

■ R E V I E W

Viruses and the brain: from inflammation to dementia

Tongguang WANG, Jeffrey A. RUMBAUGH and Avindra NATH

Department of Neurology, Johns Hopkins University, 600 N. Wolfe St, Baltimore, MD 21287, U.S.A.

A B S T R A C T

Many viruses cause encephalitis, but understanding the mechanisms by which viral infection leads to encephalopathy or dementia remain elusive. In many cases, inflammation generated by the host's attempt to combat the infection is itself implicated as a primary factor in causing neuronal dysfunction or degeneration. In this review, we outline the current state of knowledge regarding the pathophysiology of CNS (central nervous system) injury in viral infection. We focus our review on the neuropathogenesis of HIV type 1 (HIV-1)-associated dementia, because, within this class of infection, it is the best studied. We will also discuss the key similarities and differences in the pathological mechanisms of other important viral encephalitides. Understanding these mechanisms should ultimately enable development of immunomodulatory therapies for treating these infections, as well as other neuro-inflammatory conditions.

INTRODUCTION

Although many viruses affect the brain and cause encephalitis, relatively little is known about the pathological mechanisms of these infections. Frequently, in fact, in cases of presumed viral encephalitis, there is not even a diagnostic test available to identify the particular viral agent. Often, the immune response triggered by the infection may itself be detrimental to the host. Such immune cascades may persist long after the viral infection has been controlled or eradicated. This persistent immune activation can lead to neuronal injury, resulting in neurocognitive impairment. Diseases such as multiple sclerosis, transverse myelitis and Bechet's disease are characterized by episodic immune activation, which clearly results in

CNS (central nervous system) injury. Although a viral aetiology has long been suspected in these diseases, none has been associated conclusively. Other chronic neurodegenerative diseases, such as Alzheimer's disease, also have chronic glial cell activation. It remains unknown if this chronic activation is needed to provide trophic support for injured neurons or if the cytokines and other host factors released by these cells may be injurious.

In vitro and *in vivo* models of viral encephalitis enable the study of the generation of immune responses and their effects on the nervous system. The aetiological agent can be controlled and manipulated to modulate the immune responses. This review examines the pathophysiology of CNS injury caused by some well-characterized viral agents. It is hoped that the study of these diseases will

Key words: dementia, encephalitis, HIV, immunomodulation, inflammation, neuropathogenesis.

Abbreviations: CNS, central nervous system; COX, cyclo-oxygenase; EAA, excitatory amino acid; ECM, extracellular matrix; FADD, Fas-associated death domain; HAART, highly active antiretroviral therapy; HIV type 1, HIV-1; HIVD, HIV-associated dementia; HIVE, HIV-1 encephalitis; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; IL-1R, IL-1 receptor; IL-1RI, type I IL-1 receptor; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MIP-1, macrophage inflammatory protein-1; MMP, metalloproteinase; NF- κ B, nuclear factor κ B; NMDA, *N*-methyl-D-aspartate; NOS, nitric oxide synthase; iNOS, inducible NOS; PG, prostaglandin; PML, progressive multifocal leucoencephalopathy; RANTES, regulated upon activation, normal T-cell expressed and secreted; ROS, reactive oxygen species; SDF-1 α , stromal-derived factor-1 α ; TGF- β , transforming growth factor- β ; TIMP, tissue inhibitors of metalloproteinases; TNF, tumour necrosis factor; TNFR, TNF receptor; TNFR1, type I TNFR; TRADD, TNFR-associated death domain.

Correspondence: Dr Avindra Nath (email anath1@jhmi.edu).

be widely applicable to other auto-immune and neurodegenerative diseases in which immune activation is an important component. Of all the viruses which cause encephalitis or dementia, HIV-1 (HIV type 1) is the best studied. Although there are certain to be differences in the pathological mechanisms of these various infections, HIV-1 serves as an excellent model for our understanding of the potential inflammatory cascades initiated by these viruses when they enter the brain. We will discuss how HIV-1 infection leads to dysregulation of pro-inflammatory factors and the mechanisms for subsequent neurodegeneration, a process eventually leading to dementia. At the end of the review, we will also discuss the key similarities and differences in the pathological mechanisms of other important viral encephalitides.

HIV INFECTION

HIVD (HIV-associated dementia)

HIVD is termed a 'sub-cortical' dementia. Although memory loss can be a significant feature, as in the 'cortical' dementias, effects on other neurological domains – cognitive, motor and behavioural – are predominant. The cognitive effects are characterized mainly by psychomotor retardation. Behavioural manifestations include apathy, social withdrawal, depression, psychosis and emotional incontinence. Motor manifestations include tremors, inco-ordination, parkinsonism and impaired balance [1].

Up to 500 000 people in the United States alone are affected by HIV-associated brain disease [2], which can vary in severity from mild cognitive impairment to dementia. Incidence of severe forms of dementia can be minimized by the use of HAART (highly active anti-retroviral therapy), but, with the increased chronicity of HIV-1 infection in the setting of HAART, the prevalence of HIVD is actually rising [3–7]. Additionally, although HIVD typically affects patients with advanced immunosuppression, it can occur as the presenting symptom of HIV-1 infection [8–10]. Furthermore, many patients either do not take or, in the developing world, do not have access to HAART. Others may develop resistance to available antiretroviral drugs. Finally, a study [11] evaluating HIV-infected outpatients in the post-HAART era demonstrated that 9% died with HIVD and, of those, 92% were diagnosed with HIVD within 12 months of death.

