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Astrocyte activation and altered metabolism in normal aging, age-related CNS diseases and HAND

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Abstract

Astrocytes regulate local cerebral blood flow, maintain ion and neurotransmitter homeostasis, provide metabolic support, regulate synaptic activity, and respond to brain injury, insults and infection. Because of their abundance, extensive connectivity and multiple roles in the brain, astrocytes are intimately involved in normal functioning of the CNS and their dysregulation can lead to neuronal dysfunction. In normal aging, decreased biological functioning and reduced cognitive abilities are commonly experienced in individuals free of overt neurological disease. Moreover, in several age-related CNS diseases chronic inflammation and altered metabolism have been reported. Since people with HIV (PWH) are reported to experience rapid aging with chronic inflammation, altered brain metabolism is likely to be exacerbated. In fact, many studies report altered metabolism in astrocytes in disease such as Alzheimer's, Parkinson's and HIV. This review will address the roles of astrocyte activation and altered metabolism in normal aging, age-related CNS disease and in HIV-associated neurocognitive disorders.

Introduction

Over the past 35 years, advancements in knowledge and treatment have drastically improved the prognosis of individuals infected with HIV. The diagnosis of HIV has shifted from a life-threatening infection to a manageable chronic illness. The advent of combination antiretroviral therapy (CART) is responsible for the effective suppression of viral replication and prolongs the lives of people with HIV (PWH) to near normal life expectancy (van Sighem *et al*, 2010). PWLH are now becoming an aging population and a new set of HIV-related complications have emerged. Several groups have proposed that HIV infection can lead to accelerated aging (Cassol *et al*, 2014; Cohen *et al*, 2015; Cole *et al*, 2017; Levine *et al*, 2016; Pfefferbaum *et al*, 2014). In 2015, the Center for Disease Control and Prevention (CDC) estimated that in the US, 47% of PWH are over the age of 50 and this number continues to climb due to the success of CART (Centers for Disease Control and Prevention. HIV Surveillance Report, 2016). It is projected that by 2020, PWH over 50 years of age will increase to 70% (U.S. Special Committee on Aging, 2013). A large portion of PWH experience cognitive decline prematurely when compared to age-matched HIV negative controls and often more closely resemble the prolife of older adults. Even individuals with undetectable viral loads show decline in memory, attention, psychomotor ability and executive function. Collectively, these deficits are referred to as HIV-associated neurocognitive disorders (HAND). HAND describes a range of neurological deficits associated with HIV infection with increasing severity, from asymptomatic neurocognitive

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impairment (ANI), mild neurocognitive disorder (MND), to HIV-associated dementia (HAD). HAND impacts survival, quality of life and everyday functioning in PWH and is therefore, a major public health concern. Approximately 52% of PWH experience HAND (Heaton *et al*, 2010).

In normal aging, decreased normal biological function and reduced cognitive abilities are commonly experienced in individuals free of overt neurological disease (Dumas, 2015). Healthy older adults show impairments in attention, working memory, and episodic memory relative to younger adults (Verhaeghen and Cerella, 2002). Further, advancing age is a major risk factor for the development of neurological disease, with a sharp increase in incidence after 60 years of age (Fjell *et al*, 2014). Reductions in brain volume, loss of myelin, and region-specific loss of synaptic density are just a few of the many changes observed in aged individuals (Lindenberger, 2014; Raz and Rodrigue, 2006). Living longer creates opportunities for the population at risk for developing HAND to undergo overlapping pathological changes in biological pathways associated with normal aging. Deviations from the typical trajectory of brain aging is reported in PWH. In fact, it has been reported that PWH on CART have a higher burden of cognitive impairments with advancing age and these disorders present at a younger age than are observed in HIV negative control groups (Mateen *et al*, 2012). One study of 3,945 male participants (2,083 HIV negative and 1,862 HIV positive) found the median age of first neurologic diagnosis in HIV positive men receiving antiretroviral therapy was 48 years old compared to 57 years old in the uninfected men (Mateen *et al*, 2012). Normal brain aging is not associated with significant neuronal loss. Similarly, HAND is often not associated with a drastic loss of neurons leading to the notion that neuronal dysfunction without cell death is likely a main source of cognitive impairments. Even though substantial neuronal death is observed in most other neurodegenerative diseases, there are many commonalities between HAND and other neurodegenerative diseases that have been revealed by studies examining individual disease etiologies. At the brain transcriptome level, there are significant similarities between HAND, multiple sclerosis (MS), and Alzheimer's disease (AD) (Borjabad and Volsky, 2012). One analysis revealed that commonly downregulated genes included those linked to neuronal and synaptic function. This is not surprising since loss of neuronal integrity drives neurodegenerative diseases including HAND. A proteomic analysis of post-mortem frontal cortex from HIV positive patients with HAD revealed that abnormal expression of proteins involved in glycolysis and oxidative respiration overlap with changes in other neurodegenerative diseases including AD and Parkinson's disease (PD) (Zhou *et al*, 2010). Disturbances in energy homeostasis are often observed in various diseases including those of the central nervous system (CNS). Evidence suggests that this may be a shared pathology between HAND and other CNS diseases. Similarities in microglia- and astrocyte-mediated inflammation in the context of AD, MS, and HAND disease progression highlight another avenue in which these disorders converge (Minagar *et al*, 2002). Given the role of astrocytes in both metabolic support and inflammation, they likely play a critical role in cognitive decline.

