J Neuroimmune Pharmacol (2009) 4:163–174
DOI 10.1007/s11481-008-9143-1

INVITED REVIEW

Neurodegeneration and Ageing in the HAART Era

Bruce J. Brew · S. M. Crowe · A. Landay · Lucette A. Cysique · Gilles Guillemin

Received: 21 October 2008 / Accepted: 21 November 2008 / Published online: 6 December 2008

Abstract Cognitive impairment and neurodegeneration still occur despite highly active antiretroviral therapy (HAART). While there are many potential reasons for this, there is increasing evidence that such impairment occurs in the absence of a clear cause. Furthermore, there are data that some neurodegenerative diseases, especially Alzheimer's or an Alzheimer-like illness, are becoming more common in the context of HAART-treated human immunodeficiency virus (HIV) disease. This review will critically examine the evidence underpinning these observations. Potential mechanisms will be discussed with particular emphasis on the effect of ageing and how it overlaps with the effects of HIV disease itself thereby leading to neurodegeneration. The nature of this overlap will then be explored for its potential role in the facilitated expression and development of neurodegenerative diseases. Lastly, there will be a brief discussion of interventions to minimize such neurodegeneration including optimization of HAART for brain entry.

Keywords HIV · HAART · neurodegenerative diseases · dementia · Alzheimer's

B. J. Brew (✉) · L. A. Cysique · G. Guillemin
Department of Neurology, St Vincent's Hospital,
Level 4, Xavier Building, Victoria Street, Darlinghurst,
Sydney, Australia
e-mail: B.Brew@unsw.edu.au

B. J. Brew · G. Guillemin
Applied Medical Research Centre, St Vincent's Hospital,
Darlinghurst,
Sydney, Australia

S. M. Crowe
Department of Medicine, Monash University,
Melbourne, Victoria, Australia

S. M. Crowe
Centre for Virology, Burnet Institute,
Melbourne, Victoria, Australia

A. Landay
Department of Immunology and Microbiology, Rush University,
Chicago, USA

L. A. Cysique
Brain Sciences Institute, University of New South Wales,
Sydney, Australia

G. Guillemin
Department of Pharmacology, University of New South Wales,
Sydney, Australia

Introduction

The introduction of highly active antiretroviral therapy (HAART) in 1996–1997 has led to dramatic changes in human immunodeficiency virus (HIV) disease. Patients are now living for a significantly longer time; indeed the number of patients aged over 50 and even 60 years is increasing. Most of these have been living with HIV disease for many years, some in excess of 20 years. Furthermore, the number of patients over 50 years who have recently acquired HIV infection is increasing. Despite the benefits of HAART, cognitive impairment remains. While the incidence of HIV-associated dementia (HAD) has significantly fallen with HAART, its prevalence is increasing as patients live longer with fixed deficits (Cysique et al. 2005; Dore et al. 2003; Brew et al. 2007). Furthermore, the prevalence of milder cognitive impairment, now termed minor neurocognitive disorder and included under the broader term HIV-associated neurocognitive disorder (HAND; Antinori et al. 2007), has not changed despite the introduction of HAART (Cysique et al. 2004a; Antinori

et al. 2007). While there are many potential reasons for this, there is concern that the longer duration of HIV disease, as a consequence of HAART, together with the increasing age of infected persons may have a compounding detrimental effect on cognitive function. Additionally, these two factors may facilitate and perhaps enhance the expression of a variety of neurodegenerative diseases as HIV-infected patients approach the age where such disorders become increasingly common.

This manuscript will first review the evidence for the potential compounding effect of age on cognition in HIV disease by examining the evidence for persistent and developing neurodegeneration in HAART-treated patients. This is best done by focusing on those who have persistent and developing cognitive impairment in the absence of any other explanation most particularly in the context of maximal suppression of HIV viral load in the blood and cerebrospinal fluid (CSF). In relation to the second issue, namely the facilitation of neurodegenerative diseases by HIV and age, data from CSF and neuropathological studies will be reviewed.

After discussion of the evidence, a delineation of the potential mechanisms will be presented. This will be approached firstly by a review of the general aspects of the pathogenesis of neurodegenerative diseases. Then the effects of normal ageing and how they intersect with HAND will be discussed, followed by a review of the overlapping features and mechanisms in HIV and neurodegenerative diseases.

The last section will deal with a discussion of two potential therapeutic interventions. First, the rationale for optimizing HAART to ensure adequate brain penetration of antiretroviral drugs will be presented. Second, evidence supporting the clinical value of risk factor reduction for neurodegenerative diseases will be reviewed.

The evidence for persistent neurodegeneration in HAART-treated patients

There are data from several investigators that have pointed to the existence of persistent neurodegeneration in the context of successful viral suppression in HAART-treated patients though there has not been a study specifically designed to address the issue. Cysique et al. (2006a) prospectively assessed 101 clinically stable subjects who had been on HAART for at least 5 years and who had had an AIDS defining illness in the past. All subjects were then followed every 12 months for the next 27 months. Changes to HAART were made by their HIV physician independent of the assessments. Patients who were impaired neuropsychologically were evaluated medically to exclude treatable causes. Between 8% and 34% (depending on the time point of the assessment) showed significant cognitive decline over the study period despite an undetectable plasma viral load. Increased age (mean 48 years) was not associated with impairment, but this was thought to reflect regression towards the mean. The nadir CD4 cell count (mean 73 cells/μl), a surrogate measure for disease duration, was significantly associated with cognitive decline. Similar results were recently published by Robertson et al. (2007) from the ALLRT study, a prospective observational cohort consisting of 1,160 subjects participating in ACTG clinical trials of HAART. The median age was 41 years. At baseline, 39% had mild cognitive impairment while 26% had moderate impairment. This was sustained in 22% and a further 21% developed impairment while on study independent of viral load suppression. Age was associated with impairment but duration of HIV infection was not assessed except for a relationship with the nadir CD4 cell count. Another study by Sevigny et al. (2004) reported on 203 non-demented subjects with CD4 lymphocyte counts less than 200/μl, or less than 300/μl but with cognitive impairment who were followed for a median time of 20.7 months. Seventy-four (36%) subjects developed dementia during the study period despite an undetectable plasma viral load in 21% and an undetectable CSF viral load in 43%. The incidence of dementia increased over time: 20% at 1 year and 33% at 2 years but was not related to the age of the patients or the duration of HIV disease. This may have been a consequence of the patients being younger (mean age 41 years) and the duration of HIV infection being shorter (mean 7 years approximately) than in other studies. Valcour et al. (2004), however, did observe the effect of age on cognitive impairment. In a prospective study of two cohorts one aged over 50 years and the other aged between 20 and 39 years, there was a significantly higher prevalence of dementia in the older group (25% vs 13%). Impairment was not related to plasma viral load as approximately half had undetectable levels but the exact number with cognitive impairment with a concomitant undetectable plasma viral load is not clear from the published data. Bhaskaran et al. (2008) in the largest cohort thus far published (15,380 patients) noted 222 that had developed HAD. This was an observational cohort across a large number of countries. Older age at seroconversion and the duration of infection, both significantly increased the risk of HAD. While HAD was noted to be associated with a detectable plasma viral load, no data were presented on the occurrence of HAD in patients with an undetectable viral load.

Thus, there is a consistent theme that cognitive impairment in HIV-infected individuals can occur in the context of maximal viral suppression with just over half the studies showing a relationship to increased age. The lack of a consistent relationship to age and duration of HIV disease

across studies may relate to issues specific to the study populations but there is also the possibility that a more general issue is at play. The effects of age and disease duration on cognitive impairment are probably interlinked: the risk of cognitive impairment in a 40 year old with 20 years of HIV infection is likely to be different to that of a 60 year old with 20 years of HIV infection. Future studies should perhaps examine this effect more thoroughly, an effect that we have tentatively termed "the age-duration effect". It may be more accurate to add the two together to arrive at a single score, "the age-duration index".

