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Infectious agents and age-related neurodegenerative disorders

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Abstract

As with other organ systems, the vulnerability of the nervous system to infectious agents increases with aging. Several different infectious agents can cause neurodegenerative conditions, with prominent examples being human immunodeficiency virus (HIV-1) dementia and prion disorders. Such infections of the central nervous system (CNS) typically have a relatively long incubation period and a chronic progressive course, and are therefore increasing in frequency as more people live longer. Infectious agents may enter the central nervous system in infected migratory macrophages, by transcytosis across blood–brain barrier cells or by intraneuronal transfer from peripheral nerves. Synapses and lipid rafts are important sites at which infectious agents may enter neurons and/or exert their cytotoxic effects. Recent findings suggest the possibility that infectious agents may increase the risk of common age-related neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and stroke. While scenarios can be envisioned whereby viruses such as *Chlamydia pneumoniae*, herpes simplex and influenza promote damage to neurons during aging, there is no conclusive evidence for a major role of these pathogens in neurodegenerative disorders. In the case of stroke, blood vessels may be adversely affected by bacteria or viruses resulting in atherosclerosis.

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1. Aging and the pathogenesis of neurodegenerative disorders caused by infectious agents

Other articles in this special issue of *Ageing Research Reviews* describe the alterations in immune function that occur during normal aging that may increase the vulnerability of the elderly to many different types of infectious agents. Bacteria, viruses and unconventional pathogens such as prion proteins can cause inflammatory processes and neuronal degeneration in the central nervous system (CNS). The CNS may be particularly vulnerable to infectious agents during aging (Fig. 1) because: (1) the blood–brain barrier and cellular immune mechanisms are compromised during aging such that infectious agents can “hide” in the CNS without being detected by the immune system; (2) some infectious agents (e.g. herpes virus) can be transferred transcellularly from infected peripheral nerves into the CNS; (3) age-related increases in oxidative stress and impaired energy production can render neurons vulnerable to the toxicity of viral or prion proteins; (4) signaling pathways that promote the survival and plasticity of neurons, such as those activated by neurotrophic factors, may be impaired during aging.

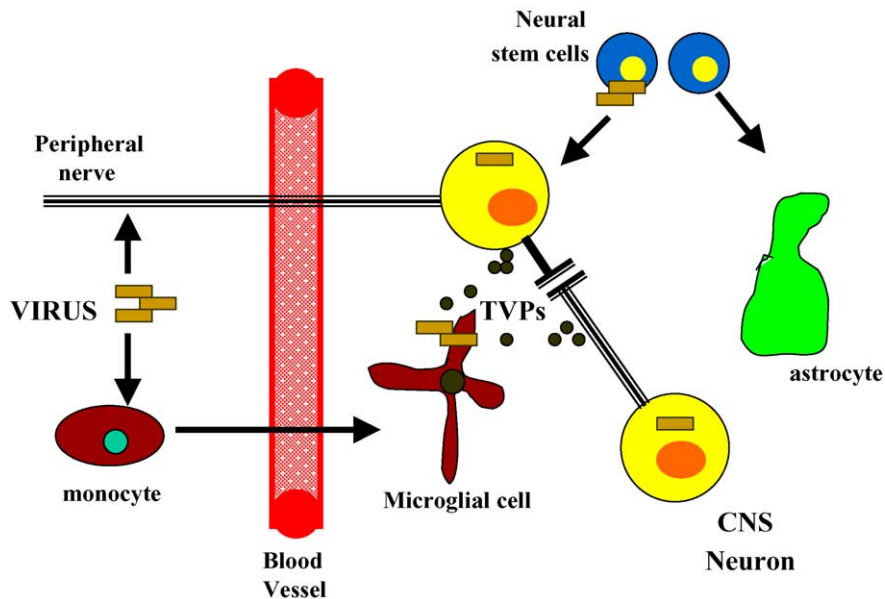


Fig. 1. Mechanisms whereby viruses infect the CNS and cause neuronal dysfunction and death. Two routes of entry of viruses into the CNS are by infection of cells that cross the blood–brain barrier (e.g. cells of the monocyte–macrophage/microglia lineage) and intra- and transneuronal transfer from peripheral neurons. Microglia and neural stem cells appear to be cell types in which viruses may replicate at a high rate; viruses may also infect neurons and astrocytes, but may not replicate in such postmitotic cells. Viruses can produce toxic viral proteins (TVPs) with the HIV-1 proteins gp120 and Tat being exemplary.