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A role of astrocytes in health, aging and disease

Astrocytes are stellate cells with elongated processes that are in contact with neurons, synapses, myelin sheath, oligodendrocytes, microglia, and blood vessels (Ferrer, 2017). Astrocytes constitute a major cellular compartment in the CNS and carry out various functions to maintain normal brain function. It is estimated that a single astrocyte makes contact with between 250,000 and 2 million synapses in the human brain (Oberheim *et al*, 2006). The heterogeneity of astrocytes allows for vast functional diversity so that their roles in the brain range from regulation of local cerebral blood flow, maintenance of ion and neurotransmitter homeostasis, metabolic support, regulation of synaptic activity, to responses to brain injury, insults and infection. Because of their abundance, extensive connectivity and multiple roles in the brain, astrocytes are intimately involved in normal functioning of the CNS and their dysregulation can lead to neuronal dysfunction.

Classically astrocytes are categorized into two major subpopulations: fibrous astrocytes which have long thin processes and are star-like in appearance and protoplasmic astrocytes which have highly complex branching processes that contact synapses and blood vessels (Miller and Raff, 1984). Fibrous astrocytes are typically found in the white matter whereas protoplasmic astrocytes are found in the gray matter (Miller and Raff, 1984). However, recent morphological and biochemical evidence has proven this classification to be oversimplified. Using a transgenic hGFAP-GFP mouse line, one group identified nine distinct astrocyte classes based on three complementary methods for astrocyte labeling (hGFAP-GFP, GFAP, and s100β) (Emsley and Macklis, 2006). From this, the authors concluded that there are considerable region-specific differences in morphology, density and proliferation rates in astrocytes (Emsley and Macklis, 2006). Astrocytes can differ not only in morphology but also in developmental origin, gene expression prolife, physiological properties and function (Zhang and Barres, 2010). Translational profiling approaches and microarray analyses have revealed gene expression can vary substantially between astrocytes from different brain regions (Doyle *et al*, 2008; Yeh *et al*, 2009). Even GFAP, which is often considered to be a pan-astrocyte marker, is differentially expressed in various subpopulations of astrocytes (Cahoy *et al*, 2008). Diversity in gene expression suggests there is likely functional diversity among astrocytes as well. This was highlighted by one group which utilized a fluorescence-activated cell sorting-based approach in combination with cell surface markers to identify five distinct astrocyte subpopulations(John Lin *et al*, 2017). These subpopulations were further characterized based on their molecular signatures. This analysis revealed one of the astrocyte subpopulations was enriched for genes associated with synapse formation. When directly tested using a co-culture system, compared to the other subpopulations, this specific population of astrocytes had the ability to promote synaptogenesis. Overall, this indicates differences in gene expression profiles can contribute to functional differences in astrocytes. Given the extensive diversity of astrocytes, it is not surprising that the responses of astrocytes in pathological conditions are also very heterogenous. In some conditions, astrocytes become hypertrophic, proliferate, and can release various cytokines (Sofroniew and Vinters, 2010). However, under other pathological circumstances astrocytes can degenerate and lose their normal physiological functions (Scuderi *et al*, 2013). Recently, the roles of astrocytes in normal brain aging and

