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Review

Role of oxidative damage in the pathogenesis of viral infections of the nervous system

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Summary. Oxidative stress, primarily due to increased generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), is a feature of many viral infections. ROS and RNS modulate the permissiveness of cells to viral replication, regulate host inflammatory and immune responses, and cause oxidative damage to both host tissue and progeny virus. The lipid-rich nervous system is particularly susceptible to lipid peroxidation, an autocatalytic process that damages lipid-containing structures and yields reactive by-products, which can covalently modify and damage cellular macromolecules. Oxidative injury is a component of acute encephalitis caused by herpes simplex virus type 1 and reovirus, neurodegenerative disease caused by human immunodeficiency virus and murine leukemia virus, and subacute sclerosing panencephalitis caused by measles virus. The extent to which oxidative damage plays a beneficial role for the host by limiting viral replication is largely unknown. An enhanced understanding of the role of oxidative damage in viral infections of the nervous system may lead to therapeutic strategies to reduce tissue damage during viral infection without impeding the host antiviral response.

Key words: Brain, Lipid peroxidation, Nervous system, Oxidative damage, Oxidative stress, Viral pathogenesis, Virus

Viral infections of the nervous system

The numerous neurotropic RNA and DNA viruses that produce central nervous system (CNS) disease use a variety of pathologic mechanisms (reviewed by Tyler and Nathanson, 2001; Love and Wiley, 2002). As a group, viruses target almost all cell types and regions in the human nervous system and affect persons of all ages. Viruses can undergo lytic replication in host cells and spread to other cells, or viral gene expression can be limited or absent, which may lead to viral persistence. In either case, most viral infections evoke host inflammatory and immune responses, which may augment disease pathogenesis.

Viruses cause a wide array of neurological diseases. Both viral products and host mediators can cause tissue damage, and depending on the cell type and site of nervous system involvement, this damage can lead to such varied pathological processes as meningitis, neuritis, myelitis, encephalitis, vasculitis, or demyelinating disease (reviewed by Tyler and Nathanson, 2001; Love and Wiley, 2002). Viral infections of the fetus can induce congenital malformations, and others may contribute to the pathogenesis of some forms of nervous system neoplasia. Furthermore, viral infections have been proposed to contribute to the pathogenesis of some of the most common neurological and neuropsychiatric diseases including Alzheimer disease, autism, and schizophrenia, although these associations remain unproven (Itzhaki et al., 1997; Buka et al., 2001; Dickerson et al., 2004; Yolken, 2004).

Molecular mechanisms by which productive and persistent viral infections cause nervous system disease are extremely diverse and not completely understood. The large body of information available about mechanisms whereby viruses and virus-induced inflammatory and immune responses interfere with cellular metabolism and lead to cellular dysfunction or death are beyond the scope of this work. Here, we summarize available information about the role of oxidative damage - an emerging general mechanism of tissue injury induced by viral infection - in the pathogenesis of viral infections of the nervous system.

Reactive oxygen and nitrogen species and tissue injury

Injury produced by reactive oxygen species (ROS) and reactive nitrogen species (RNS) is an important

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common pathway of tissue damage in such varied acute and chronic processes as radiation damage, chemical and traumatic injury, ischemia-reperfusion injury, microbial killing by phagocytic cells, inflammatory damage, neurodegenerative diseases, and aging (reviewed by Knight, 1995; Halliwell and Gutteridge, 1999; Love and Jenner, 1999; Toyokuni, 1999; Halliwell and Whiteman, 2004). ROS and RNS can be initiated within cells by redox reactions associated with normal physiologic processes or by enzymatic and nonenzymatic mechanisms associated with pathologic processes. ROS and RNS include free radicals that contain one or more unpaired electrons and reactive nonradicals that are oxidizing agents or are easily converted into radicals (reviewed by Halliwell and Whiteman, 2004). Examples of ROS and RNS that are free radicals include superoxide (O_2^-), hydroxyl (OH), nitric oxide (NO), and nitric dioxide (NO_2). Examples of ROS and RNS that are reactive nonradicals include hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO_2$). ROS and RNS readily enter into reactions in cells with macromolecules, particularly with key components of membranes and nucleic acids.

O_2^- and NO are the most important mediators among ROS and RNS induced by inflammatory processes, including microbial infections (Akaike, 2001). O_2^- and other ROS are generated in inflamed tissues by infiltrating NADPH oxidase-expressing phagocytic cells and by humoral responses involving xanthine oxidase (XO) (Fig. 1). NO is mainly produced by inducible nitric oxide synthase (iNOS), which is expressed by a variety of cell types including phagocytic cells. NO and ROS, particularly O_2^-, may form reactive nitrogen oxides like peroxynitrite that are particularly potent oxidants of proteins, nucleic acids, and membrane unsaturated lipids. Importantly, free radicals can cause lipid peroxidation, an autocatalytic process that damages lipid-containing structures and yields reactive by-products, primarily 4-hydroxy-2-nonenal (HNE) and malondialdehyde (MDA).