The evidence for facilitated expression of neurodegenerative diseases

Introduction

Before reviewing this evidence, it is important to briefly revise the markers that are used in the identification of such diseases. In CSF, Alzheimer disease (AD) is characterized by the finding of low concentrations of amyloid beta (AB) 1-42 and elevated total tau (t-tau) as well as phosphorylated tau (p-tau). In brain tissue, AD is notable for the presence of amyloid plaques (containing amyloid fragments) and neurofibrillary tangles (containing hyperphosphorylated tau). Amyloid plaques are often categorized as either diffuse or neuritic, the latter being directly associated with abnormal neuronal and glial processes. Parkinson's disease is associated with the presence of Lewy bodies (containing alpha synuclein, ubiquitin, lipids, proteasomal subunits, parkin, and synphilin-1) and tau deposition, while fronto-temporal dementia has neurofibrillary tangles, ubiquitin deposits, and TAR DNA binding protein-43; progressive supranuclear palsy is associated with tau deposition, and multisystem atrophy with alpha synuclein inclusions and tau deposits. There is evidence for the increased expression in HIV-infected individuals (presumably facilitated by HIV) of each of the latter diseases with the exception of fronto-temporal dementia, progressive supranuclear palsy, and multisystem atrophy. However, some of the data that have been published showing abnormal expression of the aforementioned markers may have relevance to these diseases.

CSF studies

In the CSF, Brew et al. (2005) found markedly low concentrations of amyloid beta 1-42 and raised t-tau as well as p-tau in patients with HAD. The levels were comparable to those of the group of AD patients. These data have been replicated in a larger data set with the exception that the p-tau values were normal (Brew et al. 2008). Clifford et al. (2008) have also noted the same findings including the normal p-tau. The unreplicated finding of elevated p-tau concentrations in the earlier study is unexplained. It is not likely related to sample size but it maybe an infrequent finding in a subgroup of patients who are in the process of developing an AD-like illness. Raised p-tau levels thus far seem to be specific for AD (Andreasen et al. 2003).

Neuropathological studies

Neuropathologically, there have been several publications establishing a link between HIV infection and AD. Esiri et al. (1998) were the first to observe significant amyloid deposition in the brains of HIV-infected patients, while Green et al. (2005) had the largest number of patients. Several other groups have made similar observations (see Table 1 for full description of the studies). There is usually a consistent relationship with increased age as best detailed by Esiri et al.: a prevalence of 18% in the fourth decade rising to 50% in the seventh decade in AIDS cases. In controls, the equivalent figures were none in the fourth decade and 36% in the seventh decade. The differences between AIDS and controls in the fourth decade and in the series as a whole were significant (p 0.014 and 0.004, respectively). Rempel and Pulliam (2005) on the other hand found a correlation with years of infection rather than age. This may reflect the smaller number of subjects studied or the interaction between age and years of infection—the age-duration effect as previously mentioned. Not all studies have rigorously examined all parts of the brain but there does seem to be a preponderance of deposition in the hippocampus and frontal lobe, the latter being unusual for AD. Another consistent theme is the lack of a clear relationship to the presence of any other pathology most especially HIV encephalitis. The latter finding is curious but it may reflect the small numbers of patients examined who had HIV encephalitis. Most studies found diffuse plaques, only occasionally were there "neuritic" plaques which are directly associated with AD. These observations do not mitigate the significance of diffuse plaques. They are consistently seen in patients with Down's syndrome who invariably develop AD if they live long enough and are the only type of plaque seen in particular areas of AD brains. Finally, most investigators consider the diffuse plaque to be the forerunner of the neuritic plaque. Not all studies have found amyloid deposition, however. Giometto et al. (1997) did not find any evidence of amyloid plaques but the ages of the patients are not stated, the number of patients was relatively small, and the sections examined were not optimal. Gelman and Schuenke (2004) were unable to find any significant increase in amyloid plaques in HIV-infected patients when compared to an age-matched control popu-

Table 1 Summary of neuropathological studies of amyloid deposition in HIV disease

Study	Number of patients	Age	HIV stage	Number of patients with plaques	Distribution of amyloid deposits	Diffuse or neuritic plaques
Esiri et al. (1998)	97	47±10.2	87 AIDS 10 pre-AIDS	28 (significantly greater than controls)	Temporal > frontal	Both (only 6 had neuritic)
Izycka-Swieszewska et al. (2000)	15	34 (24–48)	AIDS	3	Neocortex more than hippocampus	Diffuse
Green et al. (2005)	162	44 (24–75)	103 had AIDS	50% of AIDS (no controls)	Frontal especially (from frontal cortex, hippocampus, caudate, putamen, and globus pallidus)	Diffuse
Rempel and Pulliam (2005)	14	44 (31–58)	HAD in 6	14	Frontal examined only	Diffuse
Khanlou et al. (2008)	36 (frontal and temporal)	55(50–76)	HAD in 11, 38 of 49: CD4<200	35	Frontal and temporal	Neither: intraneuronal or within vessel walls
Anthony et al. (2006)	29	40 (33–46)	9 presymptomatic, 11 AIDS, 9 HAART	13 (of borderline significance)	Medial temporal lobe (from hippocampus and pons)	Diffuse
Giometto et al. (1997)	27	Not stated	AIDS	0	Anterior frontal and parietal lobes	
Gelman and Schuenke (2004)	25	53 (22–75)	AIDS	7 (not different from controls)	Medial temporal lobe (from hippocampus, entorhinal cortex and parahippocampal gyrus)	

lation. There may be three explanations: the sample size is smaller than other studies, the patients may have had a shorter duration of HIV disease, and the whole brain was not assessed—only the hippocampus, entorhinal cortex, and parahippocampal gyrus.

There are emerging studies of other neurodegenerative disorders in the setting of HIV infection. Gelman and Schuenke (2004) noted the significantly greater presence (in 48% of AIDS patients with 100% in those aged between 62 and 75 years) of ubiquitinylated deposits in all age groups predominantly in the temporal lobe white matter compared to controls. The nature of the deposits was unable to be determined precisely but thought to be related to synaptic components. Similar ubiquitinylated deposits have been noted by others in HIV-infected patients (An et al. 1997; Adle-Biassette et al. 1999; Izycka-Swieszewska et al. 2000). Khanlou et al. (2008) have observed increased α-synuclein expression in the substantia nigra in 16% of HIV-infected patients aged between 50 and 76 years while there was no α-synuclein expression in the controls.

Thus, the evidence is compelling for the existence of persistent and evolving neurodegeneration even in the presence of well-controlled HIV disease at least systemically. Furthermore, the neurodegeneration does not appear to be closely linked to HAD. While there is the possibility that the neurodegeneration could be related to antiretroviral drug toxicity, this seems unlikely given the nature of the neuropathological changes and the fact that these changes were seen even before the introduction of HAART. The fact that they are now more common in HAART-treated patients more likely reflects the longer life span of such patients thereby providing the setting in which neurodegeneration can occur.

Potential mechanisms

To understand how neurodegeneration may be occurring despite maximal HIV suppression, one first has to review the most generally accepted framework for the pathogenesis of neurodegenerative diseases. With this background, how the effects of normal ageing overlap with the effects of HIV will be discussed. This will be followed by a review of how in general these neurodegenerative diseases intersect with HIV, and a discussion related to specific neurodegenerative diseases. The last section will integrate the intersection of ageing, neurodegenerative diseases, and HIV.

General pathogenetic framework for neurodegenerative diseases

While there are many aspects of neurodegenerative diseases that are specific to the disease in question, there are mechanisms that are common to most if not all of the neurodegenerative diseases. A frequently articulated model is that there is a breakdown of cellular defense mechanisms which then leads to a cascade of damage. From the

available literature, a model of the pathogenesis of neurodegenerative diseases can be advanced, as detailed in Fig. 1. In broad terms, a pathogenic insult, in the case of most neurodegenerative diseases, seems to be a misfolded protein that leads to activation of cellular defense pathways. These include heat shock proteins, endoplasmic reticulum chaperones, the ubiquitin–proteasome complex, autophagy, the kynurenine pathway through production of picolinic acid, and the P-glycoprotein system. Most of these defenses are well known and documented but the importance of picolinic acid is only emerging. It is one of the near-final products of the kynurenine pathway that is upregulated in a variety of disease states (Guillemin et al. 2007). Picolinic acid itself is the most potent endogenous metal chelator and therefore may be important in cellular defense against the effects of protein misfolding (Cherny et al. 1999). The pathogenic insult and the defense mechanisms are in a dynamic equilibrium until the burden of the insult exceeds the defense capacity or the defense pathways become exhausted. The consequences then are the activation of further inflammation, excitotoxicity, oxidative and nitrosative stress, mitochondrial dysfunction, and transcription dysregulation. The inter-relationships among these are complex and often bi-directional. Nonetheless, the end result is cell dysfunction and death.