2. Infectious agents that cause neurodegenerative disease

Due in part to the low level of immune surveillance the CNS is particularly vulnerable to chronic infection and long-term damage as the result of systemic infection with many relatively common pathogens. Because of the decline in immune function that occurs during aging, and because of an age-related increase in vulnerability of neurons to many different insults, the brain and spinal cord may be hot spots of smoldering infections in the elderly. For example, it is well-established that the elderly are vulnerable to central nervous system damage caused by West Nile virus (Nedry and Mahon, 2003), Lyme disease (Hayes, 2002) and tuberculosis (Hosoglu et al., 2002).

3. HIV dementia

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV-1) virus. HIV-1 infects lymphocytes and impairs their immune function, thereby increasing the risk of several different opportunistic infections and certain types of cancers. Although effective treatments for AIDS, such as protease inhibitor cocktails have been developed, the resulting increase in survival of infected patients has resulted in a dramatic increase in the number of individuals in which serious neurological consequences of HIV-1 infection arise (Gartner, 2000; McArthur et al., 2003). Dementia is now common in treated AIDS patients and results from degeneration of synapses and neurons in brain regions such as the hippocampus and related limbic and cortical structures. HIV encephalitis also takes a toll on neurons in the basal ganglia-dysfunction and degeneration of neurons in the basal ganglia result in motor dysfunction and may also contribute to cognitive impairment, particularly in older patients infected with HIV (Berger and Arendt, 2000; Nath et al., 2000). As is the case with Alzheimer's disease (AD), dementia in HIV-infected patients is more severe in those with an E4 allele of apolipoprotein E (Corder et al., 1998).

The mechanism by which HIV-1 causes dysfunction and degeneration of neurons in the brain is not fully understood. The cells in which HIV-1 replicates in the CNS may include microglia/brain macrophages (McArthur et al., 2003) and neural stem cells (Haughey and Mattson, unpublished data). HIV-1 does not infect neurons and it is therefore believed that neurons are damaged by HIV-1 proteins released from infected cells. Two such neurotoxic HIV-1 proteins have been identified, namely, the coat protein gp120 and the transcriptional regulator Tat, both of which have been shown to be present in soluble forms in the brains of HIV-1 dementia patients. Both gp120 and Tat can kill cultured neurons and can increase the vulnerability of neurons to excitotoxicity and apoptosis (Haughey and Mattson, 2002). Patients with HIV dementia exhibit evidence of oxidative damage in their brains including increased amounts of peroxynitrite, 4-hydroxynonenal and protein carbonyls (Turchan et al., 2003). gp120 and Tat have been shown to increase oxidative stress, and antioxidants can protect cells from the damaging effects of these proteins, suggesting an important role for oxidative damage in the pathogenesis of HIV dementia (Kruman et al., 1998). Inflammatory cytokines that are known to be increased in the brains of HIV dementia patients (TNF α , IL1, IFN γ and Fas/FasL) can induce ceramide production in non-neural cells by increasing the

