavage results in the inhibition of *de novo* cap-dependent translation and rapid cell death (59). Coxsackievirus B3 (CVB3) targets the CNS as well as the heart, lung, and pancreas and is considered the most common human pathogen for viral myocarditis. Neonates are particularly susceptible to CNS infection resulting in meningitis, encephalitis and long-term neurological sequelae. Loss of neurons by apoptosis in specific brain areas (hippocampus, entorrhinal and temporal cortex, olfactory bulb) may explain the CNS pathogenesis (60). At least in non-neuronal cells, apoptosis/cytopathic effects

appear to be due to activation of the Ras-initiated ERK signaling pathway, which is required for CVB3 replication. In these cells, ERK activation consists of an early phase that is transient and a late phase that is sustained and precedes caspase-3 activation (61). The late phase may be due to cleavage of the Ras inhibitor Ras-GAP. The viral proteinase $3CD^{pro}$ interacts with Sam68, a cellular adaptor protein that binds Ras-GAP, and is believed to be responsible for this effect (62). Ras-GAP cleavage is also caused by echoviruses (22), suggesting that it is a common event in enterovirus infection. Echoviruses also upregulate transcription factors c-jun, junB, and c-fos, that stimulate apoptotic pathways in some cell types.

3.4. *Reoviridae*

Reovirus is the prototype of the Orthoreovirus genus and Colorado tick fever (CTF) is the prototype of the Coltivirus genus. CTF is transmitted to humans by the adult hard-shelled wood tick *Dermacentor andersoni* and causes an acute febrile often diphasic but mild dengue-like illness (also known as mountain fever). Occasionally, CTF may cause encephalitis and even hemorrhagic fever (63). Human reovirus infection of the CNS with encephalitis symptoms was demonstrated in infants and adults.

Reoviruses infect the gastrointestinal tract. Following replication at this site, they spread through blood to distal organs such as brain, liver, heart, spleen and kidneys. Serotype 1 (T1) is believed to enter the CNS by the hematogenous route (via the meninges or through the blood vessel epithelium along the choroids plexus, hypothalamus, or area postrema). Despite its presence in the bloodstream, Serotype 3 (T3) uses a neuronal route (along the vagal autonomic nerve fibers), resulting in distinct neurological syndromes for the two serotypes (self-limiting hydrocephalus *vs* lethal encephalitis). Reovirus strain T3 preferentially infects the cortex, hippocampus, and thalamus areas of the neonatal mouse brain and induces neuronal apoptosis more efficiently than the T1 serotype. In the neonate, apoptosis is triggered by virus binding to the cell surface receptor (JAM, junction adhesion molecule). It is accompanied by NF-kB activation, suggesting that tight junctions are involved in signal transduction and integration of inflammatory and apoptotic responses (64). However, the adult mouse brain becomes resistant to T3-induced pathogenesis, presumably due to the loss of the receptor JAM. In non-neuronal cells, reovirus-induced apoptosis is inhibited by overexpression of Bcl-2 (65) and it requires binding of TRAIL (TNF related, apoptosis-inducing ligand) to its cellular receptors DR4 and DR5 (76). Apoptosis involves upregulation of DR5 (and to a lesser extent DR4) and triggers the release of TRAIL from infected cells in a FADD/caspase-8-dependent manner (66). While reovirus also activates the JNK/c-Jun and ERK pathways, their role in CNS disease is still unclear (67).