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neurological disease have gained much attention. A delicate balance of downstream signaling is critical to maintain normal brain functioning. In neurodegenerative diseases, deviations in astrocyte homeostasis can manifest differently. In fact, astrogliosis or astrocyte atrophy, can contribute to the disease process. Astrocyte atrophy is observed in frontotemporal dementias such as Pick's Disease and frontotemporal lobar degeneration (Broe *et al*, 2004). In both cases, early and prominent apoptotic death and atrophy of astrocytes is reported, and the degree of astrocyte loss is correlated with disease severity (Broe *et al*, 2004). However, astrogliosis is more commonly reported in neurological disease and seems to have a leading pathological role in AD, PD, HD, and ALS (Rodríguez *et al*, 2009). The concept of astrogliosis as a purely pathological response with negative outcomes has been replaced by the concept that astrocyte reactivity is a defense process intended for neuroprotection (Rodríguez-Arellano *et al*, 2016). Activated astrocytes increase their trophic support for neurons under stress and isolate areas of damage by the formation of a glial scar. However, under certain circumstances astrocyte activation can become pathological and is referred to as astrocytopathy (Ferrer, 2017). Astrocytopathy can manifest as impaired glutamate transport, abnormal glucose and lipid metabolism, and altered calcium signaling (Ferrer, 2017). Loss of astrocytic neurotrophic function and activation therefore contributes to brain aging and neurodegenerative disease.

Astrocyte Activation in the Normally Aging Brain and age-related CNS Diseases

Astrocyte activation is marked by hypertrophic morphology, increased expression of glial acid fibrillary protein (GFAP), secretion of proinflammatory cytokines such as TNF-a and IL-1b, and generation of reactive oxygen species (ROS) (Borjabad *et al*, 2010). There are signs of age-related increases of astrocyte activation (Lynch *et al*, 2010; Porchet *et al*, 2003; Soreq *et al*, 2017). Myo-inositol, a marker of astrocyte activation, is increased with normal brain aging in humans and in animal models (Harris *et al*, 2015; Harris *et al*, 2014; Zhang *et al*, 2013) supporting aging-related increased astrogliosis. Increased GFAP expression and cell body enlargement is also used as a common indicator of astrocyte activation and like myo-inositol, progressively increases during aging in humans and in animal models of normal aging (Morgan *et al*, 1999; Nichols *et al*, 1993; Rodríguez *et al*, 2014; Weber *et al*, 2015; Yoshida *et al*, 1996). Interestingly, this is not the result of greater numbers of astrocytes, instead it is associated with greater cell volume (Middeldorp and Hol, 2011). Studies reveal that when neurons are co-cultured with activated astrocytes, there is a significant reduction of synaptic contacts compared to less activated astrocyte co-cultures (Emirandetti *et al*, 2006). Activated astrocytes increase oxidative stress, upregulate production of proinflammatory cytokines, and facilitate chronic inflammation, all of which contribute to decreased neuronal fitness. In many CNS diseases, increased GFAP expression is a hallmark of neuropathology, establishing a link between astrocyte activation, disease progression, and cognitive deficits.

When compared to younger mice, in the aged mouse brain, a high percentage of astrocytes take on a partially reactive phenotype made apparent by upregulation of potentially harmful reactive genes associated with complement activation, cytokine response, and antigen

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presentation pathways in brain regions especially vulnerable to neurodegeneration, such as the hippocampus and striatum (Boisvert *et al*, 2018; Clarke *et al*, 2018). Reactive astrocytes lose their ability to carry out their normal functions that include the ability to promote neuronal survival, outgrowth and synaptogenesis (Liddelow *et al*, 2017). The term inflammaging describes the progressive changes during aging characterized by low-grade chronic upregulation of proinflammatory responses (Franceschi *et al*, 2007). This process occurs in various organs including the brain, where normal aging is characterized by a variety of neurobiological changes consistent with low-grade chronic neuroinflammation (Lana *et al*, 2016). Several reports highlight increased levels of proinflammatory cytokines in the hippocampus and cortical areas of the aged brain (Maher *et al*, 2004; Nolan *et al*, 2005; Terao *et al*, 2002). In a microarray study, 35% of the total mRNA that was upregulated in the aged mouse brain were inflammatory-related proteins (Lee *et al*, 2000). Astrocytes from aged rat brains show increased basal expression of various cytokines including IL-1β, IL-6, and TNF-α in the cortex and striatum (Campuzano *et al*, 2009). Undoubtedly, chronic exposure to astrocyte-derived proinflammatory cytokines can impair neuronal functioning. Adding insult to injury, the aged brain is primed to generate an exacerbated inflammatory response to pathogenic stimuli such as lipopolysaccharide (LPS) and possibly other factors such as low levels of HIV proteins produced in reservoirs such as the CNS (Clarke *et al*, 2018). This may be of great significance in the context of the aging HIV brain.