Normal ageing and HIV

Neuropsychology

There is now converging evidence that with normal ageing, particular cognitive abilities are affected. Interestingly, this

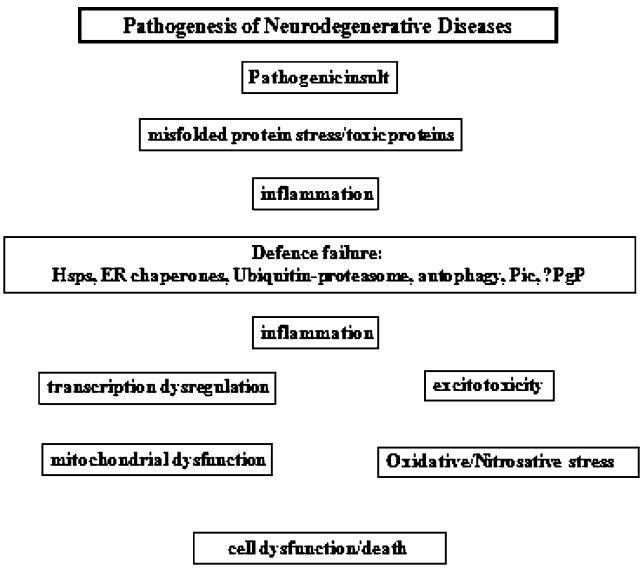

Fig. 1 Hypothetical model of the general aspects of the pathogenesis of neurodegenerative diseases. *Hsps* hear shock proteins, *ER* endoplasmic reticulum, *Pic* picolinic acid, *PgP* P-glycoprotein system

neuropsychological pattern of impairment shares many similarities with HAND. This was empirically demonstrated in a study comparing young adults with HAND and older healthy individuals (Hinkin et al. 1990).

Specifically, attentional processes inclusive of complex attention, speed of information processing, and working memory are primarily affected by ageing (Glisky 2007; Kramer and Madden 2008) as well as HAND (Cysique et al. 2006b; Reger et al. 2002; Woods et al. 2008b). Neuropsychological findings for attentional deficits in ageing show a decreased capacity for dividing and switching between tasks. These difficulties have also been interpreted as being related to working memory impairment, in the sense that working memory involves the ability to manipulate information on which attentional resources are currently focused. Several mechanisms have been implicated but the most likely is that older persons are slower to process information (Salthouse 1996). Indeed, a large part of the variance in working memory is due to a general slowing of information processing. A non-exclusive alternative explanation is a failure to inhibit irrelevant information (Harsher et al. 1999). Interestingly, the same interpretative framework has been proposed in HAND (Hardy and Hinkin 2002). In addition, psychomotor slowing has been shown to be predictive of further deterioration (Sacktor et al. 1996).

Memory function is also commonly affected by ageing, particularly episodic memory—the memory for particular events at a specific time and place. While encoding and storage capacities may be affected, it is mostly effortful retrieval that is primarily impaired in normal ageing. Interestingly, this pattern of impaired retrieval and preserved long-term storage (when aided with cues) is also predominant in HAND in addition to learning deficits. In both conditions, the pattern of effortful learning/recall disturbances has been interpreted as being partially dependent on working memory deficits and slowing of cognitive processes (Peavy et al. 1994; Hartley 2006). Another interpretative framework that has been proposed in ageing research is that of a deficiency of executive control (West 1996). This involves a range of processes such as planning, organizing, coordinating, implementing, and evaluating mental activities and actions. In HAND, executive dysfunctions in the form of alteration of abstract reasoning and problem solving are also common findings especially in the moderate and more advanced stages of the disease (Cysique et al. 2006b). Lastly, there is accumulating evidence for prospective memory alteration in both HAND (Woods et al. 2008a) and normal ageing (Henry et al. 2004). Prospective memory represents the ability to remember things that are to happen in the future. In both ageing and HAND, prospective memory deficits are more obvious in tasks with high strategic load. These difficulties have also been interpreted as partially dependent on working memory abilities.

Finally, as in ageing, the milder stages of HAND are characterized by a relative preservation of language abilities (when no speed-based test is involved), semantic knowledge, and visuo-spatial abilities (Cysique et al. 2006b; Glisky 2007).

Putative brain macro-structural changes associated with the neuropsychological pattern detailed above also share similarities with normal ageing (Raz and Rodrigue 2006) and HAND (Tucker et al. 2004). Macrostructural changes mainly in the form of atrophy and white matter lesions have been shown to preferentially involve striato-frontal networks. From this brief review, it is plausible that ageing and HAND may act in concert to increase the cognitive difficulties that are common to both (processing speed, working memory, and effortful learning/retrieval), thus favoring an earlier onset of this type of difficulties. Further, there maybe acceleration of cognitive decline potentially leading to severe cognitive deficits in these same cognitive domains. Lastly, the overlap between the two may lead to an altered neuropsychological profile reflecting the partly hybrid nature of the interaction.

Neuropathology

There is intersection between ageing and HIV particularly in relation to the frontal lobe and hippocampus. Increasing age eventually leads to approximately a 50% neuronal loss in the basal forebrain and locus coeruleus (Rosene 1993; Kemper 1993). With age, there is less efficient myelination by oligodendrocytes—especially in the frontal lobes (Nielsen and Peters 2000). Microscopically, there is loss of synaptic integrity especially in the CA3 region of hippocampus (Rosenzweig and Barnes 2003), an area also affected by HIV (Torres-Munoz et al. 2001). Both are also characterized by dopamine deficiency (Berger et al. 1994; Arnsten et al. 1995; Berger and Arendt 2000). Lastly, impairment of the blood–brain barrier (Buckner et al. 2006; Young et al. 2008) is common to both.

Physiology

Ageing is notable for disturbances in the cellular disposal of toxins. An abnormal form of ubiquitin, UBB+, is increased intracellularly leading to inhibition of protein degradation (van Leeuwen et al. 1998, 2002). Additionally, heat shock proteins (Hsps) are decreased intracellularly due to defective activation of transcription factor HSF1 (Heydari et al. 1994, 2000) and the lysosomal pathway is impaired (Cuervo and Dice 1998). HIV, particularly tat, and some of the protease inhibitors used to treat HIV disease also disturb the ubiquitin–proteasome complex as well as autophagy, thereby impairing the cellular disposal of toxins (Apcher et al. 2003; Gelman and Schuenke 2004; Haorah et al. 2004; Piccinini et al. 2005; Goila-Gaur and Strebel 2008; Alirezaei et al. 2008a, b). Similarly, ageing is characterized by impaired autophagy (Rajawat and Bossis 2008).

Immunology

Inflammation-associated genes are increased with ageing (Blalock et al. 2005) and perhaps more importantly there is evidence, albeit preliminary, of raised serum levels of lipopolysaccharide (Landay, personal communication) which is pro-inflammatory. HAND is also associated with inflammation as well as elevated lipopolysaccharide concentrations (Ancuta et al. 2008).

HIV and neurodegenerative diseases

There are several areas of commonality in the pathogenesis of HAND and neurodegenerative diseases in general as well as in specific diseases which will be discussed later.

Common general mechanisms

Inflammation

Intersecting pathogenesis pathways relate to both particular cells and their products. Activated microglia and astrocytes are important and common to both HIV and neurodegenerative diseases (Minagar et al. 2002; Kadiu et al. 2005; Ting et al. 2007). TNFa, IL6, MCP-1, and quinolinic acid and other kynurenine pathway products are elevated in HAND both in the serum and CSF and many neurodegenerative diseases (Stone 2001; Guillemin et al. 2005; Town et al. 2008; Björkqvist et al. 2008; Sokolova et al. 2008). In the context of immune activation, it is always a concern as to whether the inflammation is "beneficial" or truly detrimental. However, as pointed out by Wyss-Coray (2006) chronic exposure of microglia to MCP-1, and lipopolysaccharide for that matter, is associated with a more neurotoxic microglial phenotype while acute exposure is linked to a more phagocytic phenotype. The increase in such immune activation products especially MCP-1 is therefore likely to render a more neurotoxic microglial environment. Toll-like receptor-4 (Walter et al. 2007) and decreased immune surveillance are common themes in HAND and neurodegenerative diseases (Richartz-Salzburger et al. 2007; Salaria et al. 2007; Tahara et al. 2006). Lastly, the blood–brain barrier is frequently impaired in both HAND and neurodegenerative diseases (Banks 1999; Bowman et al. 2007).