It is thus apparent that HAART is not sufficient therapy to control HIVD. The probable reason for this failure is that HIV-1 infection initiates an inflammatory cascade which leads to encephalitis and dementia and which HAART fails to target. Development of neuroprotective and anti-inflammatory strategies thus are of prime importance in the fight against HIVD [12,13] and may be useful in other viral inflammatory CNS disorders

as well. Research into the pathogenesis of neurotoxicity in HIV-1 infection will enable development of these important therapies.

Loss of neurons

Neurons are rarely infected by HIV-1 [14]. Nevertheless, neuronal loss is common in patients with HIV-1, probably due to indirect effects of viral proteins and inflammatory mediators. Apoptotic neurons have been detected by identification of TUNEL-positive cells, DNA laddering and electron microscopic changes at autopsy in HIV-infected patients. Apoptosis occurs predominantly in neurons, active caspase-3-like immunoreactivity is localized to the soma and dendrites of neurons in the affected regions of the brain [15], and neuronal apoptosis is more severe in atrophic brains [16]. However, apoptosis may also be seen in some astrocytes and endothelial cells [16–19]. Neuronal apoptosis correlates with microglial activation and axonal damage [20], suggesting that the inflammatory mediators secreted by microglia and other immune cells play a major role in initiating the apoptotic cascades. The dementia of HIV is probably due to neuronal dysfunction via multiple mechanisms, including apoptosis and other inflammatory pathways. Some of these pathways, and related dysfunction, may be reversible with strategic neuroprotective and immunomodulatory strategies [21]. Autopsy studies have demonstrated types of injury which are likely to be reversible, including morphological changes in dendrites and loss of neurites without neuronal cell loss [22]. It is unclear if brain atrophy is a marker of HIVD or only of HIV-1 infection [23]. Even in patients with minimal or no clinical deficit, patients with HIV infection frequently have cerebral atrophy on brain imaging [24–30]. This atrophy is usually subcortical [31] and other white matter abnormalities are also commonly seen [28–30]. Although frequently present, these radiological findings do not necessarily correlate with dementia severity [32]. However, by the time a patient reaches end-stage HIV disease, atrophy and white matter abnormalities are frequently extensive, affecting both the cortex and subcortical regions.

Astrocytes

Reactive astrocytes are also common in HIV-infected brain specimens [33,34]. In the brain, only macrophages and microglia are productively infected, whereas astrocytes have a restricted infection in which viral proteins are expressed, but replication of the viral genome does not occur [35]. Although not producing actual viral progeny, astrocytes with such latent infection can produce large amounts of potentially toxic viral proteins, such as Tat [36,37]. Glial cells and macrophages are induced by these toxic proteins to produce other neurotoxic substances [38], such as TNF (tumour necrosis factor)- α [39], and other inflammatory mediators.

Periventricular white matter pallor is frequently seen in HIVD. This is associated with subtle changes of the blood–brain barrier secondary to inflammation and not with effects on myelin [40–42]. Sometimes these white matter changes can be reversed by initiation of HAART, with associated cognitive improvement [43]. Endothelial cells and astrocytes functionally form the blood–brain barrier, so injury to either of these cell types can compromise the blood–brain barrier. A recent magnetic resonance spectroscopy study demonstrated that blood–brain barrier compromise is correlated with increased glial activation [44].

Activated macrophages and microglia

The key events of inflammation in the CNS include peripheral monocyte infiltration and the activation of microglia, the resident immune cells in the brain. HIV-1 infection or virus components, such as gp120 and Tat, can activate the uninfected cells directly [45,46]. The best pathological correlate of HIVD is the number of activated macrophages in the white matter [47]. Multinucleated giant cells, representing virally induced fusion of macrophages, are also commonly seen [48]. Finally, microglial nodules and perivascular mononuclear inflammation are common [33,49]. The amount of circulating activated monocytes is clearly associated with the development of HIVD [50,51]. In an attempt to eradicate the infection in the brain, these immune cells are probably most responsible for the neuro-inflammatory and neurotoxic cascades which lead to viral encephalitis. They express TNF- α , IL (interleukin)-1, IFN- α (interferon)- α and NOS [NO (nitric oxide) synthase], among other inflammatory mediators [52,53]. It should be noted, however, that recent work has shown that these cells may have neuroprotective properties, especially early in the infection [54,55], suggesting that the immune response has a desired effect initially and does not become damaging until the infection becomes chronic.

Virotoxins and associated phenomena

The study of the interactions of viral proteins with the nervous system has uncovered some key concepts that are widely applicable to other viral encephalitides. That viral proteins can be toxic to neurons is not unique to HIV-1, but can also be seen with several other viruses. In most instances, it is the envelope protein or the viral regulatory proteins that have neurotoxic properties. These toxic viral proteins have been termed ‘virotoxins’ [56].

The domino effect

Unlike neurons which may undergo cell death upon interaction with viral proteins such as gp120 and Tat, uninfected microglia, monocytes and astrocytes get activated following such interactions. The activated cells produce and release a variety of pro-inflammatory fac-

tors, including cytokines, chemokines, free radicals, MMPs (metalloproteinases) and prostanoids, which may result in secondary neuronal toxicity or further immune cell activation and reactive gliosis. This amplification of the immune cascade after an initial trigger by viral proteins has been termed the ‘domino effect’ [57].

Hit and run phenomenon

Once the domino effect has been initiated, the inflammatory process could be self-propelled and maintained, even if the virus were to be cleared. This has been termed the ‘hit and run’ phenomenon [58].