AD and PD are age-related neurodegenerative diseases and are often accompanied by astrocyte activation. AD is characterized by progressive memory loss and cognitive decline as a result of widespread neuronal and synaptic loss in the hippocampus, entorhinal area, and cerebral cortex. Pathological features associated with AD are deposits of beta-amyloid into plaques, neurofibrillary hyperphosphorylated tau tangles and substantial neuronal death (De Strooper and Karran, 2016). Several groups have reported that the activity of monoamine oxidase B (MaoB), a mitochondrial membrane protein overexpressed by activated astrocytes, is increased in AD patients indicating ongoing astrogliosis (Gulyás *et al*, 2011; Saura *et al*, 1994). Interestingly, increased MaoB activity occurs early during the progression of AD suggesting that astrogliosis contributes in the beginning stages of disease (Carter *et al*, 2012). Post-mortem AD brain tissue shows signs of astrogliosis (Ingelsson *et al*, 2004). In AD patients, astrogliosis increases linearly as the disease progresses and is negatively correlated with cortical thickness (Serrano-Pozo *et al*, 2011). GFAP+ astrocytes cluster around amyloid plaques (Nagele *et al*, 2004) and can be found in close proximity to neurofibrillary tangles thickness (Serrano-Pozo *et al*, 2011). Many of the rodent models for AD also exhibit substantial astrocyte activation (Rodríguez *et al*, 2009). Treatment of astrocytes *in vitro* with aggregated b-amyloid or with amyloid plaques isolated from human AD brains induced activation made evident by morphological changes and increased GFAP expression (Garwood *et al*, 2011; Hoppe *et al*, 2013; Hou *et al*, 2011). Astrocyte activation is reported to contribute to plaque formation by accumulating large amounts of amyloid-beta (Nagele *et al*, 2003). Furthermore, amyloid beta-induced activation of astrocytes, increased proinflammatory cytokine release, and accelerated neurotoxicity were observed in mixed neuronal-astrocyte cultures (Garwood *et al*, 2011; Jana and Pahan, 2010). Neurofibillary tangle burden in the AD brain is positively correlated with astrocytosis and disease severity (Serrano-Pozo *et al*, 2011).

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Astrocyte Activation in the HIV Brain

The consensus view is that HIV infection of astrocytes is very limited and does not result in production of mature virions. Thus, HIV neuropathogenesis is mediated largely through the release of virions, neurotoxic viral proteins, and proinflammatory products produced by macrophages and microglia. However, astrocytes are recognized as contributors to HIV neuropathogenesis through their response to these factors. Signs of astrocyte activation, or astrogliosis, are often observed in brain imaging studies of PWH and in post-mortem brain tissues despite the use of antiretroviral therapy (Desplats *et al*, 2013; Edén *et al*, 2007; Sabri *et al*, 2003; Vitkovic and da Cunha, 1995; Yang *et al*, 2016; Young *et al*, 2014). In fact, even in the absence of detectable viral production, astrocytes show considerable signs of activation in PWH (Edén *et al*, 2007; Harezlak *et al*, 2011; Young *et al*, 2014). Astrocyte activation is detected early in the course of HIV infection of the CNS (Masliah *et al*, 1996). Similarly, in animal models of HIV infection, astrogliosis is common (Kim *et al*, 2003; Toggas *et al*, 1994; Tyor *et al*, 1993).