Degradation pathways

Perhaps of most significance is the intersection of cellular degradation pathways in HAND and neurodegenerative

diseases. Evidence from several investigators points to HIV inhibiting the ubiquitin–proteasome complex as previously mentioned (Gelman and Schuenke 2004; Haorah et al. 2004; Goila-Gaur and Strebel 2008). In AD, Parkinson's, and motor neuron disease similar inhibition occurs (Chung et al. 2001; McNaught et al. 2001). Moreover, autophagy is inhibited by HIV (Alirezaei et al. 2008a, b) and in neurodegenerative diseases (Zatloukal et al. 2002; Nagaoka et al. 2004). Lastly, P-glycoprotein expression is deliberately inhibited in HIV therapy to enhance the efficacy of particular antiretroviral agents, the protease inhibitors. Other antiretroviral drugs such as efavirenz may also inhibit its expression. However, there is some evidence that the P-glycoprotein system is important in the normal clearance of amyloid from the brain (Lam et al. 2001). If the clearance is impeded by P-glycoprotein inhibition, then, it is likely that there will be accumulation of amyloid in the brain with consequent tissue damage. The P-glycoprotein system is thought to have a role in the pathogenesis of some neurodegenerative diseases, most particularly Parkinson's disease and in the removal of potential toxins (Christensen et al. 1998; Lee and Bendayan 2004).

Oxidative and nitrosative stress

Oxidative stress is increasingly thought to be a final common pathway for HAND (Nath et al. 2008) as well as some neurodegenerative diseases such as Alzheimer's disease (Lovell et al. 2007). Furthermore, nitrosative stress with peroxynitrite formation leading to modification of tyrosines in proteins is considered to enhance the aggregation of α-synuclein which in turn is pathogenetically significant in Parkinson's, Lewy body dementia, progressive supranuclear palsy, multisystem atrophy, as well as HAND (Haughey et al. 2008; Li et al. 2008).

Mechanisms common to specific diseases

Specific characteristics of several neurodegenerative diseases intersect with HIV in unique ways. Each of these will now be discussed in detail.

Parkinson's disease Both Parkinson's disease and HIV have a common anatomical substrate namely the substantia nigra (Brew et al. 1995) and a common neurochemical disturbance namely dopamine deficiency (Berger and Arendt 2000). Furthermore, both diseases are associated with testosterone deficiency (Okun et al. 2004).

Alzheimer's disease AD and HIV also share a common anatomical substrate namely the hippocampus (Torres-Muñoz et al. 2001). Furthermore, there are risk factors for AD that are common in HAART-treated patients, including insulin resistance, raised cholesterol especially in mid-life, and testosterone deficiency, which occurs in approximately 30% of patients with advanced HIV disease (Brew 2004; Mylonakis et al. 2001; Okun et al. 2004). Additionally, apoE4 is a risk factor for HAND in some studies especially those who are older (Pemberton et al. 2008; Valcour et al. 2008). There is also commonality in the cytokines that are elevated: S100b, TNFa, IL1b, and IL6 (Pemberton et al. 2001; Brew 2001). Furthermore, elevations in lipopolysaccharide concentrations in the blood are associated with HAND (Ancuta et al. 2008) and with AD (Kitazawa et al. 2005; Herber et al. 2006; Landay, personal communication). The significance of raised lipopolysaccharide concentrations in AD is still open: acute elevation may be beneficial while chronic elevation may be detrimental (Wyss-Coray 2006). It remains to be determined whether AD patients have chronically elevated concentrations although the preliminary data from Landay et al. (personal communication) are suggestive. CD69+ monocytes in blood are also increased in both (Kusdra et al. 2000) as are elevated concentrations of QUIN (Guillemin and Brew 2007). Furthermore, AB1-42, the neurotoxic fragment of amyloid beta, can lead to QUIN production by macrophages and microglia (Guillemin et al. 2003). Lastly, Tat, the regulatory protein of HIV, inhibits neprilysin the chief amyloid β degrading enzyme (Rempel and Pulliam 2005).

Integration of the effects of ageing, HIV, and neurodegenerative diseases

As can be seen from the discussion detailed above, there are many areas where all three effects, ageing, HIV, and neurodegenerative diseases, intersect. As hypothetically conceptualized in Fig. 2, the risk of developing a neurodegenerative disease is progressively increased according to host susceptibility factors, age, HIV infection, and certain medications, particularly ritonavir and probably other protease inhibitor drugs. This proposed model can be tested for validity and for definition as to the nature of the incremental risk when there is more than one factor.

At the subcellular level, from the data discussed previously, there appear to be more specific intersections in the pathophysiology of HAND, ageing, and neurodegenerative diseases. This is diagrammatically represented in Fig. 3 and affords a testable model.

If these models are correct then HAND, especially in HAART treated patients, can be seen as a form of premature ageing sometimes facilitating the expression of the diseases of ageing, namely the neurodegenerative diseases.

Potential therapeutic interventions

The validation of the latter hypothetical models will clearly take several years. What can be done now to minimize the

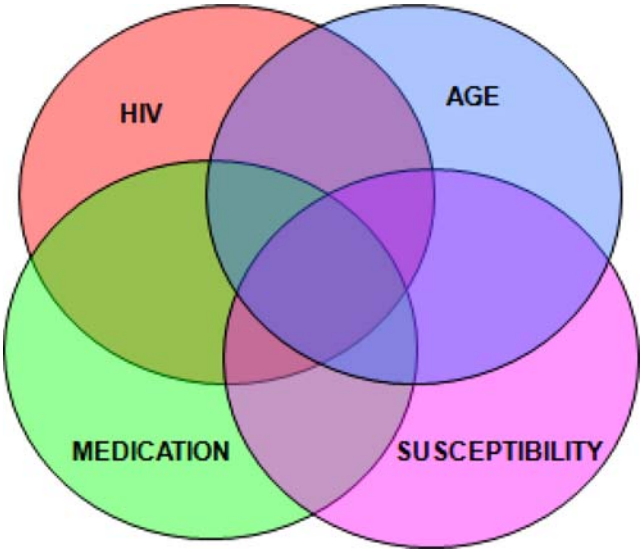

Fig. 2 Diagrammatic representation of the interplay of the key factors in the expression of neurodegenerative diseases in the context of HIV disease

risk of persistent neurodegeneration and the facilitation of neurodegenerative diseases? There are two broad approaches: optimization of HAART to enhance central nervous system (CNS) penetration and risk factor reduction.

Optimization of HAART

The use of antiretroviral drugs in a regimen to specifically enhance CNS penetration is still controversial. There is a body of clinicians and researchers who consider that antiretroviral drugs do not need to penetrate the CNS to have CNS efficacy. This view until recently has been given credence by past studies that have tried to examine the issue and found no benefit. However, mainly, these studies had significant methodological flaws. Some were predicated on all HIV patients developing HAND, which is now known not to be the case. Some only studied the effect of adding one or two CNS penetrant drugs to a background regimen. As it is known that the brain and systemic compartments can behave quite independently especially in HAND patients, it seems illogical to treat with so few drugs. Systemic disease is by and large not treated with one or two drugs so why should it be different for the brain? The next common methodological flaw is to not assess the blood–brain barrier. It is known that some HAND patients have an impaired blood–brain barrier. If these patients are included in a study to assess the benefit of CNS penetrating drugs vs non-penetrating drugs then the study will be uninterpretable. Fourthly, some studies may not have included patients with active HAND—some may have had an inactive or at least indolent form of the disorder where the study time period may have been too short.