HNE and MDA are electrophilic species that can covalently modify and damage cellular macromolecules. At physiologic concentrations, HNE and MDA are potent regulators of cell growth and differentiation, affecting both cellular transcription and cell cycle progression (Ji et al., 1998, 2000; Keller and Mattson, 1998; Poli and Schaur, 2000; Kakashita and Hattori, 2001). In neuronal cell cultures, HNE has been reported to activate the c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) pathway, inhibit NF-κB activity, and induce apoptosis (Kruman et al., 1997; Camandola et al., 2000; Soh et al., 2000; Kalyankrishna et al., 2002).

Oxidative cellular injury can cause cellular dysfunction and, when severe, this form of injury can cause cell death (Fig. 1). Steady-state levels of oxidative tissue damage represent a balance between rates of damage caused by pro-oxidant stimuli and rates of antioxidant and tissue repair mechanisms that decrease ROS/RNS levels and remove oxidatively damaged molecules (reviewed by Halliwell and Gutteridge, 1999; Halliwell and Whiteman, 2004). Components of the antioxidant defense system include enzymes, like the superoxide dismutases and glutathione peroxidase, and antioxidants, like vitamins E and C. Host functions that may not be directly involved in the generation or removal of ROS and RNS also play important roles in determining the extent of free radical-mediated tissue injury; an example is apolipoprotein E, which is involved in tissue repair (Fig. 1).

Our current understanding of the significance and pathogenesis of oxidative cell injury was made possible by advancements in immunohistochemical and biochemical methods to localize and quantify oxidative macromolecular damage (reviewed by Halliwell and Whiteman, 2004). Methods available for the detection of oxidative damage include the immunohistochemical localization of protein adducts from the chemically reactive lipid peroxidation product HNE or 8-hydroxyguanosine (8OHG), the most abundant adduct formed on nucleic acids by hydroxyl radical attack (Uchida et al., 1995; Yin et al., 1995; Hartley et al., 1997; Montine et al., 1997a,b; Eaton et al., 1999). Immunohistochemistry also can be used to detect carbonylated proteins and peroxynitrite-induced protein and DNA modifications in tissues (Frank et al., 2002; Lorch et al., 2002)

Biochemical quantification methods of free radical-

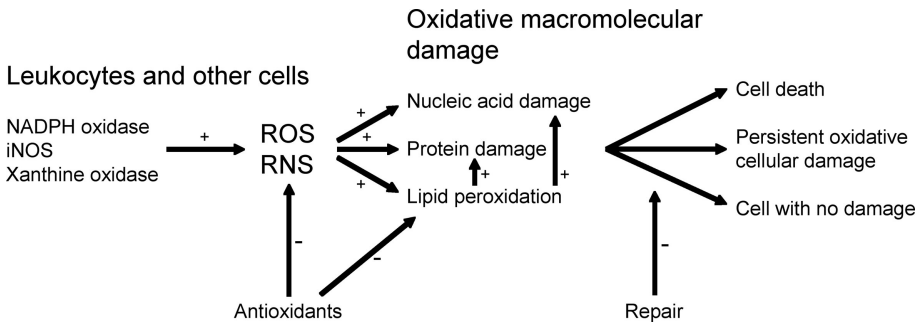

Fig. 1. Pathways leading to oxidative damage in inflammatory processes.

mediated injury are numerous and include the gas chromatography/negative ion chemical ionization mass spectrometric detection of F_2-isoprostanes (IP) and F_4-neuroprostanes (NP). These molecules are exclusive, stable products of free radical-mediated damage to arachidonic acid (AA) and docosahexaenoic acid (DHA), respectively (Morrow and Roberts, 1997; Roberts et al., 1998). AA is relatively evenly distributed in the brain with similar concentrations in gray and white matter and within glia and neurons. Measurement of F_2-IP is a reflection of lipid peroxidation in the entire brain. Unlike AA, DHA is highly concentrated in neuronal membranes to the exclusion of other cell types. Therefore, measurement of F_4-NP provides a highly selective, quantitative window into neuronal lipid peroxidation.