Although astrocytes are not capable of productive viral infection, they have been shown to contain and release HIV proteins including Tat, Rev, and Nef (Atwood *et al*, 1993; Brack-Werner, 1999; Ensoli *et al*, 1993; Ranki *et al*, 1995). *In vitro* studies demonstrate that astrocytes become activated when exposed to viral particles or proteins. Tat and gp120 activate astrocytes and stimulate the production of proinflammatory cytokines, chemokines, and nitric oxide, all of which can cause synaptic damage (Ru and Tang, 2017). Tat expression increases GFAP expression in astrocytes (Zhou *et al*, 2004). Subsequently, cell culture supernatants from Tat-expressing astrocytes induce significant neuron death (Zhou *et al*, 2004). Markers of inflammation continue to bedetected in the cerebrospinal fluid (CSF) and brains of PWH even with long-term stable treatment of antiretroviral therapy (Edén *et al*, 2007; Harezlak *et al*, 2011). Although HIV-infected astrocytes make up a small fraction of the infected cells of the CNS, they are still a critical population to investigate. HIV-infected astrocytes show higher production of inflammatory mediators in response to LPS suggesting an increased sensitivity to inflammatory triggers (Serramía *et al*, 2015). Astrocytes are key components of the blood brain barrier (BBB) where they come into direct contact with HIV-infected cells that enter the CNS. Direct infection or exposure to viral proteins at this site can disrupt astrocyte ability to structurally support BBB integrity leading to increased permeability, thereby allowing entrance of additional toxic factors to enter the brain and propagate inflammation and induce greater astrocyte activation. HIV infection or exposure to HIV-related products can significantly alter astrocyte physiology and therefore modulate the essential interactions between astrocytes and neighboring neurons resulting in the deficits associated with HAND.

Altered Metabolism in the Aging Brain and age-related CNS Diseases

Brain aging is accompanied by a hypometabolic state that involves decreased glucose uptake (Jiang and Cadenas, 2014; Kalpouzos *et al*, 2009). Under normal conditions, astrocytes rely on anaerobic respiration to generate ATP and lactate. The release of lactate from astrocytes and subsequent uptake by neighboring neurons, known as the astrocyte-neuron lactate shuttle (ANLS), is essential to meet the high-energy requirements of neurons, since they rely

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on aerobic respiration. Many genes related to mitochondrial bioenergetics and function are upregulated in the brains of aging individuals with mild cognitive impairments relative to age-matched controls (Berchtold *et al*, 2014). This is in stark contrast to the extensive downregulation of mitochondrial genes in the AD brain (Berchtold *et al*, 2014), suggesting an intermediate increase in mitochondrial function energy may be an early contributor to a neurodegenerative state and precede hypometabolic conditions. However, due to dynamic glial/neuronal energetic profiles, it can be difficult to tease apart which cell population is driving these changes. Recently, a magnetic resonance spectroscopy study reported decreased neuronal mitochondrial metabolism and increased glial mitochondrial metabolism in healthy adults 76±8 years of age when compared to young volunteers 26±7 years of age (Boumezbeur *et al*, 2010), indicating that astrocytes are likely responsible for the increased energetics in the aging brain. Astrocyte activation requires enhanced protein synthesis and trafficking thereby increasing cellular energy demands. Upregulation of mitochondrial function may be an energy efficient way for astrocytes to meet their energy demands when under stress. With reports of elevated astrocyte activation in aging individuals, it is likely that astrocytic energy profiles are also altered with age. This was validated by one group that demonstrated an age-dependent metabolic shift from anaerobic metabolism towards increased mitochondrial metabolism and mitochondrial biogenesis in primary cortical astrocytes isolated from 7-, 13-, 18-month old rats (Jiang and Cadenas, 2014). It is likely that increased mitochondrial metabolism is needed to support metabolically expensive inflammatory responses. Interestingly, considering the intimate coupling of astrocyte anaerobic glycolysis with neuronal bioenergetics, a shift in astrocytes away from anaerobic respiration would reduce lactate production and deprive neurons of this key metabolite. Overall, this may help explain, in part, the hypometabolic state reported in the aged brain. Furthermore, upon aging, the activity of pyruvate carboxylase, a key mitochondrial anaplerotic enzyme, in astrocytes increases and decreasing its activity ameliorated age-related memory impairments in *Drosophila* (Yamazaki et al, 2014). Overall, enhanced astrocytic mitochondrial function appears to have detrimental effects on the aging brain and may represent a key pathology in neurodegenerative disorders.