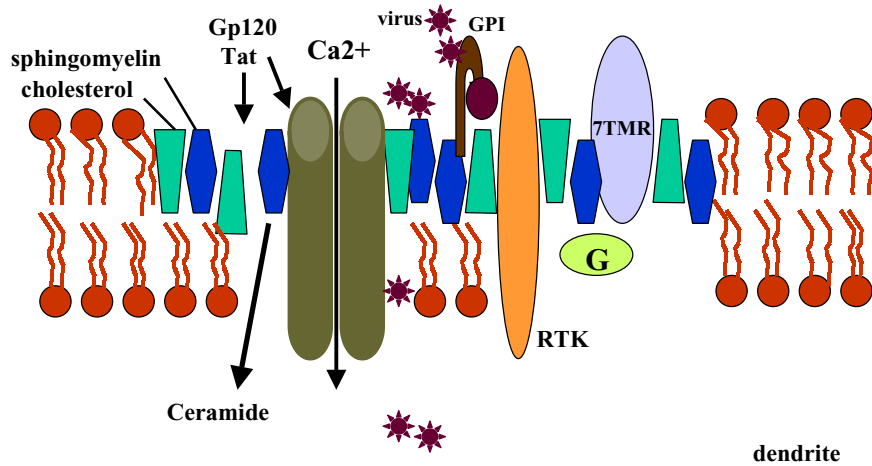


Fig. 2. Roles of membrane lipid rafts in infections of the central nervous system. Lipid rafts are microdomains of the plasma membrane in which the outer leaflet of the phospholipid bilayer contains relatively high levels of cholesterol and sphingomyelin. A variety of receptors and associated signal transduction proteins (receptor tyrosine kinases, RTK; seven transmembrane receptors, 7TMR coupled to GTP-binding proteins), and ion channels are concentrated in lipid rafts. Viruses may gain entry to cells by binding to proteins (e.g. GPI-anchored receptors) or lipids in lipid rafts. Lipid rafts may also be regions of membranes that are damaged by cytotoxic viral proteins such as the HIV-1 proteins gp120 and Tat.

activity of sphingomyelinases (Shi et al., 1998; Wiegmann et al., 1994). Prominent increases in the pro-inflammatory cytokines TNF α , IL1, IL2, IL6 and Fas/FasL have been reported in brain and CSF of HIV dementia patients (Wesselingh et al., 1993). Antiretroviral treatment can dramatically slow cognitive decline and restore the cytokine balance, suggesting that inflammatory products play important roles in HIV associated CNS dysfunction (McArthur et al., 2003).

Emerging findings suggest that membrane microdomains called lipid rafts play important roles in the pathogenesis of HIV dementia. Lipid rafts are regions of the plasma membrane that have high levels of cholesterol and sphingomyelin, and receptors for many different cytokines and growth factors are concentrated in these membrane microdomains (Fig. 2). Lipid rafts are believed to be portals through which many different types of viruses, including HIV-1 enter cells (Campbell et al., 2001). In addition, lipid rafts may be regions of the cell at which gp120 and Tat exert their neurotoxic actions. Activation of cytokine receptors and oxidative stress can induce the production of ceramide from membrane sphingomyelin and ceramide, in turn can trigger a form of programmed cell death called apoptosis. We discovered that levels of ceramide and sphingomyelin are significantly increased in brain tissues and cerebrospinal fluid of patients with HIV dementia (Haughey et al., 2003). When cultured neurons were exposed to gp120 and Tat, levels of ceramide increased greatly. The ceramide precursor palmitoyl-CoA sensitized neurons to Tat and gp120 toxicities, and an inhibitor of ceramide production protected the neurons, demonstrating a critical role for ceramide in the neurotoxic actions of HIV-1. A better understanding of the roles of lipid

rafts in the pathogenesis of HIV-1 dementia may lead to novel approaches for preventing and treating this disorder.

4. Prion disorders

There has been much interest in prion disorders because of their transmissibility among humans and the potential for their transmission from animals, and animal products such as beef, to humans. Prion disorders affect primarily the CNS. Examples include scrapie in sheep, bovine spongiform encephalopathy in cattle, and Kuru, Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker disease and fatal familial insomnia in humans (Mastrianni and Roos, 2000; Giese and Kretzschmar, 2001; McKintosh et al., 2003). These disorders are characterized by the intracellular accumulation of insoluble aggregates of prion protein, abnormal (scrapie) forms (PrP^{sc}) of a normal protein called the cellular prion protein (PrP^c). Because prion disorders can be transmitted from one individual to another it was initially assumed that these diseases were caused by a virus. However, intensive investigations failed to identify a virus and the emerging evidence led to the remarkable conclusion that the disease is transmitted by an abnormal form of the prion protein itself. PrP^{sc} adopts a structure that fosters an interaction with PrP^c that results in PrP^c being converted to the pathogenic PrP^{sc} form (Fig. 3). In some cases the abnormal prion protein may result from a mutation in the PrP^c gene, while in other cases the abnormal conformation of PrP^{sc} may result from posttranslational modifications (Wiessmann, 2002).