Viral infection-induced oxidative damage

Increased generation of ROS and RNS is a feature of many viral infections and can be caused by both direct effects of virus on cells and inflammatory responses of the host (reviewed by Schwartz, 1996; Peterhans, 1997a,b; Akaike et al., 1998; Akaike, 2001) (Fig. 2). In tissue-culture systems, a number of viruses have been found to induce increased production of ROS and RNS. Such effects of viral infection have been described in studies of differentiated monocytes and macrophages, murine neuroblastoma cells, and coronary artery smooth muscle cells following infection with herpes simplex virus type 1 (HSV-1) (Lopez-Guerrero and Alonso, 1997; Fujioka et al., 2000), Japanese encephalitis virus (Liao et al,, 2002, Lin et al., 2004), and human cytomegalovirus (Speir, 2000), respectively. Other prominent examples involve the induction of iNOS expression in mixed neuronal-glial cultures by the human immunodeficiency virus (HIV) proteins gp41 and gp120 (Adamson et al., 1999; Walsch et al., 2004) and induction of ROS by gp120 in glial cultures (Viviani et al, 2001). Mechanisms of virus-induced ROS and RNS induction in many instances are not well understood, but they most likely range from receptor-mediated signaling induced by virion components to cytotoxic effects of viral proteins expressed during viral replication (Palu et al., 1994; Lopez-Guerrero and Alonso, 1997; Fujioka et al., 2000; Speir, 2000, Liao et al., 2002; Lin et al., 2004; Walsch et al., 2004).

Inflammatory responses of the host precipitated by viral infections may involve the generation of O_2^- and other ROS by infiltrating phagocytic cells and XO-mediated humoral responses (Fig. 2). Inflammatory cytokines such as interferon-γ lead to induction of iNOS during many viral infections including those caused by Borna disease virus, HSV-1, influenza virus, and rabies virus (reviewed by Akaike, 2001). NO has antiviral effects against some viruses including coxsackievirus, Epstein-Barr virus, and HSV-1 (Croen, 1993; Zaragoza, 1999), but it has no antiviral effect against a number of other viruses in cell culture (reviewed by Akaike, 2001). ROS, RNS, and secondary lipid peroxidation products like HNE and MDA may affect viral replication through modulation of the activation state of cells, regulation of host inflammatory and immune responses, and by causing oxidative damage to host tissues and viral components (Schwarz, 1996; Peterhans, 1997a,b; Akaike, 1998; Beck, 2000) (Fig. 2). Oxidative damage of infected and adjacent cells also may limit viral spread.

For most viral infections, the extent to which oxidative damage plays a beneficial role for the host by limiting viral replication is not well understood. Some studies suggest that oxidative damage induced by virus infection can be purely deleterious to the host. For example, pharmacologically reduced or genetically deficient iNOS activity in mice is associated with reduced tissue damage during influenza virus and HSV-1 pneumonia and flavivirus encephalitis without a compromised antiviral response (Akaike et al., 1996; Kreil and Eibl, 1996; Adler et al., 1997; Karupiah et al., 1998). However, HSV-1-infected, iNOS-deficient mice demonstrate increased replication and an increased rate

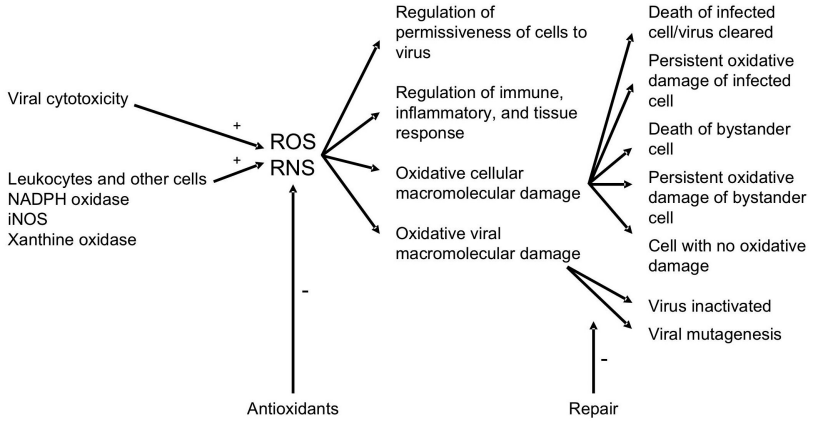

Fig. 2. Pathways leading to oxidative damage in viral infections.

of viral reactivation in the nervous system (McLean et al, 1998).

Oxidative damage in virus-infected nervous system tissues

Oxidative nervous system damage has been reported as a consequence of HIV (Boven et al., 1999; Turchan et al., 2003; Haughey et al., 2004) and measles virus (Hayashi et al, 2002) infections of humans, HSV-1 (Valyi-Nagy et al., 2000; Milatovic et al., 2002) and reovirus (Valyi-Nagy et al., 1999) infections of mice, and murine leukemia virus infection of rats (Wilt et al, 2000). Each is reviewed here.