The trebuchet phenomenon

The brain lacks a lymphatic system and the extracellular space is small, tortuous and has a lot of cellular protrusions, adhesion molecules and proteases that impede the spread of viruses. Several viruses have developed unique ways of spreading in the CNS. For example, rabies, herpes simplex and varicella zoster travel within neuronal axons and dendrites using axonal transport mechanisms for their spread. Since neuronal axons stretch over long distances, this provides a mechanism for dissemination of the virus.

We have recently discovered that this phenomenon is not restricted to whole virus, but occurs with viral proteins as well. For example, the Tat protein of HIV-1 can be transported along neuronal pathways [59]. While within the cell, Tat has anti-apoptotic properties [60], but extracellularly when it comes in contact with the neuronal cell membrane, it can trigger a cascade of events leading to neurotoxicity [61]. We have termed the ability of virotoxins to transport and cause toxicity at sites distant from the virus the ‘trebuchet phenomenon’.

Cytokines

Cytokines are multifunctional humoral proteins that regulate individual cells and tissues under either physiological or pathological conditions. Originally discovered as systemic immune cell mediators, involvement of cytokines in a variety of normal and pathological neurological conditions has now been clearly demonstrated. They are important mediators for communication between nervous tissues and cells, and also key participants in the induction and regulation of inflammation in the CNS, which in turn influences progression or inhibition of neurodegeneration [62]. The cytokines present in the CNS are produced by peripheral immune cells which have entered the brain, often across a defective blood–brain barrier, and by activated glial cells and even certain neurons. In HIVD, both pro- and anti-inflammatory cytokines increase.

The most extensively studied cytokines are TNF- α and IL-1 β . Produced as biologically inactive precursors (pro-TNF- α and pro-IL-1 β), these factors must be

activated by enzymatic cleavage. The detrimental roles of TNF- α and IL-1 β in HIVD have been suggested by several lines of evidence: (i) HIV-infected macrophages and microglia increase their release of TNF- α and IL-1 β before neuronal death occurs [58,63,64]; (ii) concentrations of the mRNA and protein for TNF- α are markedly higher in the brains of HIVD patients compared with controls [65]; (iii) the temporal profile of TNF- α expression correlates with the onset, progression and severity of HIVD [66]; and (iv) TNF- α inhibitors markedly reduce brain inflammation and neuronal injury in a murine model of HIVD (HIV-1 encephalitis) [67].

Furthermore, primary glial cells increase their production of IL-1 β when treated with the HIV-1 glycoprotein gp120, which is directly and specifically involved in neuronal death [68]. This neurotoxicity could be completely attenuated either by reducing IL-1 β overexpression with the antioxidant, Trilox, or by treatment with a neutralizing anti-(IL-1 β) antibody [69]. These results are consistent with previous observations that inhibition of endogenous IL-1 and TNF- α by the natural IL-1R (IL-1-receptor) antagonist, the soluble TNF- α receptor, or neutralizing antibodies, markedly attenuates neuronal damage in neurodegenerative conditions [70,71].

Despite this substantial evidence, there is still some controversy about the role of IL-1 β and TNF- α in HIVD. It has not been confirmed that these cytokines cause neuronal death in healthy brain tissue or normal neurons [72] and a few studies have indicated a neuroprotective role for both TNF- α and IL-1 β in certain conditions [73–75]. TNF- α -knockout animals suffer more severe neuronal damage than controls in some studies [76]. These conflicting data may be due to the intricate properties of the inflammatory regulative network, where the outcome is the result of the overall balance between anti- and pro-inflammatory factors. Thus the cell activities induced by a particular cytokine can be influenced considerably by many factors, including the growth state of the cells (proliferation or differentiation), combinations and concentrations of other cytokines present at the same time and even the temporal sequence of the same cytokines acting on the same cell.

TNF- α exerts its effects by interaction with two different receptors: TNFR I [type I TNFR (TNF receptor)] and TNFR II (type II TNFR) [77]. TNFR I activation can trigger complex formation with FADD (Fas-associated death domain) and TRADD (TNFR-associated death domain), which activates pro-caspase 8, initiating the caspase cascade, involving caspases 3, 6 and 7, ultimately leading to direct neuronal apoptosis [78]. In addition, TNFR I and associated adapter protein FAN (factor associated with neutral sphingomyelinase activation) are responsible for the activation of neutral and acidic sphingomyelinases for the degradation of sphingomyelin to phosphocholine and ceramide [79]. The latter may work

as an important second messenger to mediate some of the cytotoxic effects of TNF- α , including the caspase 8 activation [79,80].

Besides direct neurotoxicity through activation of caspases and apoptosis, TNF- α can also exert neurotoxicity indirectly by modulating the function of glia and infiltrated monocytes. It is known that TNF- α is a main inducer of NF- κ B (nuclear factor κ B) in activated glial cells, resulting in up-regulation of many pro-inflammatory genes, including IL-1 β , iNOS (inducible NOS) and RANTES (regulated upon activation, normal T-cell expressed and secreted) [81]. Extensive glial activation leads to the excessive accumulation of pro-inflammatory products in the neuronal vicinity, causing neurotoxicity. TNF- α can also affect the EAAs (excitatory amino acids) and NMDA (*N*-methyl-D-aspartate) receptor systems. It has been reported that blocking TNF- α with a neutralizing antibody attenuated gp120-induced release of L-cysteine, an EAA, from activated microglia and macrophages [82]. TNF- α can also elevate the free level of glutamate by increasing the release and inhibiting the uptake of glutamate in astrocytes [83,84]. The accumulation of excessive amounts of glutamate in the microenvironment of neurons can activate NMDA-receptor-operated channels on the neuronal surface, resulting in the loss of cellular homeostasis, leading to either acute lysis of the cell or apoptosis [85–87].