Prion disorders may have a long incubation time and acquired cases of prion disease are more common in older individuals. Prion proteins may damage and kill neurons by inducing oxidative stress, disrupting calcium homeostasis and triggering apoptosis (Haughey and Mattson, 2002). Inflammatory processes involving microglial activation and production of pro-inflammatory cytokines may also contribute to the pathogenesis of prion disorders (Eikelenboom et al., 2002). Changes that occur in brain cells during normal aging, including increased oxidative stress and metabolic impairment, may render neurons vulnerable to the toxicity of PrP^{sc}.

5. Possible contributions of infectious agents to common age-related neurodegenerative disorders

It is known that inflammation-like processes occur in the brains of patients with Alzheimer's, Parkinson's (PD) and Huntington's diseases, but whether such inflammatory processes are pathogenic or simply represent responses to neuronal degeneration is unclear. It has been suggested that certain childhood infections may increase the risk of age-related neurodegenerative disorders, although the evidence is as yet meager (Martyn, 1997). There are certainly a variety of viruses that infect cells in the nervous system and some of these viruses can be retained in neurons for long periods and even for the lifetime of an individual. Examples include herpes simplex-1, Sindbis virus, measles and rabies (Kristensson et al., 1996; Griffin, 1998; Schneider-Schaulies et al., 2001; Mettenleiter, 2003). In addition,

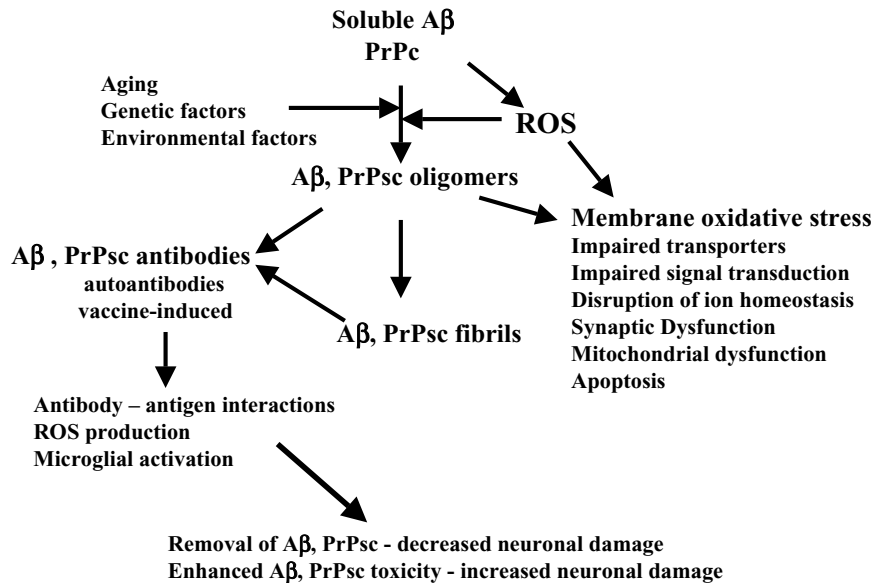


Fig. 3. Similarities in the neurotoxic actions of pathogenic forms of prion proteins and amyloid β -peptide ($A\beta$). Normal forms of $A\beta$ (soluble $A\beta$) and prion proteins do not self aggregate, whereas in prion disorders and Alzheimer's disease the proteins generate reactive oxygen species (ROS) and acquire abnormal conformations. Genetic factors (e.g. mutations in the genes encoding the prion protein or $A\beta$) and environmental factors (e.g. high caloric intake or folate deficiency) and the aging process may cause or promote formation of pathogenic forms of $A\beta$ and PrPsc. During the process of peptide oligomer and fibril formation, $A\beta$ and PrPsc induce membrane-associated oxidative stress and disrupt membrane ion transporter and channel functions resulting in synaptic and mitochondrial dysfunction and apoptosis. It has recently become evident that autoantibodies against abnormal conformations of $A\beta$ and PrPsc can be generated by the immune systems in patients and in subjects immunized with $A\beta$ or prion peptides. The autoantibodies may promote clearance of the endogenous pathogenic proteins from the brain and/or they may enhance the neurotoxicity of $A\beta$ or PrPsc.

transient infections might trigger neurodegenerative cascades when the infection occurs in aged individuals who may be at risk of the disease.