AIDS Dementia Complex (ADC)

HIV/AIDS is associated with a high frequency of neurological complications (reviewed by Love and Wiley, 2002). These complications can be due to opportunistic infections, neoplasms, vascular disease, treatment effects, and neuropathology induced directly by HIV. Between 20 and 30% of patients with late-stage AIDS develop motor and cognitive deficits that are thought to be caused by direct effects of HIV infection of the brain. These deficits may progress to AIDS dementia complex (ADC). The pathogenesis of ADC is not well understood. HIV infection in the brain predominantly involves macrophages; significant viral infection of neurons has not been demonstrated. However, HIV infection is associated with dendritic pruning, simplification of synaptic contacts, and neuronal loss (Everall et al., 1991, 1993, 1999; Reyes et al., 1991; Mesliah et al., 1992; Weis et al., 1993; Oster et al,. 1995). Neuronal damage is thought to be an indirect effect of soluble neurotoxic factors released by macrophages, microglial cells, and astrocytes. Infected macrophages release quinolinic acid, tumor necrosis factor-α (TNFα), platelet activating factor, interleukin-1α, interferons, NO, and ROS (Wesselingh et al., 1993; Bukrinsky et al., 1995; Hayes et al., 1998; Perry et al., 1998; Pulliam et al., 1998; Krivine et al., 1999; Rostasy et al., 1999). Neurotoxicity also may be mediated by HIV proteins including Tat, gp41, and gp120 (Adamson et al., 1999; Viviani et al., 2001; Nath, 2002; Walsch et al., 2004). Cytokines and viral proteins released from infected cells can activate uninfected astrocytes and microglia. iNOS activity is upregulated in microglial cells and astrocytes in HIV-infected brain tissue (Boven et al., 1999). NO is released from glial cells following addition of inflammatory cytokines and soluble HIV antigens, such as gp120 (Mollace et al., 2001; Walsch et al., 2004). Soluble gp120 also may induce ROS in astrocytes (Viviani et al., 2001). A consequence of the altered cytokine and redox balance in ADC is oxidative brain damage. Levels of the lipid peroxidation product HNE are significantly increased in brain tissues and cerebrospinal fluid of persons with ADC (Haughey et al., 2004). Brain sections of ADC patients show intense parenchymal and perivascular nitrotyrosine staining, indicating that reaction between NO and O_2^- has led to peroxynitrite formation and oxidative damage in HIV-infected tissues (Boven et al., 1999). HIV-induced damage of neurons provides a prime example of virus-induced oxidative neural injury that appears to be purely deleterious to the host and has no role in limiting viral replication.

Acute HSV-1 Encephalitis

HSV-1 is the most common cause of sporadic encephalitis (reviewed by Johnson and Valyi-Nagy, 1998; Whitley, 2001). During HSV-1 encephalitis there is viral replication in neurons and non-neuronal cells and necrotizing inflammation. Survivors suffer severe neurological impairment due to permanent damage to neural structures including extensive loss of neurons. Studies using a murine HSV-1 neuropathogenesis model show that HSV-1 encephalitis is associated with neuronal and non-neuronal HNE- and 8-OHG-specific immunoreactivity in infected areas of the brain, indicating oxidative damage to proteins and nucleic acids (Valyi-Nagy et al., 2000) (Figs. 3A, 4A). Furthermore, levels of F_2-IP and F_4-NP are markedly elevated during acute HSV-1 encephalitis (Valyi-Nagy et al, 2000) (Figs. 5, 6), indicating damage to AA and DHA, respectively (Morrow and Roberts, 1997; Roberts, 1998).

Molecular mechanisms leading to oxidative damage during acute HSV-1 encephalitis are not well understood. HSV-1 infection of nervous system tissues of mice is associated with the expression of iNOS and the release of cytokines including TNFα from inflammatory cells (Koprowski et al., 1993; Shimeld et al., 1997; Meyding-Lamade et al., 1998; Fujii et al., 1999). NO and TNFα have anti-HSV-1 activity and can either generate potent oxidizing radical byproducts through direct interactions (NO) or induce free radical-mediated injury indirectly through membrane signaling (TNFα) (Matthews et al., 1987; Liochev an Fridovich, 1997; Sanchez-Alcazer et al., 2000). HSV-1 infection causes lipid peroxidation in cultured HeLa cells and induces NO production in differentiated monocytes and macrophages in culture (Palu et al., 1994; Lopez-Guerrero and Alonso, 1997; Fujioka et al., 2000). However, it is not known whether HSV-1 infection of neurons and glia can directly induce ROS or RNS.

Latent HSV-1 infection

Primary HSV-1 infection leads to the establishment of life-long latent infection in the nervous system of most humans by adulthood. Latent HSV-1 infection most commonly involves neurons of the trigeminal ganglia, but involvement of other ganglia of the peripheral nervous system, the brainstem, and the cerebrum, although somewhat less frequent, approaches 50% of adults (Baringer and Pisani, 1994; Sanders et al, 1996;

Itzhaki et al., 1997). HSV-1 latency is characterized by maintenance of the HSV-1 genome in neuronal nuclei, production of latency-associated transcripts, and absence of detectable viral protein and infectious virus production (reviewed by Roizman and Knipe, 2001).