IL-1 β acts mainly through IL-1RI (type I IL-1R) [88] and indirectly regulates neurotoxicity. When IL-1RI is activated, IL-1RAcP (IL-1R accessory protein) is recruited to form a high-affinity receptor complex necessary for signal transduction. This complex, with the adaptor molecule MyD88, then recruits several kinases {IRAK (IL-1R-associated kinase) and TAK [TGF- β (transforming growth factor- β)-activated kinase]} and activates NF- κ B, AP-1 and MAPKs (mitogen-activated protein kinases). Similar to TNF- α , substantial evidence has also suggested the existence of a functional interaction between IL-1 β and NMDA receptors. In adult rat brain, IL-1 β exacerbates the neuronal damage induced by NMDA application [70], and selective antagonism of NMDA receptors blocks the proconvulsant actions induced by the intrahippocampal injection of IL-1 β in rats [89].

Other cytokines are also likely to be involved in HIV-associated neurodegeneration. For example, increased production of oncostatin-M by lymph cells from patients with HIVD has been reported [90]. Oncostatin M is a member of the IL-6 family of cytokines and may be one of the most damaging cytokines, potentially mediating neuronal injury in both the developing and the mature brain through the induction of apoptotic mechanisms. Low TGF- β 1 concentrations were capable of enhancing oncostatin M-mediated neuronal alterations, indicating a synergistic effect of oncostatin M with other cytokines [91].

Chemokines

Chemokines are chemotactic cytokines belonging to a superfamily of small (8–14 kDa) secreted proteins. Initially identified by their ability to selectively modulate leucocyte trafficking in inflammatory processes, chemokines also play important roles in the modulation of cell adhesion, phagocytosis, cytokine secretion, cell activation, cell proliferation, apoptosis, angiogenesis and viral pathogenesis [92]. The chemokine family consists of more than 40 members and is subdivided into four groups, named CXC, CC, CX3C and C, according to the number of amino acids separating two cysteine residues within a highly conserved region of the chemokines. Chemokines exert their biological effects via interaction with G-protein-coupled receptors. These receptors are classified according to the group of chemokines they bind and are named CXCR1–CXCR6, CCR1–CCR11, CX3CR1 and XCR1 [93]. However, the chemokine–chemokine receptor interaction is not exclusive, as most chemokines bind to more than one receptor and most receptors bind to several chemokines [94].

Fractalkine/CX3CL1 and SDF-1 α (stromal-derived factor-1 α)/CXCL12 are the only chemokines constitutively expressed in the brain, principally by neurons and astrocytes respectively [95]. Many chemokine receptors, including CCR3, CXCR1, CXCR3 and CCR10, have been identified on microglia from humans and rodents [96–100]. This suggests that chemokines play important roles in the regulation of microglial activation in the CNS.

Although it is evident that chemokines and chemokine receptors play important roles in physiological conditions, modulating cellular proliferation and providing trophic support to neurons, their involvement in CNS pathology, particularly neuro-inflammation and neuro-degeneration, has also been intensively studied. Chemokines and their receptors play important roles in HIV-1 infection and migration into the brain. HIV-1 enters the brain via the passage of infected monocytes and CD4⁺ T-lymphocytes across the blood–brain barrier. Several chemokine receptors are co-receptors with CD4 for HIV-1 entry into target cells. Macrophage-tropic HIV-1 viruses use CCR5 as a co-receptor, whereas T-cell-line-tropic HIV-1 viruses use CXCR4. Dual-tropic viruses use both co-receptors [101].

It is reported that the number of immune-activated mononuclear phagocytes (including perivascular and parenchymal macrophages and microglia) is the best pathological correlate of HIVD [102]. Productive viral replication in brain occurs predominantly in these cells [103]. Chemokines play an important part in the process of infiltration and activation of these cells in the brain. They participate in blood–brain barrier compromise and the recruitment of additional macrophages to the brain, thus amplifying the inflammation and neural injury [104]. For example, using an *in vitro* blood–brain barrier system, MCP-1 (monocyte chemotactic protein-

1) was demonstrated to be a primary chemoattractant for monocytes, and astrocytes, stimulated by pro-inflammatory cytokines, were shown to be the major source of this chemokine [105].

Post-mortem studies have also revealed up-regulation of some chemokines and chemokine receptors in the brains of patients with HIV and HIVE. The temporal and topographical expression of several chemokines and their receptors is relevant to the severity and clinical symptoms of HIVE [106]. The presence of chemokines and chemokine receptors was found to be most abundant in microglial nodules. The expression levels of CCR1, CCR3, CCR5 and CXCR4 were all increased on macrophages/microglia, especially in microglial nodules during HIVE [106]. Also, the presence of MCP-1/CCL2, MIP-1 (macrophage inflammatory protein-1) α /CCL3 and RANTES/CCL5 is associated with the histopathological signs of HIVE [107,108]. Other reports have indicated that the CX3C chemokine fractalkine/CX3CL1 is over-expressed in brain tissues of AIDS patients with HIVD when compared with AIDS patients without HIVD.