6. Alzheimer's disease

AD is characterized by the accumulation of amyloid β -peptide ($A\beta$), synaptic dysfunction and degeneration, and neuronal death in brain regions involved in learning and memory processes (Mattson, 1997a,b, 2002). Mutations in three different genes (the amyloid precursor protein, presenilin-1 and presenilin-2), and studies of cultured cells and transgenic mice expressing AD-linked APP and presenilin mutations have provided evidence that a critical event in AD is altered proteolytic processing of APP resulting in increased production of $A\beta$. $A\beta$ may damage neurons and render them vulnerable to excitotoxicity and apoptosis by inducing membrane lipid peroxidation and impairing the function of ion-motive ATPases, glucose and glutamate transporters, and ion channels (Mattson et al., 1992; Mark et al.,

1997; Guo et al., 1998, 1999a,b) (Fig. 3). In addition to the degeneration of synapses and neurons that occurs in AD, damage to the oligodendrocytes that myelinate axons in the brain have been documented in mouse models of AD (Pak et al., 2003). Environmental factors that may increase the risk of AD include a high caloric intake and dietary folate deficiency (Zhu et al., 1999; Kruman et al., 2002a,b).

Altered immune responses have been documented in studies of AD patients and in animal models and may result, in part, from perturbed calcium signaling in lymphocytes and microglia (Mattson et al., 2001; Lee et al., 2002). A β may play an important role in triggering activation of microglia in AD by a mechanism involving the activation of CD40 (Tan et al., 1999), and A β can also perturb astrocyte function in ways that may impair their ability to communicate with neurons (Haughey and Mattson, 2003). Peripheral or central stimulation with lipopolysaccharide induces a transient increase in expression of pro-inflammatory cytokines such as TNF, interleukin 1 beta and interleukin 6, and these cytokine changes are associated with microglial activation and altered processing of APP (Brugg et al., 1995; Lee et al., 2002), suggesting roles of immune responses in neurodegenerative cascades in AD. While it has been proposed that the immune system can be stimulated by immunization with A β , the specific antibodies produced may determine whether such immunization is beneficial or promotes neuronal degeneration instead (Nath et al., 2003).

Systemic infection can result in inflammatory processes in the brain including microglial activation. Infections in the elderly can result in cognitive impairment that outlasts the infection; in patients with AD who encounter a systemic infection, cognitive function can be impaired for several months after the resolution of a systemic infection and the cognitive impairment is preceded by raised serum levels of interleukin 1 beta (Holmes et al., 2003). Soininen et al. (1993) analyzed circulating immune complexes in the blood of patients with AD and individuals with age-associated memory impairment. AD patients with severe dementia had significantly elevated levels of circulating immune complexes compared with AD patients with mild or moderate disease and to control subjects and individuals with age-associated memory impairment. It is unclear whether the increased immune complexes in severe AD patients contribute to the pathogenic process.

Nucleic acids prepared from postmortem brain tissue samples from AD patients and control subjects were screened by polymerase chain reaction assay for DNA sequences from *Chlamydia pneumoniae*; brain areas with typical AD-related neuropathology were positive for the organism in 17/19 AD patients, whereas 18/19 control patients were negative (Balin et al., 1998). The latter study also showed that cultures from affected AD brain tissues were strongly positive for *C. pneumoniae*, while identically performed analyses of non-AD brain tissues were negative. In a subsequent study by this the same investigators it was reported the *C. pneumoniae* is present in glial cells in areas of neuropathology in the brains of AD patients (Balin and Appelt, 2001). The cells in the brains of AD patients that might be infected by *C. pneumoniae* include vascular endothelial cells and monocytes; these cells may play roles in the inflammatory processes and neuronal degeneration in AD (MacIntyre et al., 2003). However, a role for *C. pneumoniae* in AD pathogenesis remains to be established and negative data have been obtained. For example, in a study of centenarians there was no association between *C. pneumoniae* infection and dementia (Bruunsgaard et al., 2002).

Dobson and Itzhaki reported that herpes simplex type 1 virus (HSV1) is present in the brain of many elderly people, and that it may be a risk factor for AD, particularly in

individuals with the apolipoprotein E4 allele (Dobson and Itzhaki, 1999). However, in other studies there was no evidence of herpes virus RNA in the hippocampus of demented individuals with extensive neuropathological changes of AD (Deatly et al., 1990). Finally, in an interesting study it was shown that caregivers of AD patients have significantly poorer immune responses to influenza virus vaccine when compared to age-matched control subjects (Kiecolt-Glaser et al., 1996), which may result from the chronic stress associated with caregiving leading to increased vulnerability to infection and perhaps to increased vulnerability to age-related neurodegenerative disorders as well.