Studies using a murine model of HSV-1 latent infection show that HSV-1 latent infection is associated with modest but consistently detectable neuronal and non-neuronal HNE- and 8-OHG-specific immunoreactivity and moderately elevated levels of F_2-IP (Valyi-Nagy et al., 2000; Milatovic et al, 2002) (Figs. 3C, 4C, 5). Oxidative damage appears to affect latently infected neurons and possibly uninfected neurons and glial cells (Valyi-Nagy et al, 2000). Latent HSV-1 infection of the murine nervous system is associated with persistent, chronic inflammation, persistently elevated levels of cytokines, and increased iNOS activity, which may play a role in the prevention of HSV-1 reactivation from latency (Koprowski et al, 1993; Cantin et al, 1995; Meyding-Lamade et al, 1998). These observations raise the possibility that host defenses responsible for the maintenance of HSV-1 latent infection in the human nervous system also may cause oxidative neural injury to latently infected and bystander cells. The presence of HSV-1 DNA in brain has been proposed to be an independent risk factor for Alzheimer disease (Itzhaki et al, 1997). Whether oxidative damage induced by latent HSV-1 infection contributes to the pathogenesis of Alzheimer disease or other degenerative diseases is unknown.

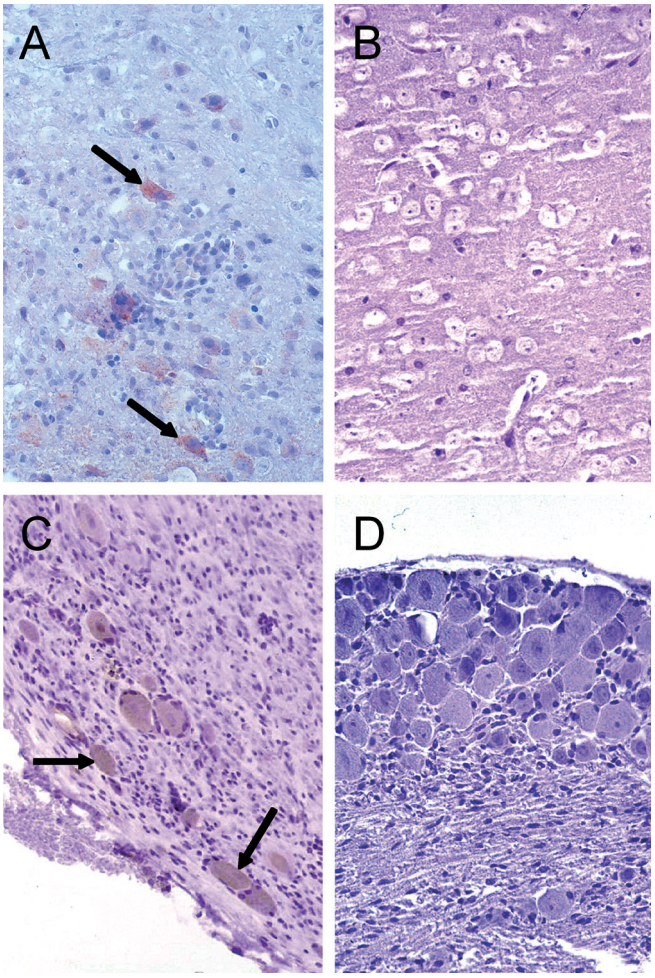

Fig. 3. Immunohistochemical localization of protein adducts from the chemically reactive lipid peroxidation product 4-hydroxy-2-nonenal (HNE) in the nervous system of HSV-1-infected or mock-infected mice. **A.** Brainstem 7 days after inoculation with HSV-1 (acute encephalitis). Arrows indicate representative neurons in the section immunoreactive for HNE-protein adducts. **B.** Cerebral cortex 7 days after mock infection. Trigeminal ganglion 220 days after inoculation with **(C)** HSV-1 (latent infection) or **(D)** mock-infection. Arrows in panel C indicate a neuron immunoreactive for HNE-protein adducts. (Modified from Valyi-Nagy et al., Virology 278, 309-321, 2000.)