Recently though, there has been an increasing number of studies showing the benefit of a CNS penetrating regimen (Cysique et al. 2004b; Letendre et al. 2004) in achieving a more favorable clinical outcome. The nature of a CNS penetrant regimen is the subject of ongoing studies but according to one group a central nervous system penetration effectiveness score of 3 or more is associated with a

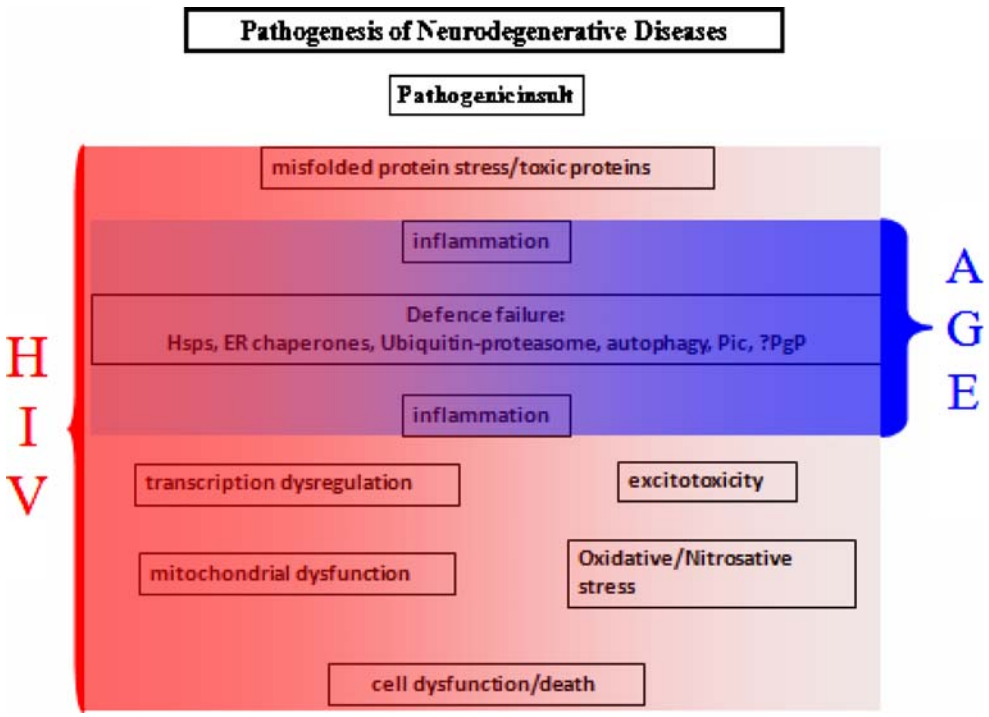

Fig. 3 Intersection between HIV, ageing, and neurodegenerative diseases at the subcellular level

better outcome (Letendre et al. 2008). While it seems likely that the adoption of such a regimen will be beneficial, there is the possibility that it will not be as effective as hoped, chiefly because drugs do vary in the ability to suppress chronic infection. Furthermore, there is increasing evidence of the importance of astrocytic infection in HAD (Clarke et al. 2006; Churchill et al., personal communication). The efficacy of antiretroviral drugs in astrocytes remains largely unexplored, but as it is not a productive infection, it is unlikely that antiretroviral drugs would have much benefit.

Risk factor reduction

At present, there are no rigorously proven measures that can reduce the risk of developing neurodegenerative diseases in general. Nonetheless, regular exercise both physical and mental appears to be helpful in minimizing the effects of ageing as well as perhaps delaying the onset of AD (Lautenschlager et al. 2008). Secondly, improvement in glucose control seems to be beneficial (Stranahan et al. 2008; van Harten et al. 2007; Whitmer 2007). Thirdly, better control of hypertension appears to be helpful although the recent HYVET trial did not show a benefit (Peters et al. 2007). The explanation is purely speculative but the length of follow-up of the study participants may have been too short. Lastly, control of hypercholesterolemia is becoming accepted as important (Cramer et al. 2008). The more controversial issues, however, are whether statin therapy carries benefit independent of cholesterol reduction and whether a statin that has good brain penetration is superior or even necessary.

Conclusion

HAART has led to dramatic improvements in HIV patients but the neurological complications remain problematic in some. Moreover, there is increasing evidence that the expression and progression of neurodegenerative diseases may be facilitated by HIV. Future studies will need to address the mechanisms by which these occur to allow the development of effective therapies.

References

Adle-Biassette H, Chretien F, Wingertsmann L, Hery C, Ereau T, Scaravilli F, Tardieu M, Gray F (1999) Neuronal apoptosis does not correlate with dementia in HIV infection but is related to microglial activation and axonal damage. Neuropathol Appl Neurobiol 25:123–133 doi:10.1046/j.1365-2990.1999.00167.x

Alirezaei M, Kiosses WB, Flynn CT, Brady NR, Fox HS (2008a) Disruption of neuronal autophagy by infected microglia results in neurodegeneration. PLoS ONE 3(8):2906

Alirezaei M, Kiosses WB, Fox HS (2008b) Decreased neuronal autophagy in HIV dementia: a mechanism of indirect neurotoxicity. Autophagy 4(7):963–966

An SF, Giometto B, Groves M, Miller RF, Beckett AA, Gray F, Tavolato B, Scaravilli F (1997) Axonal damage revealed by accumulation of beta-APP in HIV-positive individuals without AIDS. J Neuropathol Exp Neurol 56:1262–1268

Ancuta P, Kamat A, Kunstman KJ, Kim EY, Autissier P, Wurcel A, Zaman T, Stone D, Mefford M, Morgello S, Singer EJ, Wolinsky SM, Gabuzda D (2008) Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. PLoS One 3:e2516 doi:10.1371/journal.pone.0002516

Andreasen N, Sjögren M, Blennow K (2003) CSF markers for Alzheimer's disease: total tau, phospho-tau and Aβ42. World J Biol Psychiatry 4:147–155 doi:10.1080/15622970310029912

Anthony IC, Ramage SN, Carnie FW, Simmonds P, Bell JE (2006) Accelerated tau deposition in the brains of individuals infected with human immunodeficiency virus-1 before and after the advent of highly active anti-retroviral therapy. Acta Neuropathol 111:529–538 doi:10.1007/s00401-006-0037-0

Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE (2007) Updated research nosology for HIV-associated neurocognitive disorders. Neurology 69:1789–1799 doi:10.1212/01.WNL.0000287431.88658.8b

Apcher GS, Heink S, Zantopf D, Kloetzel PM, Schmid HP, Mayer RJ, Kruger E (2003) Human immunodeficiency virus-1 Tat protein interacts with distinct proteasomal alpha and beta subunits. FEBS Lett 553:200–204 doi:10.1016/S0014-5793(03)01025-1

Arnsten AF, Cai JX, Steere JC, Goldman-Rakic PS (1995) Dopamine D2 receptor mechanisms contribute to age-related cognitive decline: the effects of quinpirole on memory and motor performance in monkeys. J Neurosci 15:3429–3439

Banks WA (1999) Physiology and pathology of the blood–brain barrier: implications for microbial pathogenesis, drug delivery and neurodegenerative disorders. J Neurovirol 5(6):538–555 doi:10.3109/13550289909021284

Berger JR, Arendt G (2000) HIV dementia: the role of the basal ganglia and dopaminergic systems. J Psychopharmacol 14(3):214–221

Berger JR, Kumar M, Kumar A, Fernandez JB, Levin B (1994) Cerebrospinal fluid dopamine in HIV-1 infection. AIDS 8(1):67–71 doi:10.1097/00002030-199401000-00010

Bhaskaran K, Mussini C, Antinori A, Walker AS, Dorrucci M, Sabin C, Phillips A, Porter K (2008) Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. Ann Neurol 63:213–221 doi:10.1002/ana.21225

Björkqvist M, Wild EJ, Thiele J, Silvestroni A, Andre R, Lahiri N, Raibon E, Lee RV, Benn CL, Soulet D, Magnusson A, Woodman B, Landles C, Pouladi MA, Hayden MR, Khalili-Shirazi A, Lowdell MW, Brundin P, Bates GP, Leavitt BR, Möller T, Tabrizi SJ (2008) A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. J Exp Med 205(8):1869–1877

Blalock EM, Chen KC, Stromberg AJ, Norris CM, Kadish I, Kraner SD, Porter NM, Landfield PW (2005) Harnessing the power of gene microarrays for the study of brain aging and Alzheimer's disease: statistical reliability and functional correlation. Ageing Res Rev 4:481–512