Although astrocyte mitochondrial metabolism appears to increase with age, glucose uptake is reduced and glucose transporter 1 (GLUT-1) protein levels are decreased in astrocytes isolated from aged rats compared to those obtained from newborn rats (Souza *et al*, 2015). Although glucose is utilized as the primary energy source in the brain, fatty acids can also be used (Ebert *et al*, 2003; Panov *et al*, 2014). Increased utilization of free fatty acids and ketone bodies has been observed as the brain ages (Kadish *et al*, 2009; Laranjeira *et al*, 2016). Fatty acid oxidation is believed to occur most exclusively in astrocytes (Ebert *et al*, 2003). B-oxidation of fatty acids occurs in the mitochondria and results in the generation of acetyl-CoA that can be used for the TCA cycle. Intrinsic properties of astrocytic mitochondria suggest oxidation of fatty acids may be the preferred substrate for acetyl-CoA generation (Halim *et al*, 2010; Panov *et al*, 2014). In summary, increased fatty acid utilization observed during aging likely coincides with a metabolic shift that occurs in astrocytes to support enhanced mitochondrial metabolism.

Various aspects of brain energy homeostasis ranging from dysfunction in glucose metabolism to mitochondrial function coincide with AD disease pathology resulting in an

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overall hypometabolic state within the CNS (Förster *et al*, 2012; Yao *et al*, 2011). Positron emission tomography (PET) studies have demonstrated diminished glucose utilization in AD patients (De Santi *et al*, 2001; Duara *et al*, 1986; Ibáñez *et al*, 1998). In fact, a decline in glucose metabolism can appear prior to histopathological and clinical features (Mosconi *et al*, 2009). Recently, studies have revealed a connection between brain regions with abnormal glucose metabolism and areas vulnerable to AD pathology (Bero *et al*, 2011; Oh *et al*, 2016). Many genes associated with the glycolytic pathway and mitochondrial bioenergetics are altered in AD brains (Berchtold *et al*, 2014; Brooks *et al*, 2007). Transcriptome analysis of laser-capture micro-dissected neurons from AD brains revealed that genes influencing mitochondrial energy metabolism have reduced expression (Liang *et al*, 2008). However another study found the activity of key glycolytic enzymes is altered in AD patients, where glucose 6-phosphate dehydrogenase (G6PDH) activity is significantly reduced in the hippocampus yet phosphofructokinase (PFK), lactate dehydrogenase (LDH) and pyruvate kinase (PK) are increased in the frontal and temporal cortices (Bigl *et al*, 1999). Increased activity of PFK, LDH, and PK was positively correlated with GFAP levels and colocalized with GFAP+ astrocytes suggesting neuronal metabolism may be reduced, whereas, astrocyte metabolism is enhanced (Bigl *et al*, 1999; Liang *et al*, 2008). Animal models of AD further delineate metabolic dysregulation within the brain. For example, in transgenic McGill-R-Thy1-APP rats, reduced TCA cycle turnover was detected in hippocampal and cortical neurons as well as cortical astrocytes suggesting mitochondrial metabolism is perturbed in both cell populations (Nilsen *et al*, 2014).

Astrocyte involvement in AD has recently gained significant attention (Cai *et al*, 2017). *In vitro*, amyloid beta has been shown to disrupt normal astrocyte metabolic function in multiple ways. For example, in mouse hippocampal astrocytes, glucose uptake is impaired upon treatment with amyloid-beta peptides (Abeti *et al*, 2011). Impaired glycolysis in human fetal astrocytes promotes increased amyloid aggregation and internalization (Fu *et al*, 2015), which would therefore contribute to the formation of amyloid deposits. Furthermore, amyloid beta was found to trigger calcium (Ca^{2+}) release from the endoplasmic reticulum leading to transient elevations in intracellular (Ca2+) (Alberdi *et al*, 2013) and induce loss in mitochondrial potential (Abramov *et al*, 2004). This subsequently results in reduced mitochondrial oxidative consumption and metabolic failure in astrocytes (Abeti *et al*, 2011). In line with this, amyloid beta treatment of U87 glioblastoma cells, diminished mitochondrial membrane potential and reduced ATP generation (Yao *et al*, 2018). Taken together, changes in brain energy homeostasis likely stem from astrocyte dysfunction and loss of their innate ability to support neuronal energy demands ultimately causing neuronal dysfunction and loss. It is possible that this phenomenon may also occur during HIV infection.