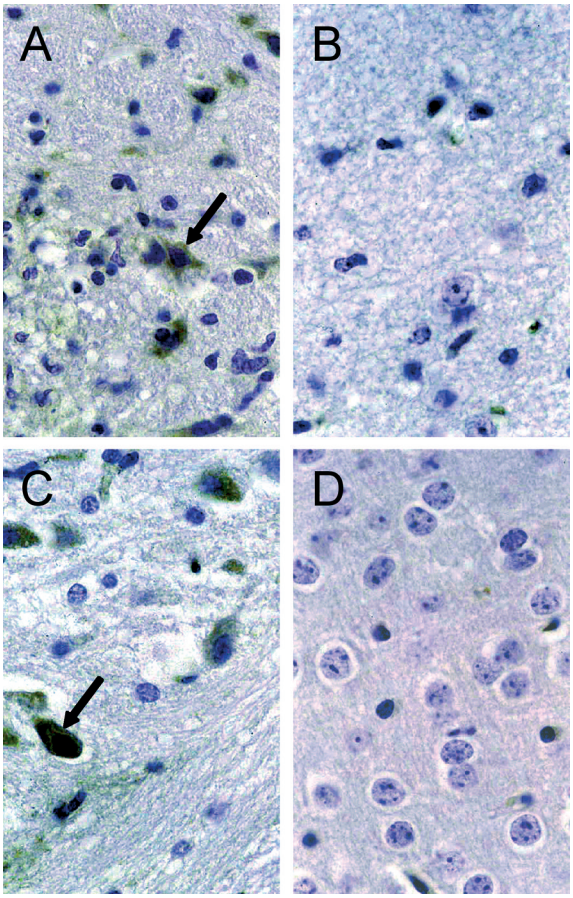

Fig. 4. Immunohistochemical localization of adducts from 8-hydroxyguanosine (8OHG), the most abundant adduct formed on nucleic acids by hydroxyl radical attack, in the CNS of HSV-1-infected and mock-infected mice. Brainstem 7 days after inoculation with **(A)** HSV-1 (acute encephalitis) or **(B)** mock-infection. **C.** Brainstem 220 days after HSV-1 infection (latent HSV-1 infection). **D.** Cerebral cortex 220 days after mock infection. Arrows in panels A and C indicate 8OHG-immunoreactive neurons in HSV-1-infected tissues. (Modified from Valyi-Nagy et al, Virology 278, 309-321, 2000.)

Acute reovirus encephalitis

Infection of newborn mice with reovirus provides a well-established experimental model for studies of viral pathogenesis. Reoviruses are nonenveloped viruses that contain a genome of 10 segments of double-stranded RNA (reviewed by Nibert and Schiff, 2001). Reoviruses infect many mammalian species, including humans, but disease is restricted to the very young (reviewed by Tyler, 2001; Forrest and Dermody, 2003; Tyler et al, 2004). After infection of newborn mice, reoviruses cause injury to a variety of organs, including the CNS, heart, and liver, depending on the viral strain. The best characterized of these models is reovirus pathogenesis in the murine CNS, in which different reovirus serotypes display distinct patterns of neural injury (Weiner et al., 1977, 1980). Serotype 3 reovirus spreads to the CNS neurally and infects neurons (Tyler et al., 1986; Morrison et al., 1991). Infection of newborn mice with serotype 3 reovirus leads to fulminant encephalitis with widespread inflammation and neural injury including neuronal apoptosis (Weiner et al., 1977; Oberhaus et al., 1997; Valyi-Nagy et al,. 1999; O'Donnell et al., 2003).

Replication of serotype 3 reovirus in the brain of newborn mice is associated with HNE immunoreactivity of infected neurons (Valyi-Nagy et al., 1999) (Fig. 7). Whether the detected oxidative neuronal damage is caused by direct viral toxicity or by ROS released from inflammatory cells is not known. Interestingly, reovirus-infected, HNE-positive neurons also often show morphologic evidence of apoptosis, raising the possibility that oxidative damage contributes to the induction of cell death.

Murine leukemia virus neurodegeneration in rats

PVC murine leukemia virus (PVC-MuLV) infects brain capillary endothelial cells in neonatal rodents. Infection is associated with reactive gliosis, spongiform vacuolation of the neuropil, and neuronal degeneration (reviewed by Wilt et al., 2000). As PVC-MuLV does not replicate in neurons, neuronal injury induced by this virus occurs by an indirect mechanism. PVC-MuLV-induced neurodegeneration is associated with oxidative damage as detected by immunoreactivity for nitrotyrosine and protein carbonyl groups (Wilt et al, 2000). Treatment of infected rats with the antioxidant vitamin E transiently protects against virus-induced neurodegeneration. Mechanisms of neuronal oxidative injury may involve release of NO and ROS from infected endothelial cells or from activated perivascular glial cells including microglial cells and astrocytes (Wilt et al., 2000). Oxidative injury can be detected in the brain before or concomitant with the appearance of activated microglia and gliosis. Therefore, endothelial cells may be particularly important sources of ROS and RNS during PVC-MuLV infection of the CNS. Since PVC-MuLV does not replicate in neurons, neuronal