Bowman GL, Kaye JA, Moore M, Waichunas D, Carlson NE, Quinn JF (2007) Blood–brain barrier impairment in Alzheimer disease: stability and functional significance. Neurology 68(21):1809–1814 doi:10.1212/01.wnl.0000262031.18018.1a

Brew BJ (2001) AIDS dementia complex, in HIV neurology. Oxford University Press, Oxford

Brew BJ (2004) Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. AIDS 18(Suppl 1):S75–S78

Brew BJ, Rosenblum M, Cronin K, Price RW (1995) The AIDS dementia complex and human immunodeficiency virus type 1 brain infection: clinical–virological correlations. Ann Neurol 38:563–570 doi:10.1002/ana.410380404

Brew BJ, Pemberton L, Blennow K, Wallin A, Hagberg L (2005) CSF amyloid beta42 and tau levels correlate with AIDS dementia complex. Neurology 65:1490–1492 doi:10.1212/01.wnl.0000183293.95787.b7

Brew BJ, Halman M, Catalan J, Sacktor N, Price RW, Brown S, Atkinson H, Clifford DB, Simpson D, Torres G, Hall C, Power C, Marder K, Mc Arthur JC, Symonds W, Romero C (2007) Abacavir in AIDS dementia complex: efficacy and lessons for future trials. PLoS Clin Trials 2(3):e13 doi:10.1371/journal.pctr.0020013

Brew B, Gisslen M, Pemberton L, Cinque P, Hagberg L, Price R, Blennow K, Zetterberg H, Spudich S CSF t-tau, p-tau and Amyloid-beta 1-42 in HIV Infection (2008) #395 15th Conference on Retroviruses and Opportunistic Infections February 3–6, Boston, MA

Buckner CM, Luers AJ, Calderon TM, Eugenin EA, Berman JW (2006) Neuroimmunity and the blood–brain barrier: molecular regulation of leukocyte transmigration and viral entry into the nervous system with a focus on neuroAIDS. J Neuroimmune Pharmacol 1(2):160–181 doi:10.1007/s11481-006-9017-3

Cherny RA, Legg JT, McLean CA, Fairlie DP, Huang X, Atwood CS, Beyreuther K, Tanzi RE, Masters CL, Bush AI (1999) Aqueous dissolution of Alzheimer's disease Abeta amyloid deposits by biometal depletion. J Biol Chem 274(33):23223–23228 doi:10.1074/jbc.274.33.23223

Christensen PM, Gotzsche PC, Brosen K (1998) The sparteine/debrisoquine (CYP2D6) oxidation polymorphism and the risk of Parkinson's disease: a meta-analysis. Pharmacogenetics 8:473–479 doi:10.1097/00008571-199812000-00003

Chung KK, Dawson VL, Dawson TM (2001) The role of the ubiquitin–proteasomal pathway in Parkinson's disease and other neurodegenerative disorders. Trends Neurosci Suppl 11:S7–S14 doi:10.1016/S0166-2236(00)01998-6

Clarke JN, Lake JA, Burrell CJ, Wesselingh SL, Gorry PR, Li P (2006) Novel pathway of human immunodeficiency virus type 1 uptake and release in astrocytes. Virology 348(1):141–155 doi:10.1016/j.virol.2005.12.004

Clifford D, Kauwe J, Teshome M, Shah A, Spinner M, Morris J, Holtzman D, Fagan A (2008) Abnormal CSF amyloid beta42 levels link HIV-associated cognitive disease and Alzheimer's disease. #396b 15th Conference on Retroviruses and Opportunistic Infections February 3–6, Boston, MA

Cramer C, Haan MN, Galea S, Langa KM, Kalbfleisch JD (2008) Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. Neurology 71(5):344–350 doi:10.1212/01.wnl.0000319647.15752.7b

Cuervo AM, Dice JF (1998) How do intracellular proteolytic systems change with age? Front Biosci 3:d25–d43

Cysique LA, Maruff P, Brew BJ (2004a) Prevalence and pattern of neuropsychological impairment in HIV/AIDS infection across pre-HAART and HAART eras: a combined study of 2 cohorts. J Neurovirol 10:350–357 doi:10.1080/13550280490521078

Cysique L, Maruff P, Brew B (2004b) Antiretroviral therapy in HIV infection: are neurologically active drugs important? Arch Neurol 61:1699–1704 doi:10.1001/archneur.61.11.1699

Cysique LA, Brew BJ, Halman M, Catalan J, Sacktor N, Price RW, Brown S, Atkinson JH, Clifford DB, Simpson D, Torres G, Hall C, Power C, Marder K, McArthur JC, Symonds W, Romero C (2005) Undetectable cerebrospinal fluid HIV RNA and beta-2 microglobulin do not indicate inactive AIDS dementia complex in highly active antiretroviral therapy-treated patients. J Acquir Immune Defic Syndr 39:426–429 doi:10.1097/01.qai.0000165799.59322.f5

Cysique LA, Maruff P, Brew BJ (2006a) Variable benefit in neuropsychological function in HIV-infected HAART-treated patients. Neurology 66:1447–1450 doi:10.1212/01.wnl.0000210477.63851.d3

Cysique L, Maruff P, Brew B (2006b) The neuropsychological profile of symptomatic, AIDS and ADC patients in the pre-HAART era: a meta-analysis. J Int Neuropsychol Soc 12:1–15 doi:10.1017/S1355617706060401

Dore GJ, McDonald A, Li Y, Kaldor J, Brew BJ (2003) Marked improvement in survival following AIDS dementia complex in the era of highly active antiretroviral therapy. AIDS 17 (10):1539–1545 doi:10.1097/00002030-200307040-00015

Esiri MM, Biddolph SC, Morris CS (1998) Prevalence of Alzheimer plaques in AIDS. J Neurol Neurosurg Psychiatry 65:29–33

Gelman BB, Schuenke K (2004) Brain aging in acquired immunodeficiency syndrome: increased ubiquitin–protein conjugate is correlated with decreased synaptic protein but not amyloid plaque accumulation. J Neurovirol 10:98–108 doi:10.1080/13550280490279816

Giometto B, An SF, Groves M, Scaravilli T, Geddes JF, Miller R, Tavolato B, Beckett AA, Scaravilli F (1997) Accumulation of beta-amyloid precursor protein in HIV encephalitis: relationship with neuropsychological abnormalities. Ann Neurol 42(1):34–40 doi:10.1002/ana.410420108

Glisky EL (2007) Changes in cognitive function in human aging. In: Riddle DR (ed) Brain aging: models, methods and mechanisms. CRC, New York

Goila-Gaur R, Strebel K (2008) HIV-1 Vif, APOBEC, and intrinsic immunity. Retrovirology 5:51

Green DA, Masliah E, Vinters HV, Beizai P, Moore DJ, Achim CL (2005) Brain deposition of beta-amyloid is a common pathologic feature in HIV positive patients. AIDS 19(4):407–411 doi:10.1097/01.aids.0000161770.06158.5c

Guillemin GJ, Brew BJ (2007) Chronic HIV infection leads to an Alzheimer's disease like illness. Involvement of the kynurenine pathway. Int Congr Ser 1304:324 doi:10.1016/j.ics.2007.07.031

Guillemin GJ, Smythe GA, Veas LA, Takikawa O, Brew BJ (2003) Abeta 1-42 induces production of quinolinic acid by human macrophages and microglia. Neuroreport 14(18):2311–2315

Guillemin G, Kerr SJ, Brew BJ (2005) Involvement of quinolinic acid in AIDS dementia complex. Neurotox Res 7(1–2):103–124

Guillemin GJ, Cullen K, Smythe G, Kapoor V, Lim E, Garner B, Takikawa O, Brew BJ (2007) Characterization of the kynurenine pathway in human neurons. J Neurosci 27(47):12884–12892 doi:10.1523/JNEUROSCI.4101-07.2007

Haorah J, Heilman D, Diekmann C, Osna N, Donohue TM Jr, Ghorpade A, Persidsky Y (2004) Alcohol and HIV decrease proteasome and immunoproteasome function in macrophages: implications for impaired immune function during disease. Cell Immunol 229(2):139–148 doi:10.1016/j.cellimm.2004.07.005