3.5. *Paramyxoviridae*

Measles virus (MV) (Rubeola) belongs to the Morbillivirus genus of the Paramyxoviridae family. The clinical spectrum ranges from mild and self-limiting to lethal disease. Although a live attenuated vaccine has been available since 1967, it is estimated that MV is a leading cause of death due to virus infection (68). In addition, 20 % of infected adults who died of unrelated causes expressed MV antigens in the CNS at the time of death, suggesting that persistent infection of the adult CNS may be the cause of seemingly unrelated CNS disorders. Neurological complications of acute measles infection include: (i) acute postinfectious encephalomyelitis characterized by demyelinization and brain inflammation (occurs in 1/1000 cases during or shortly after acute measles infection), (ii) subacute sclerosing panencephalitis (SSPE) and (iii) inclusion body encephalitis. SSPE is a rare neurodegenerative disease that may occur years after infection and is presumably due to virus persistence. It presents with seizures, coma, and death in 1/100,000 cases of acute measles infection. Inclusion body encephalitis is a measles-induced progressive infectious encephalitis that affects immunosuppressed patients several months after measles infection (69). Measles-mediated immunosuppression is considered the major cause of death in acutely infected infants. Inhibition of Akt/GSK-3β but not JAK/STAT signaling pathway in T-cells occurs early in infection and is involved in measles immunosuppression *in vivo* and *in vitro* (i.e. proliferation inhibition). This effect is mediated by the fusion (F) and hemagglutinin (H) viral glycoproteins, but it does not lead to cell death.

MV replication and neuronal apoptosis were described in CD46 (human complement regulatory protein)-transgenic mice. In this model of MV encephalitis, virus replicates in the brain and disseminates rapidly throughout the CNS. Specific areas affected early in infection (day 4) include the motor cortex, hippocampus, and the anterior olfactory nucleus. Other areas of the brain follow, and the cerebellum is extensively damaged in the course of infection. Apoptotic cells were seen in the bed nucleus of stria terminalis, paraventricular nucleus of thalamus, preoptic area of the hypothalamus, periaqueductal gray matter, and metencephalic reticular formation (70). MV persistence in neurons (virus reactivation and/or an inappropriate immune response to viral antigens) is the cause of SSPE, as suggested by MV-induced HLA class I expression on glial cells in an IFN-gamma and NF-kappaB-dependent manner (71). Apoptosis was demonstrated in human SSPE brains, but it is unclear whether it is a direct effect of virus replication or a cytokine-mediated response (72).

Mumps virus belongs to the Rubulavirus genus. It causes parotitis, meningitis (4-6 % of cases), encephalitis (1 in 1000 cases), and orchitis (40 % of adult males), but death is rare. Neurological symptoms occur in 10-20 % of cases and appear to be due to apoptosis caused primarily by cytokine responses (such as IL-1β production) (73).

3.6. *Myxoviridae*

Influenza virus is an Orthomyxovirus that is responsible for acute upper respiratory disease. Both influenza A and B can cause acute encephalitis and encephalopathy in children. The virus reaches the CNS *via* afferent fibers of the olfactory, vagal, trigeminal, and sympathetic nerves, following replication in the respiratory mucosa (74). In epithelial cells infection triggers apoptosis

by activating the JNK and p38MAPK stress pathways. They initiate with ASK-1 (apoptosis signal-regulating kinase 1), which is upstream of SEK1-JNK and MKK3/MKK6-p38 MAPK (75). P38MAPK and JNK activation was linked to production of RANTES, a cytokine that is involved in airway inflammation (76). In animal models, acute encephalitis was associated with apoptosis and the activation of the JNK pathway in virus-infected neurons, and activation of the p38MAPK pathway in astrocytes (77). It would be of interest to see whether JNK and p38MAPK activation in the brain also correlates with cytokine production, since both pathways activate the transcription factors NF-kappaB and AP-1 which induce expression of the chemokine RANTES (78). dsRNA-dependent protein kinase PKR and the Fas-mediated pathway were also implicated in influenza virus-induced apoptosis (80). Presumably, apoptosis is required for virus replication, because Bcl-2 inhibited apoptosis, virus replication and glycosylation of the viral hemagglutinin protein (81). Decreased virus replication may be advantageous for virus survival due to improved immune evasion and persistence. Apoptosis was also seen in neurons and glial cells from human brains affected by influenza encephalopathy (79).

3.7. *Adenoviridae*

Encephalitis is a rare complication of adenovirus infection, which usually affects the upper respiratory tract or eyes. Meningitis, meningoencephalitis and rhombencephalitis, characterized by inflammation of brain stem and cerebellum were also described in normal and immunocompromised patients (82). Neurological symptoms associated with adenovirus infection include headache, myalgia, anorexia, mental alteration, and seizures. They last 2 - 14 days. In addition, rhombencephalitis may be characterized by ophtalmoplegia, ataxia, and areflexia.