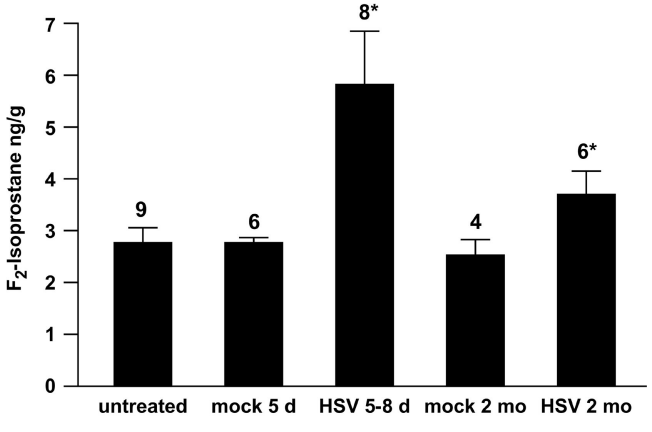

Fig. 5. F_2-isoprostane (F_2-IP) concentrations in the left brain half of BALB/c mice following intracerebral inoculation of either HSV-1 or normal saline (mock-infection) into the left cerebral hemisphere. Untreated, 4- to 6-week-old mice without treatment. Mock 5d, mice euthanized 5 days following mock-infection. HSV 5-8 d, six mice euthanized 5 days following inoculation of 10^5 PFU of HSV-1 and two mice following inoculation of 10^3 PFU of HSV-1 (acute encephalitis). Mock 2 mo, mice euthanized 60 days after mock-infection. HSV 2 mo, mice euthanized 60 days following inoculation of 10^3 PFU of HSV-1 (latent HSV-1 infection). The number of animals in each group is indicated above the bars. *, $P < 0.05$ compared to mock-infection. (Modified from Milatovic et al., J. Neurovirology 8, 297-307, 2002.)

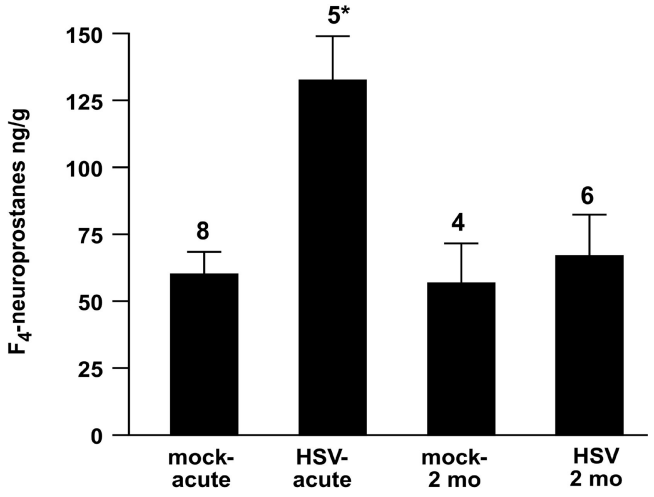

Fig. 6. F_4-neuroprostane (F_4-NP) concentrations in the left brain half of BALB/c mice following intracerebral inoculation of either HSV-1 or normal saline (mock-infection) into the left cerebral hemisphere. Mock acute, mice euthanized 5 days following mock-infection. HSV acute, three mice euthanized 5 days and two mice euthanized 8 days following inoculation of 103 PFU of HSV-1 (acute HSV-1 encephalitis). Mock 2 mo, mice euthanized 60 days following mock-infection. HSV 2 mo, mice euthanized 60 days following inoculation of 103 PFU of HSV-1 (latent HSV-1 infection). The number of animals in each group is indicated above the bars. *, $P < 0.05$ compared to mock-infection. (Modified from Milatovic et al, J. Neurovirology 8, 297-307, 2002.)

damage caused by PVC-MuLV, similar to that caused by HIV, provides a prominent example of virus-induced oxidative neural injury that appears to be purely deleterious to the host and has no role in limiting viral replication.

Measles subacute sclerosing panencephalitis (SSPE)

Measles virus can infect neurons and glial cells in the CNS. SSPE is caused by variants of measles virus selected during persistent infection of the brain (reviewed by Love and Wiley, 2002). In contrast to some other forms of neural injury induced by measles virus, persons with SSPE appear to have no immunological impairment. The disease occurs years or even decades after initial measles virus infection. Pathologic features include chronic infiltration of the brain parenchyma by lymphocytes and macrophages, astrocytosis, loss of neurons, demyelination, rare viral inclusions, and neurofibrillary tangles similar to those seen in Alzheimer disease (reviewed by Love and Wiley, 2002). In brain tissue affected by SSPE, oxidative damage to DNA, RNA, and protein has been detected by immunohistochemistry using antibodies against 8-hydroxy-2-deoxyguanosine-, 8-OHG-, and HNE-modified proteins (Hayashi et al, 2002). Interestingly, evidence of oxidative DNA and RNA damage is detectable in cells of the cerebral cortex in SSPE cases with disease duration of less than nine years. In contrast, evidence of oxidative protein damage is evident in the