Hardy DJ, Hinkin C (2002) Reaction time slowing in adults with HIV: results of a meta-analysis using brinley plots. Brain Cogn 50:25–94 doi:10.1016/S0278-2626(02)00007-6

Harsher L, Zacks RT, May CP (1999) Inhibitory control, circadian arousal and age. In: Gopher D, Koriat A (eds) Attention and performance XVII. MIT, Cambridge

Hartley A (2006) Changing role of the speed of processing construct in the cognitive psychology of human aging. In: Birren JE, Schaie WK (eds) Handbook of the psychology of aging. Elsevier, Amsterdam

Haughey NJ, Steiner J, Nath A, McArthur JC, Sacktor N, Pardo C, Bandaru VV (2008) Converging roles for sphingolipids and cell stress in the progression of neuro-AIDS. Front Biosci 1 (13):5120–5130 doi:10.2741/3068

Henry JD, MacLeod MS, Phillips LH, Crawford JR (2004) A meta-analytic review of prospective memory and aging. Psychol Aging 19:27–39 doi:10.1037/0882-7974.19.1.27

Herber DL, Maloney JL, Roth LM, Freeman MJ, Morgan D, Gordon MN (2006) Diverse microglial responses after intrahippocampal administration of lipopolysaccharide. Glia 53(4):382–391 doi:10.1002/glia.20272

Heydari AR, Takahashi R, Gutsmann A, You S, Richardson A (1994) Hsp70 and aging. Experientia 50:1092–1098 doi:10.1007/BF01923466

Heydari AR, You S, Takahashi R, Gutsmann-Conrad A, Sarge KD, Richardson A (2000) Age-related alterations in the activation of heat shock transcription factor 1 in rat hepatocytes. Exp Cell Res 256:83–93 doi:10.1006/excr.2000.4808

Hinkin CH, Cummings JL, van Gorp WG, Mitrushina M (1990) Frontal–subcortical features of normal aging: an empirical analysis. Can J Aging 9:104–119

Izycka-Swieszewska E, Zoltowska A, Rzepko R, Gross M, Borowska-Lehman J (2000) Vasculopathy and amyloid beta reactivity in brains of patients with acquired immune deficiency (AIDS). Folia Neuropathol 38:175–182

Kadiu I, Glanzer JG, Kipnis J, Gendelman HE, Thomas MP (2005) Mononuclear phagocytes in the pathogenesis of neurodegenerative diseases. Neurotox Res 8(1–2):25–50

Kemper TL (1993) The relationship of cerebral cortical changes to nuclei in the brainstem. Neurobiol Aging 14:659–660 doi:10.1016/0197-4580(93)90061-F

Khanlou N, Moore DJ, Chana G, Cherner M, Lazzaretto D, Dawes S, Grant I, Masliah E, Everall IP (2008) Increased frequency of alpha-Synuclein in the substantia nigra in HIV infection. J Neurovirol (in press)

Kitazawa M, Oddo S, Yamasaki TR, Green KN, LaFerla FM (2005) Lipopolysaccharide-induced inflammation exacerbates tau pathology by a cyclin-dependent kinase 5-mediated pathway in a transgenic model of Alzheimer's disease. J Neurosci 25 (39):8843–8853 doi:10.1523/JNEUROSCI.2868-05.2005

Kramer AF, Madden DJ (2008) Attention. In: Craik FIM, Salthouse TA (eds) The handbook of aging and cognition. Psychology, New York

Kusdra L, Rempel H, Yaffe K, Pulliam L (2000) Elevation of CD69+ monocyte/macrophages in patients with Alzheimer's disease. Immunobiology 202:26–33

Lam F, Liu R, Shapiro AB, Renoir JM, Sharom FJ, Reiner PB (2001) B-amyloid efflux mediated by P-glycoprotein. J Neurochem 76:1121–1128 doi:10.1046/j.1471-4159.2001.00113.x

Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP (2008) Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 300(9):1027–1037 doi:10.1001/jama.300.9.1027

Lee G, Bendayan R (2004) Functional expression and localization of P-glycoprotein in the central nervous system: relevance to the pathogenesis and treatment of neurological disorders. Pharm Res 21(8):1313–1330 doi:10.1023/B:PHAM.0000036905.82914.8e

Letendre S, McCutchan J, Childers M, Woods S, Lazzaretto D, Heaton R, Grant I, Ellis RH (2004) Enhancing antiretroviral therapy for human immunodeficiency virus cognitive disorders. Ann Neurol 56:416–423 doi:10.1002/ana.20198

Letendre S, Marquie-Beck J, Capparelli E, Best B, Clifford D, Collier AC, Gelman BB, McArthur JC, McCutchan JA, Morgello S, Simpson D, Grant I, Ellis RJ (2008) Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. Arch Neurol 65:65–70 doi:10.1001/archneurol.2007.31

Li W, Malpica-Llanos TM, Gundry R, Cotter RJ, Sacktor N, McArthur J, Nath A (2008) Nitrosative stress with HIV dementia causes decreased L-prostaglandin D synthase activity. Neurology 70:1753–1762

Lovell MA, Markesbery WR (2007) Oxidative DNA damage in mild cognitive impairment and late-stage Alzheimer's disease. Nucleic Acids Res 35(22):7497–7504 doi:10.1093/nar/gkm821

McNaught KS, Olanow CW, Halliwell B, Isacson O, Jenner P (2001) Failure of the ubiquitin–proteasome system in Parkinson's disease. Nat Rev Neurosci 2(8):589–594 doi:10.1038/35086067

Minagar A, Shapshak P, Fujimura R, Ownby R, Heyes M, Eisdorfer C (2002) The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. J Neurol Sci 202:13–23 doi:10.1016/S0022-510X(02)00207-1

Mylonakis E, Koutkia P, Grinspoon S (2001) Diagnosis and treatment of androgen deficiency in human immunodeficiency virus-infected men and women. Clin Infect Dis 33(6):857–864 doi:10.1086/322695

Nagaoka U, Kim K, Jana NR, Doi H, Maruyama M, Mitsui K, Oyama F, Nukina N (2004) Increased expression of p62 in expanded polyglutamine-expressing cells and its association with polyglutamine inclusions. J Neurochem 91:57–68 doi:10.1111/j.1471-4159.2004.02692.x

Nath A, Schiess N, Venkatesan A, Rumbaugh J, Sacktor N, McArthur J (2008) Evolution of HIV dementia with HIV infection. Int Rev Psychiatry 20(1):25–31 doi:10.1080/09540260701861930

Nielsen K, Peters A (2000) The effects of aging on the frequency of nerve fibers in rhesus monkey striate cortex. Neurobiol Aging 21:621–628 doi:10.1016/S0197-4580(00)00169-X

Okun MS, DeLong MR, Hanfelt J, Gearing M, Levey A (2004) Plasma testosterone levels in Alzheimer and Parkinson diseases. Neurology 62(3):411–413

Peavy G, Jacobs D, Salmon D, Butters N, Delis D, Taylor M, Massman P, Stout J, Heindel W, Kirson D, Atkinson J, Chandler J, Grant I (1994) Verbal memory performance of patients with human immunodeficiency virus infection: evidence of subcortical dysfunction. J Clin Exp Neuropsych 16:508–523

Pemberton L, Brew BJ (2001) Cerebrospinal fluid S-100beta and its relationship with AIDS dementia complex. J Clin Virol 22:249–253 doi:10.1016/S1386-6532(01)00196-2

Pemberton LA, Stone E, Price P, van Bockxmeer F, Brew BJ (2008) The relationship between ApoE, TNFA, IL1a, IL1b and IL12b genes and HIV-1-associated dementia. HIV Med 9:677–680 doi:10.1111/j.1468-1293.2008.00614.x

Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, Waldman A, Walton I, Poulter R, Ma S, Comsa M, Burch L, Fletcher A, Bulpitt C, HYVET investigators (2007) Incident dementia and blood pressure lowering in the hypertension in the very elderly trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 7(8):683–689 doi:10.1016/S1474-4422(08)70143-1

Piccinini M, Rinaudo MT, Anselmino A, Buccinna B, Ramondetti C, Dematteis A, Ricotti E, Palmisano L, Mostert M, Tovo PA (2005) The HIV protease inhibitors nelfinavir and saquinavir, but not a variety of HIV reverse transcriptase inhibitors, adversely affect human proteasome function. Antivir Ther 10:215–223