A regulatory role for CCR5 has also been indicated in a recent report [109]. The authors demonstrated that CCR5 activation by its specific ligands induced cell death via caspase-3-mediated apoptosis in a neuroblastoma cell line. Both activated microglia and supernatant from activated microglia demonstrated enhanced neurotoxicity in CCR5-expressing neuroblastoma cells. Thus CCR5 may act as a death receptor in cells of neuronal lineage and, therefore, may be involved in HIVD. Elevated levels of the chemokines MIP-1 β and low, but detectable, levels of MIP-1 α have also been associated with HIVD, although higher levels of MIP-1 α may protect against HIVD [110].

In mixed neuronal/astroglial cultures, SDF-1 α /CXCL12 has been reported to induce apoptosis in the absence of gp120, implying a direct interaction with neurons and/or astroglia. This neurotoxicity may occur through activation of p38 MAPK signalling, as blockade of MAPK was sufficient to prevent both gp120- and SDF-1 α /CXCL12-induced neuronal damage [111]. In a more recent report, SDF-1 activation of the receptor CXCR4 induced astroglial release of glutamate via a calcium-regulated exocytosis-like mechanism [84]. Activation of CXCR4 led to the rapid release of TNF- α and prostaglandin, which was necessary for the glutamate release. It was also observed that microglial activation enhances glutamate release from this pathway, implying an important role for astroglia–microglia communication in the regulation of this pathway. The normal chemokine-activated cell–cell communication system seems to be deranged and converted into a pro-apoptotic neuro-degenerative cascade. This CXCR4-dependent astrocyte–microglia signalling pathway may be one mechanism by which the HIV-1 coat glycoprotein gp120 induces neuronal apoptosis [112].

MMPs and the ECM (extracellular matrix)

ECM provides the immediate micro-environment for neurons and glia and plays important roles in mediating cell adhesion, cell-cell communication and intracellular signalling [113]. The cleavage of certain extracellular matrix molecules, such as collagen, laminin and elastin, may result in the release of biologically active remnant fragments [114]. In physiological conditions, there is a fine balance between matrix degrading MMPs and the TIMPs (tissue inhibitors of metalloproteinases). The disruption of this balance in inflammatory conditions may result in deleterious effects on the neurons [115]. During HIVD, the induction of MMPs (MMP-2 and MMP-9) and down-regulation of TIMP-1 have been reported as well as the destruction of ECM [116–119]. Degradation of ECM may cause detachment of cells from the ECM, inducing apoptosis of the detached cells. For example, degradation of laminin, an ECM component that anchors on to neuronal membrane integrin with fibronectin, disrupts the integrin survival pathways, which play a significant role in neuronal cell death [120]. Furthermore, degradation of ECM releases active residues, which may recruit and activate immuno-active cells to produce pro-inflammatory factors which, in turn, induce cytotoxicity [121]. For example, peripheral soluble elastin attracts and activates phagocytes and neutrophils through binding to an elastin-laminin receptor. These recruited cells then produce cytotoxic superoxide and nitrous oxide, playing a pivotal role in initiation of arteriosclerosis.

Increased blood-brain barrier permeability could contribute to the development of HIVD by facilitating the entry of the activated and infected monocytes, as well as potentially toxic serum proteins, into the brain [122]. The observed increased CSF (cerebrospinal fluid) levels and activities of pro-MMP-2 and pro-MMP-7 in HIVD [117] may be related to the increased blood-brain barrier permeability. It has also been reported that, in HIV-1-infected and/or immune-activated monocyte-derived macrophages and human fetal microglia, MMP expression increased significantly with mononuclear phagocyte differentiation [123]. Increased trafficking of cells across the blood-brain barrier also involves complex interaction of cell adhesion molecules, such as ICAM-1 (intercellular cell-adhesion molecule-1) and VCAM-1 (vascular cell-adhesion molecule-1), with their receptors, such as LFA-1 (leucocyte-function-associated antigen-1) and VLA-4 (very-late antigen-4) [51,124]. Accordingly, marked overexpression of these contact molecules has also been observed in the brains of patients with HIVD [125].

Free radicals

Oxidant stress is an important mechanism for neurotoxicity in many inflammation-mediated neurodegenerative diseases [12,126,127]. ROS (reactive oxygen species), in-

cluding superoxide anion, hydroxyl radical, lipid hydroperoxides and their by-products (e.g. H_2O_2), may play dual roles in neurodegenerative diseases. While intended to kill invading pathogens, ROS generated by activated microglia are also toxic to neurons by inducing lipid peroxidation, DNA fragmentation and protein oxidation [128]. Furthermore, ROS can activate diverse downstream signalling molecules, such as PKC (protein kinase C), MAPK and NF- κ B, to regulate the expression of genes encoding a variety of pro-inflammatory factors [129,130]. There is substantial evidence suggesting that HIV-infected patients are under chronic oxidative stress [12,131]. This condition is the result of an increased production of reactive stress and the depletion of endogenous antioxidant moieties. In addition, this response is enhanced by the chronic inflammatory status that is associated with activation of lymphocytes and phagocytes. It has been shown that active replication of HIV-1 in macrophages and microglia directly leads to the production of inflammatory products and, in turn, an excess formation of free radical species, including NO, superoxide, H_2O_2 and peroxynitrite [132–134].

NO is a nitrogen free radical generated via bioconversion of L-arginine into citrulline by NOSs [135,136]. It can be released by neurons in response to many stimuli, including excitatory neurotransmission and changes in calcium homeostasis, or by activated glial cells following the addition of inflammatory cytokines and soluble antigens, such as HIV-1 gp120 [137,138]. HIV-1 infection can up-regulate iNOS expression in brain tissues both directly through its viral components, such as gp41, or indirectly through pro-inflammatory cytokines, such as IL-1 β and TNF- α [134,139].