Adenovirus-induced neurological symptoms are of particular concern in view of ongoing clinical trials using adenovirus vectors for the treatment of brain disease. In immunocompromised patients adenovirus may cause disseminated disease and death. Adenovirus encodes both pro-apoptotic (E1A) and anti-apoptotic viral proteins (E1B), but their contribution to CNS pathogenesis is still unclear. When all viral genes except those necessary for virus replication and packaging are deleted, adenovirus vectors produce stable and long-term transgene expression even after vector re-administration, natural infection with the same or a closely-related serotype, or subsequent peripheral immune challenge (83). This is due to decreased virus-specific T-cell responses in the brain. However, an innate capsid-mediated inflammatory response cannot be avoided by genome deletion, and it is responsible for an initial inflammatory dose-dependent response that is characterized by leukocyte infiltration across the blood-brain barrier and microglial/astrocyte activation within 24 hrs of vector administration (84). This process may be due to the production of pro-inflammatory cytokines by infected cells, involving activation of the Raf/ERK pathway (85) or the ERK and p38MAPK pathways that respectively lead to the production of IL-8 and IP-10 (86).

3.8. *Rhabdoviridae*

Human rabies virus belongs to genus Lyssavirus of the *Rhabdoviridae* family. Following infection, the incubation period lasts 5 days - >1 year but is typically 1 - 3 months. Even though human rabies is very rare, contact with raccoons and bats may lead to the reemergence of this zoonosis. Virus replicates initially in myocytes at the site of a rabid animal bite and spreads by retrograde axoplasmic flow to the spinal cord and CNS via sensory and motor nerves. This is followed by centrifugal spread to other organs including skin and salivary glands. RV causes rapidly progressing encephalitis characterized by perivascular lymphocytic infiltration, inflammatory cytokine production and the presence of cytoplasmic eosinophilic inclusion bodies (Negri bodies) in neuronal cells, especially in the pyramidal cells of the hippocampus and Purkinje cells of the cerebellum.

Apoptosis plays an important role in rabies pathogenesis, by affecting both neuronal cells and infiltrating lymphocytes. Bcl-2 inhibits virus-induced T-cell apoptosis, whether caspase-dependent or independent (87). In experimentally-infected animal brains, apoptosis is first seen in the hippocampus and neocortex, followed by other areas such as basal ganglia, thalamus, and brain stem. Viral antigens were present in the cerebellar Purkinje cells, but the apoptotic effect was not significant in the cerebellum. Inflammatory responses may be responsible for lethality, since mortality was delayed in animals lacking the p55 kDa TNF-α receptor that is involved in cytokine signaling (88). In addition to cytokines, nitric oxide (NO) production and iNOS expression coincide with the onset of disease, and may lead to changes in the permeability of the blood-brain barrier and subsequent invasion of brain by T-cells and monocytes (89). Although the low-affinity neurotrophin receptor p75NTR was reported to function as a rabies receptor, p75NTR-deficient suckling mice were infected and evidenced similar pathologic features as wild type animals, suggesting that p75NTR is not involved in rabies infection/pathogenesis (90).

3.9. *Herpesviridae*

3.9.1. Non-simplex encephalitides

Herpesviridae family members other than HSV-1/2 occasionally affect the CNS, but there is scarce information about the molecular mechanism of their pathogenesis in the brain. Epstein-Barr virus (EBV) is a gamma herpesvirus that infects mainly B lymphocytes where it remains latent after primary infection. It causes infectious mononucleosis (glandular fever) which may be accompanied by a mild form of encephalitis in about 1 in 100 cases. Other neurological complications may also occur in about 36 % of cases (91). These might include seizures, Guillain-Barre syndrome, Bell palsy, transverse myelitis, meningitis, and cranial nerve palsies. A Parkinson-like syndrome has been reported as a neurological sequela of acute EBV encephalitis, but it is also common to other viral encephalitides such as those caused by HSV, JEV, cytomegalovirus, coxsackievirus, measles and cytomegalovirus. The Parkinson-like syndrome is characterized by involuntary hand movements,