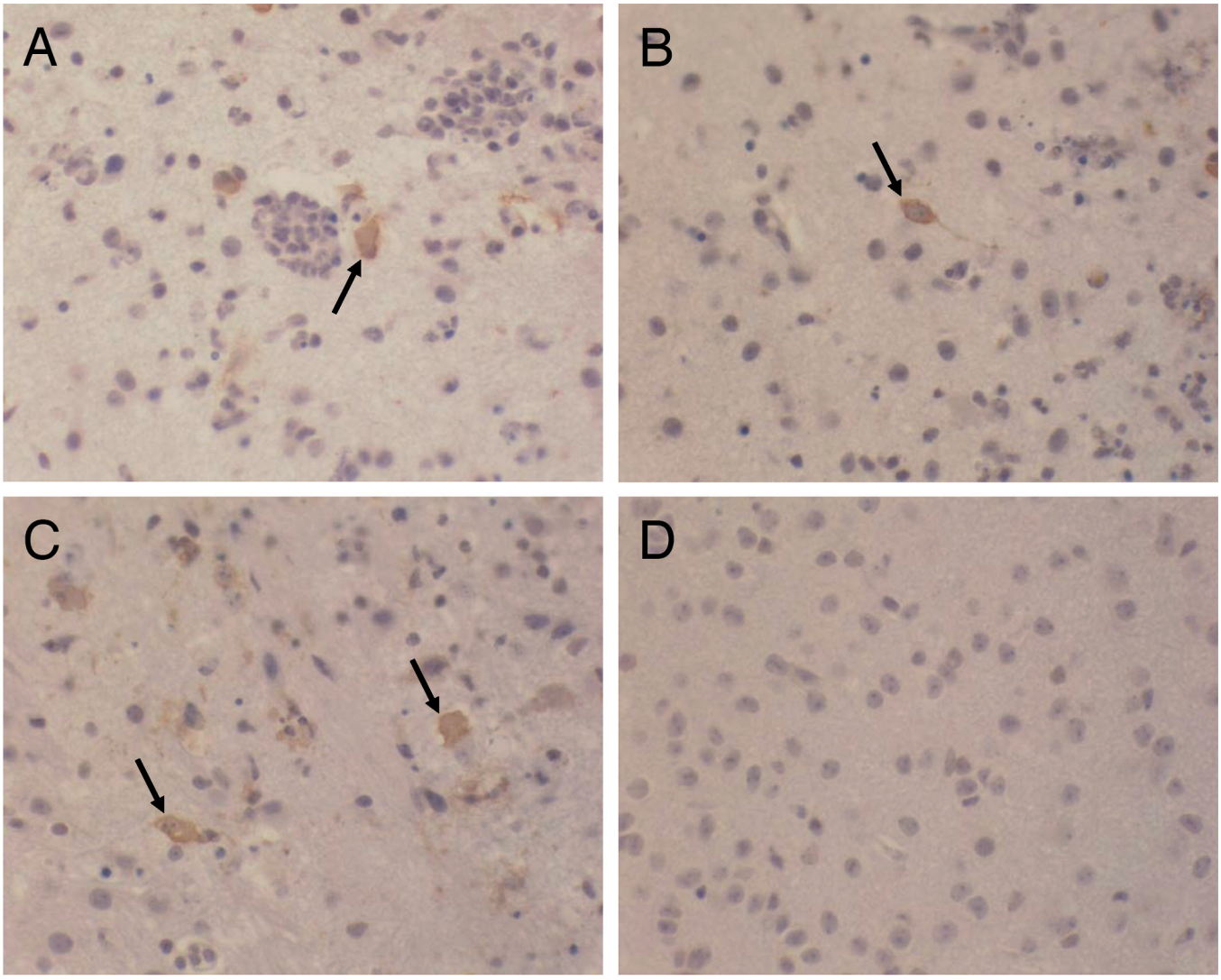

Fig. 7. Immunohistochemical localization of protein adducts from the chemically reactive lipid peroxidation product 4-hydroxy-2-nonenal (HNE) in the nervous system of **(A,B,C)** serotype 3 reovirus-infected and **(D)** mock-infected (control) mice. Arrows in panels A, B, and C indicate representative neurons immunoreactive for HNE-protein adducts in tissues with acute reovirus encephalitis.

demyelinated white matter in cases with disease duration of longer than nine years. Thus, oxidative damage to nucleic acids may contribute to early neuronal damage, whereas oxidative protein damage may be related to late neurodegeneration. It is also possible that oxidative damage to the viral genome contributes to the generation of viral variants.

Conclusions

Oxidative damage is an emerging general mechanism of nervous system injury caused by viral infection. Oxidative damage can be caused by direct effects of virus on cells and indirect effects of host inflammatory responses. As such, this form of injury can affect both infected and uninfected cells and thus may limit viral replication and spread. To what extent oxidative damage plays a beneficial role for the host by limiting viral replication is not understood for most neurotropic viral infections. However, oxidative damage of uninfected neurons in the case of HIV and PVC-MuLV infections suggests that oxidative tissue injury in the nervous system induced by viral infection can be solely deleterious to the host. A better understanding of the role of oxidative damage in viral infections of the nervous system may lead to improved treatment strategies that will reduce the extent of tissue damage during viral infections without impeding the antiviral response of the host. Furthermore, such studies may contribute to an enhanced understanding of the pathogenesis of congenital CNS malformations, CNS neoplasia, and neurodegenerative diseases for which viruses have been proposed to play an etiologic role.

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