Another free radical, superoxide, can also be produced by myeloid-monocytic cell lines following HIV-1 infection or activation by HIV component proteins [140]. Although the direct neurotoxic effects of NO are modest, and SOD (superoxide dismutase), a superoxide anion scavenger, is generated [141] to keep the concentration of superoxide low, the neurotoxicity of these two free radicals is greatly enhanced when they react with each other to form peroxynitrite, a potent oxidant that is responsible for nitration of tyrosine residues of structural proteins, including neurofilament. Neurofilament provides structural stability to neurons and nitration disrupts neurofilament assembly, thus inducing neuronal damage [141,142]. Excess NO also enhances glutamate release [143] and inhibits glutamate uptake by astrocytes [144,145], thus inducing this excitatory neurotoxicity.

The formation of free radicals can also disrupt the integrity of the blood-brain barrier, facilitating the infiltration of inflammatory cells and factors. HIV-1 Tat protein induced iNOS expression and release of NO, resulting in apoptosis and increased permeability in HBMEC (human brain microvascular endothelial cells) [146].

The increased production of free radicals is enhanced further by HIV-infection-induced down-regulation of antioxidative moieties, including the tripeptide glutathione (GSH) and catalase. GSH functions as an antioxidant and maintains the redox potential in cells by keeping sulphhydryl groups of proteins in the reduced form. High intracellular concentrations of GSH protect against a variety of different ROS. The concentrations of GSH are reported to be decreased in the CNS of HIV-infected patients [147,148]. Catalase is another enzyme that scavenges H_2O_2 . It has been reported that catalase is diminished in $CD8^+$ T-lymphocytes from HIV-infected patients [149], suggesting decreased H_2O_2 scavenger activity during HIV-infection.

The clinical significance of free radicals in HIVD has also been confirmed in recent reports. iNOS expression was examined in patients at varying stages of HIVD, demonstrating that the intensity of staining for iNOS in the basal ganglia and white matter was significantly greater in subjects with moderate to severe dementia compared with those with milder impairment. The staining for iNOS and gp41 increased linearly with HIVD severity. Double-immunolabelling studies co-localized iNOS predominantly to macrophages/microglia [150]. It has also been demonstrated that the severity and rate of progression of HIVD correlates significantly with the levels of gp41, iNOS and HAM56, a marker of microglial/macrophage activation. Thus the severity and rate of progression of HIVD correlates with indices of immune activation as well as levels of iNOS and gp41. gp41-induced iNOS may contribute to severe and rapidly progressive HIVD [150,151].

COX (cyclo-oxygenase)-2 and prostaglandins

COXs are the rate-limiting enzymes in the biosynthesis of PGs (prostaglandins). There are two isoforms of COX (COX-1 and COX-2) that convert arachidonic acid into PGH_2 (hydroxyl endoperoxide), which is then metabolized to various PGs, including PGE_2 [152]. COX-1 is constitutively expressed in most tissues and is primarily involved in cellular homeostasis [152,153]. COX-2 is induced by mitogens, cytokines and certain inflammatory agents, and plays an important role in inflammation and mitogenesis [153,154]. COX-2-knockout mice and inhibitors have been reported to have neuroprotective effects in some inflammation-related neurodegenerative diseases [155–157]. It has been observed that *in vitro* co-cultures of HIV-infected macrophages and brain endothelium showed an up-regulation of COX-2 expression by both cell types. This up-regulation occurs via an $IL-1\beta$ -dependent mechanism in macrophages and via an $IL-1\beta$ -independent mechanism in endothelial cells, indicating that the interactions between HIV-infected monocytes and brain endothelium may result in COX-2

expression and contribute to the neuropathogenesis of HIV-1 infection [158]. In gp120-treated human neuroblastoma cells, COX-2 expression increased due to increased secretion of $IL-1\beta$. The increased COX-2 expression and consequent cell death could be attenuated by inhibitors to ICE ($IL-1$ -converting enzyme). The role of COX-2 in mediating neurotoxicity was confirmed further by the observation that gp120-mediated neurotoxicity was attenuated by a COX-2 inhibitor, NS 398 [159].

It has been reported that the levels of PGE_2 in the cerebrospinal fluid of HIV-positive individuals with dementia and/or myelopathy were increased compared with those of HIV-negative patients with other neurological diseases and HIV-positive patients without dementia [160]. This increase was associated with severity of dementia and correlated with cerebrospinal fluid levels of neopterin and β_2 -microglobulin. Although $PGF_{2\alpha}$ and thromboxane B₂, additional products of the COX pathway of arachidonic acid metabolism, were also elevated in dementia, leukotriene C₄, a product of the lipoxygenase pathway, was not.

Just as with other pro-inflammatory factors, there is still a debate on the role of COX-2 and PGs in neurodegeneration. In some cases, inhibition of COX-2 actually results in enhanced neurodegeneration [157,161]. Again, this conflict may be due to the different PG products working through different receptors, or the complicated communications with other pro-inflammatory factors such as NO [162].

OTHER CNS VIRAL INFECTIONS

Although HIV-1 infection offers a well-studied and presumably generalizable model for many of the pathogenic mechanisms involved in producing virally mediated brain dysfunction, there are also differences between effects of various viruses. A brief discussion of some of the other important viral CNS pathogens, with emphasis on pathogenic differences between these viruses and HIV, is warranted.