Altered Metabolism in the HIV Brain

In PET studies of PWH on CART, varying levels of reduced glucose uptake have been reported in several brain regions (Andersen *et al*, 2010; Towgood *et al*, 2013). Additionally, CSF metabolomics in PWLH on CART reveal abnormal changes in brain bioenergetics associated with HIV infection (Cassol *et al*, 2014; Dickens *et al*, 2015). For example, PWH with neurocognitive impairments displayed alterations in the Krebs cycle, mitochondrial

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electron transport chain, and ketone body metabolism, corresponding to mitochondrial dysfunction, and the accumulation of metabolic waste products (Cassol *et al*, 2014). Interestingly, many of the CSF metabolites altered in PWLH under 50 years of age overlapped with the those found in advanced age HIV negative controls over 50 years of age, indicating accelerated aging may occur in PWH (Cassol *et al*, 2014). Enhanced aerobic glycolysis marked by accumulation of TCA cycle intermediates seems to contribute to declining cognitive status in PWH (Dickens *et al*, 2015). Increased creatine, which is tightly linked to aerobic glycolysis, along with the accumulation of citrate and acetate, provides added support that mitochondrial dysfunction is augmented in cognitive impairment in PWH (Dickens *et al*, 2015). Conversely, signs of enhanced anaerobic metabolism and lactate production are associated with improved cognitive status in PWH (Dickens *et al*, 2015). Proteomic analysis of brain tissue from HAD patients indicates a large percentage of the proteins altered are involved in the glycolytic and oxidative phosphorylation pathways, thereby highlighting the role of bioenergetic pathways in cognitive impairment (Zhou *et al*, 2010). In HIV-1 transgenic rats, which express seven out of nine HIV proteins, there are significant changes in synaptic mitochondria isolated. These abnormalities included altered expression of electron transport chain (ETC) complex subunits, increases in protein expression of TCA cycle and fatty acid metabolic processes (Villeneuve *et al*, 2016). However, some conflicting data have been reported. At the transcript level, brain gene expression analyses reveal that HAND is related to gene pathways involved in mitochondrial functioning being significantly down regulated (Levine *et al*, 2013). Taken together, this indicates that global brain mitochondrial functioning is perturbed during HIV infection. However, changes in mitochondrial activity caused by HIV may vary across distinct cellular compartments.

It is well established that various HIV proteins cause disruptions in neuronal energy homeostasis (Avdoshina *et al*, 2016; De Simone *et al*, 2016; Fitting *et al*, 2014; Norman *et al*, 2007; Rozzi *et al*, 2017; Shah and Kumar, 2016; Stevens *et al*, 2014). A recent report found that gp120 and Tat induce mitochondrial fragmentation and decrease mitochondrial membrane potential in human primary neurons (Teodorof-Diedrich and Spector, 2018). Moreover, gp120, Vpr, and Tat all cause mitochondrial depolarization and reduce ATP production in neuronal cultures (Kitayama *et al*, 2008; Wang *et al*, 2017). However, the impact of HIV on mitochondrial function in astrocytes is understudied. Exposure of astrocytes to free virus induced mitochondrial permeability transition pore (mPTP) opening and loss of mitochondrial membrane potential (Borgmann and Ghorpade, 2018). Similarly, gp120 was found to increase mitochondrial membrane depolarization in astrocytes (Yang *et al*, 2010). Recently, our group was the first to report that Tat protein induces a metabolic shift in astrocytes from glucose utilization to fatty acid oxidation leading to enhanced mitochondrial respiration, increased ATP levels, and reduced lactate production (Natarajaseenivasan *et al*, 2018) (Figure 1). Here we show that in human fetal astrocytes treated with HIV-1 Tat (1–101aa) over the course of 48 hours there is a significant increase expression of CPT1A (carnitine palmitoyltransferase 1A), a key enzyme for the activation of fatty acid oxidation (Figure 2). This indicates that enhanced aerobic respiration in astrocytes may contribute to HAND by misappropriating energy substrates essential to neurons and ultimately leading to reduced neuronal mitochondrial metabolism.