akathisia, bradykinesia, torticollis, and drooling (92). In non-neuronal cells, EBV latent membrane protein 2 A (LMP2A) activates the ERK and JNK pathways (93) while the oncogene LMP1 activates the JNK pathway and NF-kappaB (94). LMP-1 causes cell transformation involving activation of the Ras/ERK pathway (95) and it increases expression of the anti-apoptotic protein A1 (bfl-1) (96). Other EBV anti-apoptotic proteins include the Epstein-Barr nuclear antigen 1 (EBNA-1) that is anti-apoptotic in EBV lymphomas (97) and BZLF1 that inhibits TNF-alpha-mediated apoptosis (98).

Cytomegalovirus (CMV) is a beta herpesvirus that replicates in epithelial and endothelial cells, smooth muscle, microglia and macrophages and establishes latency in peripheral blood monocytes and macrophage-granulocyte progenitors. CMV encephalitis is a complication seen primarily in immunocompromised patients, where it has a high mortality rate (about 50 %). Up to 12 % of HIV patients demonstrated CMV presence in their brains at autopsy (99). In these patients, CMV may also cause ventriculitis, myelitis, retinitis, radiculoganglionitis, and peripheral neuropathies. CMV infection was also demonstrated in immunosuppressed organ transplant recipients and immunologically normal individuals (100). Pathological findings in CMV encephalitis include microglial nodules, primarily in the gray matter, but no focal necrosis (97). In non-neuronal cells CMV may induce (101) or prevent (102) cell death in a cell-type specific manner. CMV infection activates the ERK (103) and p38MAPK (104) pathways in fibroblasts, but it is not known if any of these activities also occur in infected brain cells.

HHV-6 is a ubiquitous pathogen related most closely to CMV and thought to be present in about 95 % of population. It may cause roseola infantum in children (mainly HHV-6B variant). Following primary infection (and replication in lymphocytes and salivary epithelial cells), HHV-6 establishes latency in lymphocytes and monocytes and possibly neuronal cells (105). Neurological complications in AIDS and transplant patients (viz. encephalitis) are primarily associated with HHV-6A latency reactivation. Pathological findings of HHV-6 encephalitis include focal or diffuse demyelination and are primarily the result of viral cytotoxic in oligodendrocytes. However, *in vitro* experiments suggest that cytotoxicity is indirect and is not due to apoptosis (106). The effect of HHV-6 on oligodendrocytes, microglia, and neurons, and the finding of HHV-6 in demyelinated lesions and plaques from the brains of MS patients (but not normal brains) lead to the current view that HHV-6 is involved in MS pathogenesis. However, a causal link is yet to be established.

Chickenpox, a mild self-limiting acute disease follows primary infection with Varicella-zoster virus (VZV). Zoster (shingles) is due to reactivation of the latent virus. During primary infection, VZV replicates in epithelial, T cells and neurons and establishes latency in dorsal root sensory ganglia. Complications that may ensue following chickenpox include meningitis, meningoencephalitis, transverse myelitis, and cerebellar ataxia. Complications associated with shingles include encephalitis, transverse myelitis, cerebral angitis, palsy, and post-herpetic neuralgia. Adults (>20 years of age) account for 55 % of VZV-related deaths, with encephalitis having a 10 -30 % mortality rate. VZV induces apoptosis in cultured epithelial and immune cells, but not in sensory neurons (107). It has been suggested that apoptosis inhibition may be involved in the establishment and maintenance of latency. VZV was found in a high percentage of brains from patients with neurodegenerative diseases (26.5 and 40% of Alzheimer's and Parkinson disease, respectively) together with other herpesviruses (viz. HSV-1 and HHV-6), suggesting that it may constitute a risk factor for these diseases (108).

3.9.2. HSV-1 and HSV-2

HSV-1 and HSV-2 have an overall DNA homology of 50 % (which is higher or lower in some genomic regions). They have a general predilection for different body sites: HSV-1 is mostly associated with oral (skin and mucosa) lesions, while HSV-2 causes genital lesions. The histopathological characteristics of primary HSV infection reflect virus-mediated cellular lysis and associated inflammatory responses. When cell lysis occurs, a clear (vesicular) fluid containing large quantities of virus appears between the epidermal and dermal layers. The vesicular fluid contains cellular debris, inflammatory cells, and, often, multinucleated giant cells. In the dermis, there is an intense inflammatory response. When healing occurs, the vesicular fluid becomes pustular, inflammatory cells are recruited, and scabs are being formed. Shallow ulcers in the mucosae replace the vesicles.