7. Parkinson's disease

PD is characterized by degeneration of dopamine-producing neuron in the substantia nigra resulting in progressive impairment of the patient's ability to control their body movements. Most cases of PD are sporadic and the causes are unknown, although rare cases are caused by inherited mutations in α -synuclein, Parkin or DJ-1 (Moore et al., 2003). It is believed that mitochondrial dysfunction and associated ATP depletion and oxidative stress are pivotal and relatively early events in the neurodegenerative process in PD (Duan et al., 1999a) (Fig. 4). Dopaminergic neurons may die in PD by apoptosis mediated by Par-4 (Duan et al., 1999b) and the tumor suppressor protein p53 (Duan et al., 2002a; Gilman et al., 2003). Epidemiological and experimental findings suggest a potential role for environmental toxins such as the pesticide rotenone in the pathogenesis of PD, although the data are not yet conclusive (Di Monte et al., 2002). Dietary factors such as high calorie intake and folate deficiency (Duan and Mattson, 1999; Duan et al., 2002b) and exposure to pesticides and excitotoxins (Lockwood, 2000; Ludolph et al., 2000) may also increase the risk of PD.

Some epidemiological data suggest that influenza A viral infections may increase the risk of PD and may be responsible for the formation of Lewy bodies and the later death of nigral neurons (Takahashi and Yamada, 1999). Based upon data suggesting that peptic ulcer is more frequent in PD patients and that *Helicobacter pylori* can cause ulcers, a study was performed to determine whether *H. pylori* seropositivity was associated with PD (Charlett et al., 1999). It was shown that siblings of PD patients had an increased probability of *H. pylori* seropositivity compared to control subjects. In one study there was an increased percentage of teachers and healthcare workers with PD in a large tertiary care movement disorders clinic suggesting the possibility that a high level of exposure to viral or other respiratory infections in these occupations might be a risk factor for PD (Tsui et al., 1999). The possibility that viruses can induce PD is suggested by studies showing that certain viruses can induce PD-like pathology in rodents. For example, rats infected with Japanese encephalitis virus exhibited neuronal loss with gliosis which was confined mainly to the zona compacta of the substantia nigra (Ogata et al., 1997).

8. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is characterized by degeneration of lower and upper motor neurons resulting in progressive paralysis and death. The cause(s) of most