Herpes virus infections

HSV (herpes simplex virus) type I is the most common cause of fatal encephalitis, with an identified cause, in humans. Varicella zoster virus, cytomegalovirus, Epstein Barr virus and, rarely, HSV type II and human herpes viruses-6 and -8, also all cause serious human neurological disease.

Clinically, patients with herpes infections typically present with headache, fever and altered mental status, evolving over hours to days. Focal neurological deficits may also appear, including aphasia, hemiparesis, visual field defects, autonomic dysfunction and seizures. Memory loss is frequently prominent, and behavioural

disturbances, personality changes or even psychosis can occur.

Herpes viruses are unique in their species specificity and ability to cause significant neurological disease both in primary infection and in re-activation after prolonged latency within the CNS. The most educational difference between the pathogenesis of HIVE and HSV-associated encephalitis is the role of latency in HSV. Another important difference is that HSV productively infects neurons and astrocytes and has non-productive infection of microglia, whereas HIV-1 productively infects microglia, has non-productive infection in astrocytes and rare or no infection of neurons.

Despite these differences in cell tropism, host-mediated inflammation plays a similar role in HSV encephalitis as in HIVE. Microglial cells respond to HSV-1 infection in the brain by producing TNF α , IL-1 β , RANTES/CCL5 and IP-10 (IFN-inducible protein-10)/CXCL10, which contribute to production of brain injury, just as described for HIVE [163]. IL-10 can dampen this pro-inflammatory response [164]. Interestingly, astrocytes and neurons, although productively infected by HSV (and not by HIV-1), have not been found to produce cytokines or chemokines in response to HSV [163], as they have for HIV-1. In a murine model of herpes infection, immunodepletion prior to CNS infection increased incidence of CNS infection and death, whereas immunodepletion after CNS infection delayed time to death. These results suggest that the immune response is protective against CNS invasion, but, after invasion, actually accelerates disease [165].

The meninges of the most commonly involved regions of brain in HSV encephalitis are innervated by nerves derived from the trigeminal ganglia. It is likely that spread of the virus from the trigeminal ganglia down the nerves to the face causes cold sores and trigeminal neuralgia, while relatively rare spread along the nerves to the meninges leads to encephalitis [166,167]. However, encephalitis may also occur due to primary infection and/or reactivation within the brain itself [168].

During primary infection, herpes viruses travel up nerve fibres to establish latent infection within neuronal cell bodies, usually within sensory ganglia [169]. Latent virus has also been found in human brains [170]. Neurons do not express MHC recognition molecules. As a non-replicating cell population, they can thus avoid unnecessary attack by cytotoxic T-cells; however, this same property also makes them susceptible to prolonged infection by non-lytic viruses [171–173]. Herpes viruses can spread from cell to cell by fusion of cellular membranes, thus entering cells without specific receptors for the virus, while avoiding specific antibody-mediated immune responses to the virus. During productive infection, these viruses destroy their host cell. However, during latency, they may activate a neuronal-inhibitory factor which prevents lytic infection, and they may

promote transport of viral genome from cell bodies out into axons, where replication can occur without destroying the host neuron [174].

In addition to a direct pathogenic role, the host immune response also probably plays an important role in maintaining latency, as evidenced by the high incidence of re-activation during immunodeficiency. On the other hand, unlike many of the infections discussed in this review, HSV encephalitis is not thought of as a disease of immunodeficient patients.

Arboviruses

Arboviruses are important agents of viral encephalitis around the world. They are transmitted to humans through the bite of arthropods, including mosquitoes and ticks. Involvement of the nervous system of the transmitting arthropod is thought to precede involvement of the salivary glands by days to weeks [175]. Furthermore, the viruses are highly selective in which neurons they infect, both in mosquitoes and humans [175,176]. The mosquito neurons are not killed by the virus, but neuronal dysfunction may actually alter mosquito behaviour, making them more likely to bite a human (or other mammalian) host [177].

Most people with arboviral infection are asymptomatic or develop a mild non-specific viral syndrome, which can include general malaise, fever, myalgias and headache. More severe neurological manifestations include encephalitis, meningitis and poliomyelitis. Patients typically present with 1–4 days of worsening high fevers, meningismus, fatigue, lethargy, confusion, diffuse or focal weakness, bladder dysfunction, seizures, aphasia, parkinsonism, cranial neuropathies and/or respiratory distress.

Neuropathological changes seen in humans who have died from these infections include perivascular inflammation, neuronophagia and microglial nodules, found both in brain and spinal cord. Unlike with HIVE, neurons themselves are the predominant CNS cell type involved. There is a large and varied contingent of viruses which cause arboviral CNS infections, and the specific mechanisms of CNS injury are therefore equally varied. Furthermore, despite the worldwide distribution of arboviruses and the recent emergence of West Nile virus as a prominent pathogen in the United States, relatively little is known about the pathogenesis of most of these viruses. Perhaps the best studied model is Sindbis virus infection of mice, which elicits a strong type 2 T-cell response [178]. Nevertheless, the inflammatory host response probably plays a large pathogenic role in most arboviral encephalitides, with an overall schema quite similar to that described in this review for HIVE. Although specifics obviously vary from virus to virus, the general mechanisms available to the host for response, and therefore the pathways by which viral inflammation leads to dementia, are limited.

Rabies

Rabies virus is unique in its mode of transmission via an animal bite and in its spread through the nervous system. After inoculation, the virus infects individual muscle cells and gains access to both sensory and motor nerve fibre endings [179]. The neuromuscular junction is the major site of entry into neurons [180,181]. The virus spreads to the CNS by retrograde axonal transport, replicates within neuronal cell bodies and rapidly disseminates through the CNS by axonal pathways, including trans-synaptic spread [182–184]. The limbic system seems to be preferentially involved, increasing aggressive behaviour and favouring transmission when one animal attacks another. Eventually, widespread infection of neurons leads to coma and death.