Upon infection of mucosal membranes or abraded skin, both HSV-1 and HSV-2 are transported by axonal retrograde movement (involving microtubules) to the sensory ganglia. Here (trigeminal and sacral ganglia for HSV-1 and HSV-2, respectively), they establish latency by maintaining the viral genome in a largely non-transcribed episomal state. Latently-infected ganglia provide a virus reservoir for the entire life of the infected individual by means of periodic reactivation (recurrent infections), whereby virus is transported by reverse axonal transport back (or close) to the dermatome of entry. Reactivation occurs following a variety of local or systemic stimuli such as physical or emotional stress, fever, exposure to UV light, tissue damage and immunosuppression. Recurrences occur in the presence of both humoral and cell-mediated immunity. The spectrum of disease caused by HSV includes infection of the mucous membranes (gingivostomatitis, herpes labialis, and herpes genitalis), keratoconjuctivitis, neonatal HSV infections, visceral HSV infections in immunocompromised hosts, Kaposi's varicella-like eruption, and erythema multiforme (109).

3.9.2.1. HSV Latency

A transcript designated LAT (latency associated transcript) is the only viral gene expressed in latently-infected neurons. LAT is now believed to be a stable intron, approximately 8 kb. It is not required for the establishment and maintenance of latency, but it may be involved in HSV-1 reactivation. ICP0 (110) and LAT (111) were

implicated in HSV-1 latency reactivation, the latter by virtue of its anti-apoptotic activity. Recent findings that STAT1 (signal transducer and activator of transcription 1) binds to the LAT promoter, point to a signaling connection between LAT and cytokines, which may contribute to virus reactivation (112). However, HSV-1 latency reactivation was also associated with the induction of apoptosis (113) and the induction of cAMP early repressors (ICER) that downregulate LAT (114). Possibly, the involvement of ICP0 and/or LAT is specific for some, but not other HSV-1 strains, latency models and/or stress stimuli (115). LAT does not seem to be involved in HSV-2 latency reactivation (116), a conclusion supported by the failure of the HSV-2 LAT to substitute for its HSV-1 counterpart in promoting latency reactivation (117). The large subunit of HSV-2 ribonucleotide reductase, which has protein kinase activity and is known as ICP10PK (109) was implicated in HSV-2 latency reactivation. An HSV-2 mutant deleted in ICP10PK was severely compromised for latency reactivation (118) and HSV-2 reactivation from explanted ganglia was inhibited by an ICP10PK-specific antisense oligonucleotide (119). Neurons are non-permissive for virus replication when they harbor the virus genome in a latent state. When placed in culture however, neurons taken from a latently infected tissue become permissive and virus replication ensues. NGF is essential for latency maintenance and its withdrawal triggers virus reactivation (120).

3.9.2.2. HSV infection of the CNS

Both HSV serotypes can reach and infect the CNS. HSV-1 accounts for nearly all cases of herpes encephalitis in adults (and about 10 to 20 % of all viral encephalitis cases) while both serotypes can cause encephalitis in infants. With treatment, mortality rates are 15% in newborns and 20% in others. Untreated, mortality rates are 60 - 80%. The route of HSV-2 access to the brain of infants with multiorgan disseminated infection acquired during partum is hematogenous. Infection is associated with a diffuse encephalitic process that results in generalized encephalomalacia. In adults, HSV-2 can cause aseptic meningitis, predominantly among patients who have primary genital disease. The outcome in these cases is excellent even without antiviral therapy. By contrast, HSV-1-induced encephalitis (HSE) has a high mortality rate (over 50 %) and survivors are left with neurological sequelae involving impairments in memory, cognition, and personality.