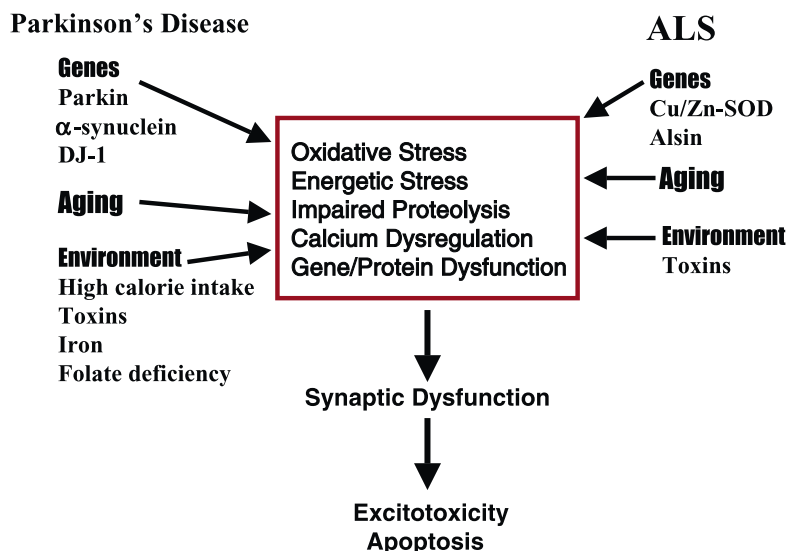


Fig. 4. Cellular and molecular mechanisms responsible for motor dysfunction in Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Some rare cases of PD and ALS are caused by mutations. Three genes have been identified in which mutations cause early onset inherited PD (Parkin, α -synuclein and DJ-1) and mutations in two genes (Cu/Zn-SOD and Alsin) are known to cause ALS. Insight into the molecular and cellular abnormalities that lead to the dysfunction and death of midbrain dopaminergic neurons in PD and of motor neurons in ALS has come from studies of cultured cells and transgenic mice expressing the disease-causing human genes. In the case of PD, each of the mutations has been linked to abnormal ubiquitin/proteasome-mediated proteolysis, cellular oxidative and metabolic stress and triggering of apoptosis. In the case of ALS, Cu/Zn-SOD mutations cause oxidative stress and disrupt cellular calcium homeostasis. The aging process and environmental factors may perturb the same or similar regulatory systems that are adversely affected by genetic mutations. Synapses are particularly vulnerable to genetic, aging and environmental factors, and are sites where excitotoxic and apoptotic cascades that cause the death of the neurons are initiated.

cases of ALS is unknown, but a few cases result from mutations in the gene encoding Cu/Zn-superoxide dismutase. The pathogenic process in ALS involves increased oxidative stress and disruption of cellular calcium homeostasis which may trigger apoptosis (Pedersen et al., 1998, 2000; Kruman et al., 1999; Guo et al., 2000) (Fig. 4). Recent findings suggest that abnormalities in lipid metabolism, involving increased levels of ceramides and cholesterol esters, also plays a role in the pathogenesis of ALS (Cutler et al., 2002).

The possibility that retroviral infection can cause ALS has recently been suggested by studies of HIV-infected patients who developed a rapid progressive ALS-like disorder as the first manifestation of their HIV-infection (Portegies and Cohen, 2002). The patients stabilized or improved with antiretroviral therapy. Enterovirus RNA has also been detected in the spinal cords of ALS patients, although it remains to be established if such viruses cause the disease (Portegies and Cohen, 2002). In a study of Gulf War veterans there was a significant association between systemic mycoplasmal infections and ALS (Nicolson et al., 2002), although it was not established if mycoplasma plays a role in the pathogenesis of ALS or if ALS patients are more susceptible to ALS. The results of another study suggested

an association between the risk of ALS and infection with certain enteroviruses and herpes virus (Cermelli et al., 2003).

9. Stroke

Ischemic stroke, a major cause of death and disability in the elderly, occurs when a blood vessel becomes occluded or ruptures. Risk factors for stroke include high calorie/high fat diets, hypertension and physical inactivity (Gorelick, 1995; Yu and Mattson, 1999; Kurth et al., 2002). Neurons in the brain region normally perfused by the affected blood vessel degenerate after a stroke as the result of decreased glucose and oxygen availability. Ischemic neuronal death involves metabolic compromise, dysregulation of cellular calcium homeostasis and increased oxidative stress (Keller et al., 1998; Liu et al., 2002). Activation of microglia and the production of pro-inflammatory cytokines also play an important role in ischemic neuronal death (Bruce et al., 1996; Yu et al., 2000). In addition to the cascades that result in the death of neurons, several important neuroprotective signaling pathways are activated after a stroke including intercellular signaling involving neurotrophic factors and cytokines, and intracellular pathways involving calcium and transcription factors such as NF- κ B and CREB (Mattson, 1997b; Mattson et al., 2000; Mattson and Camandola, 2001).

Because atherosclerosis is a major antecedent process in stroke, there is evidence that infectious agents that may promote atherosclerosis increase the risk of stroke. There is a growing body of evidence that *C. pneumoniae* can promote cerebrovascular atherosclerosis and may thereby increase the risk of stroke. Johnston et al. (2001) documented increased C-reactive protein levels and viable *C. pneumoniae* in atherosclerotic carotid arteries. However, it remains to be established whether *C. pneumoniae* induces/enhances atherosclerosis or if atherosclerotic plaques provide an environment in which *C. pneumoniae* accumulates. Similarly, it was reported that *C. pneumoniae* is present in symptomatic atherosclerotic carotids and that this is associated with increased serum antibodies, inflammation and apoptosis of T cells (Neureiter et al., 2003). Other systemic bacterial and viral infections may promote stroke by enhancing atherosclerosis and by weakening cerebral blood vessels (Emsley and Tyrrell, 2002). Acute infectious episodes may increase the risk of acute ischemic stroke in the elderly independently of other predisposing factors (Nencini et al., 2003). Another infectious agent that may increase the risk of stroke is influenza which is suggested by studies showing that elderly individuals receiving the influenza vaccine have a significantly lower risk of stroke than do those not receiving the vaccine (Meyers, 2003).