Rajawat YS, Bossis I (2008) Autophagy in aging and in neurodegenerative disorders. Hormones 7(1):46–61

Raz N, Rodrigue KM (2006) Differential aging of the brain: patterns, cognitive correlates and modifiers. Neurosci Biobehav Rev 30:730–748 doi:10.1016/j.neubiorev.2006.07.001

Reger M, Wesh R, Razani J, Martin DJ, Boone KB (2002) A meta-analysis of the neuropsychological sequelae of HIV infection. J Int Neuropsychol Soc 8:410–424 doi:10.1017/S1355617702813212

Rempel HC, Pulliam L (2005) HIV-1 Tat inhibits neprilysin and elevates amyloid beta. AIDS 19:127–135 doi:10.1097/00002030-200501280-00004

Richartz-Salzburger E, Batra A, Stransky E, Laske C, Köhler N, Bartels M, Buchkremer G, Schott K (2007) Altered lymphocyte distribution in Alzheimer's disease. J Psychiatr Res 41(1–2):174–178 doi:10.1016/j.jpsychires.2006.01.010

Robertson KR, Smurzynski M, Parsons TD, Wu K, Bosch RJ, Wu J, McArthur JC, Collier AC, Evans SR, Ellis RJ (2007) The

prevalence and incidence of neurocognitive impairment in the HAART era. AIDS 21:1915–1921 doi:10.1097/QAD.0b013e32828e4e27

Rosene DL (1993) Comparing age-related changes in the basal forebrain and hippocampus of the rhesus monkey. Neurobiol Aging 14:669–670 doi:10.1016/0197-4580(93)90065-J

Rosenzweig ES, Barnes CA (2003) Impact of aging on hippocampal function: plasticity, network dynamics, and cognition. Prog Neurobiol 69:143–179 doi:10.1016/S0301-0082(02)00126-0

Sacktor NC, Bacellar H, Hoover DR, Nance-Sproson TE, Selnes OA, Miller EN, Dal Pan GJ, Kleeberger C, Brown A, Saah A, McArthur JC (1996) Psychomotor slowing in HIV infection: a predictor of dementia, AIDS and death. J Neurovirol 2:404–410 doi:10.3109/13550289609146906

Salaria S, Badkoobehi H, Rockenstein E, Crews L, Chana G, Masliah E, Everall IP (2007) Toll-like receptor pathway gene expression is associated with human immunodeficiency virus-associated neurodegeneration. J Neurovirol 13(6):496–503 doi:10.1080/13550280701558616

Salthouse TA (1996) The processing-speed theory of adult age differences in cognition. Psychol Rev 103:403–428 doi:10.1037/0033-295X.103.3.403

Sevigny JJ, Albert SM, McDermott MP, McArthur JC, Sacktor N, Conant K, Schifitto G, Selnes OA, Stern Y, McClernon DR, Palumbo D, Kieburtz K, Riggs G, Cohen B, Epstein LG, Marder K (2004) Evaluation of HIV RNA and markers of immune activation as predictors of HIV-associated dementia. Neurology 63:2084–2090

Sokolova A, Hill MD, Rahimi F, Warden LA, Halliday GM, Shepherd CE (2008) Monocyte chemoattractant protein-1 plays a dominant role in the chronic inflammation observed in Alzheimer's disease. Brain Pathol 10:10

Stone TW (2001) Kynurenines in the CNS: from endogenous obscurity to therapeutic importance. Prog Neurobiol 64(2):185–218 doi:10.1016/S0301-0082(00)00032-0

Stranahan AM, Arumugam TV, Cutler RG, Lee K, Egan JM, Mattson MP (2008) Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. Nat Neurosci 11(3):309–317 doi:10.1038/nn2055

Tahara K, Kim HD, Jin JJ, Maxwell JA, Li L, Fukuchi K (2006) Role of toll-like receptor signalling in Abeta uptake and clearance. Brain 129(Pt 11):3006–3019 doi:10.1093/brain/awl249

Ting KK, Brew B, Guillemin G (2007) The involvement of astrocytes and kynurenine pathway in Alzheimer's disease. Neurotox Res 12(4):247–262

Torres-Muñoz J, Stockton P, Tacoronte N, Roberts B, Maronpot RR, Petito CK (2001) Detection of HIV-1 gene sequences in hippocampal neurons isolated from postmortem AIDS brains by laser capture microdissection. J Neuropathol Exp Neurol 60 (9):885–892

Town T, Laouar Y, Pittenger C, Mori T, Szekely CA, Tan J, Duman RS, Flavell RA (2008) Blocking TGF-beta-Smad2/3 innate immune signaling mitigates Alzheimer-like pathology. Nat Med 14:681–687

Tucker KA, Robertson KR, Lin W, Smith JK, An H, Chen Y, Aylward SR, Hall CD (2004) Neuroimaging in human immunodeficiency virus infection. J Neuroimmunol 157:153–162 doi:10.1016/j.jneuroim.2004.08.036

Valcour V, Shikuma C, Watters M, Poff P, Selnes O, Holck P, Grove J, Sacktor N (2004) Higher frequency of dementia in older HIV-1 individuals. The Hawaii aging with HIV-1 cohort. Neurology 63:822–827

Valcour V, Shiramizu B, Shikuma C (2008) Frequency of apolipoprotein E4 among older compared with younger HIV patients: support for detrimental effect of E4 on survival. Proc Natl Acad Sci U S A 8:8

van Harten B, Oosterman J, Muslimovic D, van Loon BJ, Scheltens P, Weinstein HC (2007) Cognitive impairment and MRI correlates in the elderly patients with type 2 diabetes mellitus. Age Ageing 36(2):164–170 doi:10.1093/ageing/afl180

van Leeuwen FW, de Kleijn DP, van den Hurk HH, Neubauer A, Sonnemans MA, Sluijs JA, Koycu S, Ramdjielal RD, Salehi A, Martens GJ, Grosveld FG, Peter J, Burbach H, Hol EM (1998) Frameshift mutants of beta amyloid precursor protein and ubiquitin-B in Alzheimer's and down patients. Science 279:242–247 doi:10.1126/science.279.5348.242

van Leeuwen FW, Gerez L, Benne R, Hol EM (2002) +1 Proteins and aging. Int J Biochem Cell Biol 34:1502–1505 doi:10.1016/S1357-2725(02)00043-2

Walter S, Letiembre M, Liu Y, Heine H, Penke B, Hao W, Bode B, Manietta N, Walter J, Schulz-Schuffer W, Fassbender K (2007) Role of the toll-like receptor 4 in neuroinflammation in Alzheimer's disease. Cell Physiol Biochem 20:947–956 doi:10.1159/000110455

West RL (1996) An application of prefrontal cortex function theory to cognitive aging. Psychol Bull 120:272–292 doi:10.1037/0033-2909.120.2.272

Whitmer RA (2007) Type 2 diabetes and risk of cognitive impairment and dementia. Curr Neurol Neurosci Rep 7(5):373–380 doi:10.1007/s11910-007-0058-7

Woods SP, Iudicello JE, Moran LM, Carey CL, Dawson MS, Grant I (2008a) HIV-associated prospective memory impairment increases risk of dependence in everyday functioning. Neuropsychology 22:110–117 doi:10.1037/0894-4105.22.1.110

Woods SP, Carey CL, Ludicello JE, Letendre SL, Grant I (2008b) Neuropsychological aspects of HIV infection. In: Grant I, Adams KM (eds) Neuropsychological assessment of neuropsychiatric disorders. Oxford University Press, New York (in press)

Wyss-Coray T (2006) Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat Med 12(9):1005–1015

Young VG, Halliday GM, Kril JJ (2008) Neuropathologic correlates of white matter hyperintensities. Neurology 71:804–811 doi:10.1212/01.wnl.0000319691.50117.54

Zatloukal K, Stumptner C, Fuchsbichler A, Heid H, Schnoelzer M, Kenner L, Kleinert R, Prinz M, Aguzzi A, Denk H (2002) p62 is a common component of cytoplasmic inclusions in protein aggregation diseases. Am J Pathol 160:255–263