The molecular mechanism responsible for the different neurological outcome of adult CNS infection with the two HSV serotypes likely involves serotype- and cell/tissues-specific anti-apoptotic proteins. The US3 viral protein has serine-threonine kinase activity. It has been shown to attenuate virus-induced apoptosis in mouse brains (cortex) by inhibiting the JNK pathway (121). In non-neuronal cells, the HSV-1 US3 protein blocks apoptosis by posttranslational modification of the pro-apoptotic protein Bad (122) or by inhibiting its caspase-mediated cleavage, which enhances pro-apoptotic activity (123). However, in view of the high homology level (75 %) between the HSV-1 and HSV-2 US3 proteins, US3 is unlikely to explain the serotype-specific outcome of CNS infection. By contrast, ICP10PK, which also has anti-apoptotic activity in the CNS, is poorly conserved in HSV-1 (109) and is likely to explain the failure of HSV-2 to cause encephalitis. We have recently shown that ICP10 PK protects hippocampal neurons from virus-induced apoptosis by activating the ERK pathway and transcription factors such as CREB, and by increasing the expression of anti-apoptotic proteins such as Bag-1. ICP10 PK also protected from apoptosis due to intrinsic genetic defects. By contrast, HSV-1 and an ICP10PK deleted HSV-2 mutant triggered JNK/c-Jun dependent apoptosis in cultured hippocampal neurons, and apoptosis was associated with HSV-1 induced encephalitis (124-127). Activation of the ERK pathway by ICP10PK may constitute a novel therapeutic approach for neurodegenerative disorders (viz. Alzheimer's disease), since ERK/ CREB are involved in neuroprotection and the induction of long-term potentiation, the molecular mechanism of learning and memory (128). ICP10PK may have evolved from a cellular gene hijacked by the virus during infection., as its eukaryotic homologue, the heat shock protein H11 also regulates apoptosis (129).

Latent HSV in the CNS was implicated in the pathogenesis of Alzheimer's disease. It was suggested that virus reactivates in elderly brain due to stress or immunosupression leading to mild encephalitis associated with a decline in cognitive functions and tissue damage-further augmented by the age-related decline in the immune system (130). The frequency of viral reactivation may be higher in individuals homozygous or heterozygous for the apolipoprotein E4 (ApoE4), suggesting that both viral and genetic factors may be involved in disease causation. Sequences in the HSV-1 glycoprotein B are homologous Amyloid beta, interact with apoE, and cause neuronal death (6), supporting the involvement of HSV-1 in the pathophysiology of sporadic cases of Alzheimer's disease. However, the viral theory of Alzheimer's disease has its opponents, since other studies failed to detect the HSV-1 genome in the brain or an association between HSV-1 and ApoE4 (131).

4. CONCLUDING REMARKS

Encephalitis as a neurological complication of virus infection can be devastating, even in the presence of antiviral therapy. In order for viruses to infect and injure the CNS they must: (i) enter the host, (ii) spread from the site of entry to the CNS, (iii) infect neuronal cells, (iv) cause death of infected neuronal cells, and (v) successfully avoid the host's immune defenses by minimizing tissue inflammation and permitting viral spread within apoptotic bodies (132). The CNS pathogenicity of the viruses described in this review probably relates to more than one mechanism. These include cytopathic effects, induction of cytokines, effects on immune function (immune suppression), and effects on other viruses (e.g. transactivation). However, a common thread with regard to virus-induced CNS pathogenesis is apoptosis of neuronal cells. It is still unclear whether apoptosis associated CNS damage is caused by virus replication or is a consequence of an immune reaction triggered by antigen expression. Virus anti-apoptotic proteins may confer selective

advantages to some oncogenic viruses as critical elements to the transformation of host cells. In neuronal postmitotic cells, however, proteins that inhibit the cell apoptotic response may foster virus persistence and/or latency. However, targeting apoptosis may prove useful in the treatment of infectious CNS diseases, such as human encephalitis. Certain viral anti-apoptotic proteins, such as the HSV-2 ICP10 PK, may also constitute the future of therapy for neurodegenerative diseases, since its neuroprotective activity (also against genetic defects) is associated with the activation of the ERK/CREB LTP pathway.

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