While atherosclerosis is an inflammatory process and is the major pathogenic process that predisposes to stroke, inflammatory mediators also play roles in modifying the neurodegenerative process that occurs as the result of an ischemic stroke. Activated lymphocytes, macrophages and microglia accumulate in ischemic brain tissue after a stroke, and these cells may produce neurotoxic cytokines and excitotoxins. Accordingly, it has been shown that anti-inflammatory drugs can reduce the extent of brain injury in animal models of stroke (Antezana et al., 2003). Not only is aging a risk factor for infection with agents that may promote atherosclerosis, but older persons who suffer a stroke have a significantly worse outcome—more brain tissue is damaged and recovery of function is limited (Duverger and MacKenzie, 1988).

10. Infectious agents and demyelinating disorders

The myelinating cells of the central (oligodendrocytes) and peripheral (Schwann cells) nervous systems are vulnerable to being damaged and killed by several viruses (Fazakerley and Walker, 2003). Progressive multifocal leukoencephalopathy is caused by the infection of oligodendrocytes by JC papovirus and is characterized by slowly progressing dementia, visual problems and ataxia. Subacute sclerosing panencephalitis is caused by the measles virus and is characterized by behavioral changes mental and visual disturbances and ataxia; it is almost always fatal. The damage to oligodendrocytes may result from infection by the virus, exposure to viral proteins and/or an autoimmune response. Certain coronaviruses can also cause demyelination. For example, the mouse hepatitis virus can cause demyelination in the brains of non-human primates and human coronaviruses related to mouse hepatitis virus have been detected in brain tissue samples from patients with multiple sclerosis.

Multiple sclerosis is the most common demyelinating disorder in humans (Cluskey and Ramsden, 2001). Although not yet conclusive, accumulating data suggest that infectious agent could be involved in the pathogenesis of multiple sclerosis. Associations between infections with measles virus, parainfluenza virus, canine distemper, human herpes virus-6 and *C. pneumoniae* have been reported (for review see Steiner et al., 2001). It is clear that there is an autoimmune component to multiple sclerosis and it is possible that infectious agents may initiate damage to oligodendrocytes or otherwise elicit targeting of oligodendrocytes by the immune system. Because it is well-established that many different viruses can cause demyelination, it will be important to establish which specific viruses play a role in the pathogenesis of multiple sclerosis.

11. Synapses: vulnerable targets of infectious agents

As a result of the large and repetitive ion fluxes associated with membrane depolarization, and neurotransmitter release and receptor activation, synapses are sites at which neurons are subjected to very high levels of oxidative and metabolic stress. Accordingly, synapses have been shown to be vulnerable to dysfunction and degeneration in each of the infectious and age-related neurodegenerative disorders described above. Synapses are where excitotoxicity is initiated, a process in which glutamate receptors are overactivated under conditions of oxidative and metabolic stress, resulting in excessive calcium influx (Gilman and Mattson, 2002; Mattson, 2003). Apoptosis may also be triggered at synapses and, indeed, biochemical cascades can be locally engaged in synapses in experimental models relevant to the pathogenesis of neurodegenerative disorders (Mattson et al., 1998a,b; Duan et al., 1999b; Glazner et al., 2000; Gilman et al., 2003). Thus, synapses are vulnerable to the kinds of factors that are promoted by infectious agents. For example, the HIV-1 proteins gp120 and Tat induce oxidative stress and promote calcium influx through glutamate receptor channels and voltage-dependent channels which are concentrated in synapses (Haughey and Mattson, 2002).

In addition to their vulnerability to aging and infectious agents, synapses may play important roles in the propagation of infectious agents in the CNS. Synapses may be portals of entry of viruses because cell surface receptors to which the viruses bind are located in lipid

rafts which are concentrated in synaptic membranes. For example, putative receptors for botulinum and tetanus toxins are located in synapses (Herrerros et al., 1997, 2000). Some viruses, such as herpes simplex, can be transferred between neurons; this transcellular transfer occurs at synapses and likely involves specific exocytotic and endocytotic mechanisms (Labetoulle et al., 2000).

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