Clinical symptoms usually develop within months, but sometimes days or years, after exposure, and generally begin with non-specific symptoms, such as fever, general malaise, headache, anxiety and irritability. There are two forms of rabies manifestation – encephalitic and paralytic. In the encephalitic form, patients are hyperexcitable with aggressive behaviour, confusion and hallucinations. Autonomic dysfunction, including hypersalivation, diaphoresis and piloerection are not uncommon. Hydrophobia may occur and may be related to dysphagia or pain and spasms with swallowing. In the paralytic form, flaccid muscle weakness develops, often beginning in the bitten extremity and spreading diffusely.

Unlike the other viral CNS infections discussed in this review, inflammation seems to play a limited role in the pathogenesis of rabies, at least pathologically. Perivascular inflammation occurs, but is rare and localized. Additionally, necrosis and neuronophagia are rare [185]. The Negri body is a pathognomonic finding in the cytoplasm of rabies-infected neurons. Given the paucity of pathological findings in patients who have died from rabies, our understanding of the molecular basis for this disease remains limited [186].

On the other hand, it seems that elaboration of pro-inflammatory molecules leads to increased limbic dysfunction and more rapid death, while patients who have a paralytic form of rabies lack immune recognition of the virus in the brain and have a delayed time to death [180]. Similarly, in mice infected with rabies virus, morbidity and mortality were associated with production of IL-6, IL-10, TNF- α , and IFN- γ , as well as infiltration of inflammatory cells into the brain [187]. Furthermore, delayed mortality was seen in knockout mice lacking the p55 subunit of the TNFR, and also correlated with higher levels of IFN- γ and IL-10 concentrations and lower amounts of inflammatory cell infiltration in the CNS [187].

Polyomaviruses

PML (progressive multifocal leucoencephalopathy) is caused by human polyomaviruses, most commonly the

JC virus. Like many of the herpes virus syndromes, PML occurs after re-activation of the virus in immunodeficient patients. Some evidence suggests that the re-activation actually occurs in B-lymphocytes, and the virus is then carried into the CNS from the blood [188]. Unlike the other infections described in this review, the JC virus primarily affects oligodendrocytes. As with HIV-1, astrocytes may have non-productive infections, while neurons seem not to be infected [189]. There has been a single patient case report in which infection of cerebellar granule neurons was clearly demonstrated [190]. JC virus granule cell neuronopathy seems to produce a clinical syndrome which is distinct from PML [191].

Presentation of typical PML can be quite variable. Onset is usually gradual and can include personality change, cognitive decline and hemiparesis or hemisensory deficits. Visual field cuts or even cortical blindness can occur as can aphasias and brainstem and cerebellar symptoms.

The pathological hallmark of PML is large distorted oligodendrocyte nuclei with intranuclear inclusion bodies surrounding areas of focal demyelination. The oligodendrocytes allow reproductive infection and are lysed. Bizarre astrocytes also appear within the areas of demyelination, frequently contain viral DNA, but rarely contain viral protein [192]. As with rabies, inflammation may play a relatively small role in this disease. In fact, functional cell-mediated immunity seems to play its role perfectly in keeping this infection in check [193,194], and clinical disease occurs only when cell-mediated immunity has become too suppressed to respond.

Approx. 10% of the time, inflammatory forms of PML occur (as determined by enhancement on brain magnetic resonance imaging or inflammation on biopsy) or PML seems to be triggered by treatment of HIV patients with HAART at a time of immune reconstitution [195]. Interestingly, these forms of PML seem to have a favourable prognosis compared with more typical non-inflammatory PML, suggesting that the inflammatory response may actually be protective against JC virus.

Enteroviruses

Enteroviruses are one of the most common CNS pathogens, causing viral meningitis, poliomyelitis and viral encephalitis [196–199]. These viruses directly infect neurons and spread from cell to cell like herpes viruses or arboviruses, or via axonal transport like rabies virus [200]. The role of inflammation in the pathogenicity of these viruses in the CNS is probably similar to that described in this review for HIV-1, herpes viruses and arboviruses. Pathologically, there is evidence of intense inflammation, neuronophagia and microglial nodules.

CONCLUSIONS

HIV-1 and other viral neuro-infections induce an inflammatory response by directly activating immune cells,

such as macrophages, microglia and astroglia, which in turn produce excessive neurotoxic pro-inflammatory factors. Neurons may be damaged either by these pro-inflammatory factors or by virotoxins. The damaged neurons themselves can enhance the inflammatory process further by releasing more pro-inflammatory factors, including, but not limited to, MMPs. It is not surprising that a prolonged poorly controlled inflammatory reaction in the CNS would result in neurodegeneration. Since the final neurological outcome of viral infection depends on the interplay of a complicated network, consisting of various cell types, pro- and anti-inflammatory factors, viral virulence factors and host susceptibility factors, it is unlikely that inhibition of any specific pro-inflammatory factor or group of factors could provide full neuroprotection. Thus a successful strategy for therapy of inflammation-mediated neurodegeneration must comprise a multifaceted approach, aiming to not only inhibit pro-inflammatory factors, but also increase neuroprotective factors. Our ability to optimally intervene during disease progression depends on detailed research and understanding of the inflammatory regulation which occurs during viral neuro-infection.

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