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Conclusion

Chronic low-grade inflammation and metabolic disturbances seem to be a point of convergence for HAND and normal brain aging resulting in cognitive impairments (Figure 3). Although the causes of inflammation in aging and HAND are quite different, as individuals approach later decades of life, the physiology of cells in the CNS can become augmented. It is plausible that pathways of inflammation and metabolism can influence one another in several ways. Energy homeostasis is likely disrupted during states of inflammation. The maintenance of even low-level inflammation requires energy levels to exceed the normal baseline requirements. In the aging or injured brain, the capacity to meet these energy demands is often compromised as seen by aberrant glucose utilization and mitochondrial dysregulation. The fundamental role of astrocytic input in neuronal metabolic homeostasis and inflammation make this cell population of great significance to CNS fitness. Astrocytes play roles in most aspects of normal brain functioning, in particular in the uptake of glucose from the periphery and supplying key metabolites to neurons. Loss of these functions, because of age-related physiological changes or insult have detrimental impacts on the whole brain. In astrocytes, chronic inflammation is observed as a state of activation. The evidence presented in this review from aging populations and PWH, suggests that astrocyte activation is increased and is maintained through a metabolic switch from glucose utilization and lactate production towards beta oxidation of fatty acids and enhanced mitochondrial respiration. This appears to provide astrocytes with additional ATP to support upregulation of a plethora of proinflammatory mediators, increase GFAP and myoinositol expression. However, this shift results in the production of oxidative stress and reduced metabolic support to neurons both of which are deleterious to overall brain functioning and cognitive health. Investigating the mechanisms leading to these changes and identifying ways to mitigate these metabolic shifts holds significant therapeutic potential for age-related disorders and PWH. Viral eradication, the ultimate cure for HIV infection, remains elusive. Therefore, efforts to restore the energy balance in the brain through approaches which increase energy substrate bioavailability including but not limited to implementation of a ketogenic diet (Cunnane *et al*, 2016; Hui *et al*, 2012; Stafstrom and Rho, 2012), intranasal insulin treatment (Mamik *et al*. 2016), or exercise (Dufour *et al*. 2013) coupled with use of anti-inflammatory drugs may provide therapeutic benefits to PWH.

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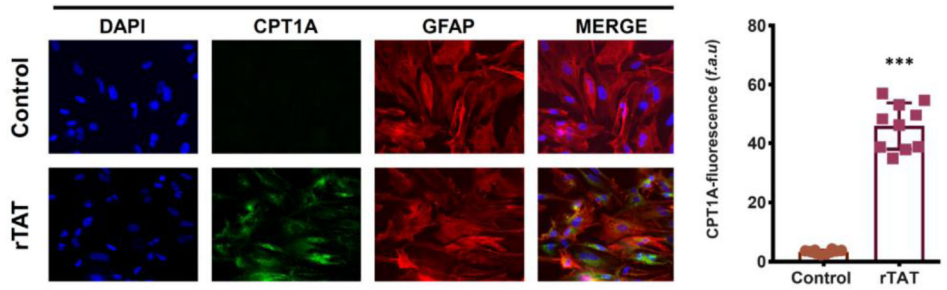

Figure 1. Schematic representation of the proposed metabolic switch in astrocytic metabolism during treatment with recombinant HIV-1 Tat protein.

Left panel: Under neurotrophic conditions, astrocytes primarily utilize anaerobic glycolysis resulting in the conversion on pyruvate to lactate by lactate dehydrogenase (LDH) which then is released from the cell via monocarboxylate transporter 4 (MCT4) into the extracellular compartment. **Right panel:** Under conditions of cell stress such as HIV-1 Tat insult, astrocytes take on a neurotoxic phenotype in which pyruvate is no longer converted to lactate. Instead, pyruvate is converted into acetyl CoA. Additionally, there is an increase in intracellular calcium into the mitochondria via the mitochondrial calcium uniporter (MCU) and an upregulation of fatty acid oxidation (FAO), providing an additional source of acetyl CoA, which fuels the TCA cycle and drives mitochondrial metabolism within astrocytes. Overall this results in increased production of mitochondrial ROS (mROS) and reduced supply of lactate.

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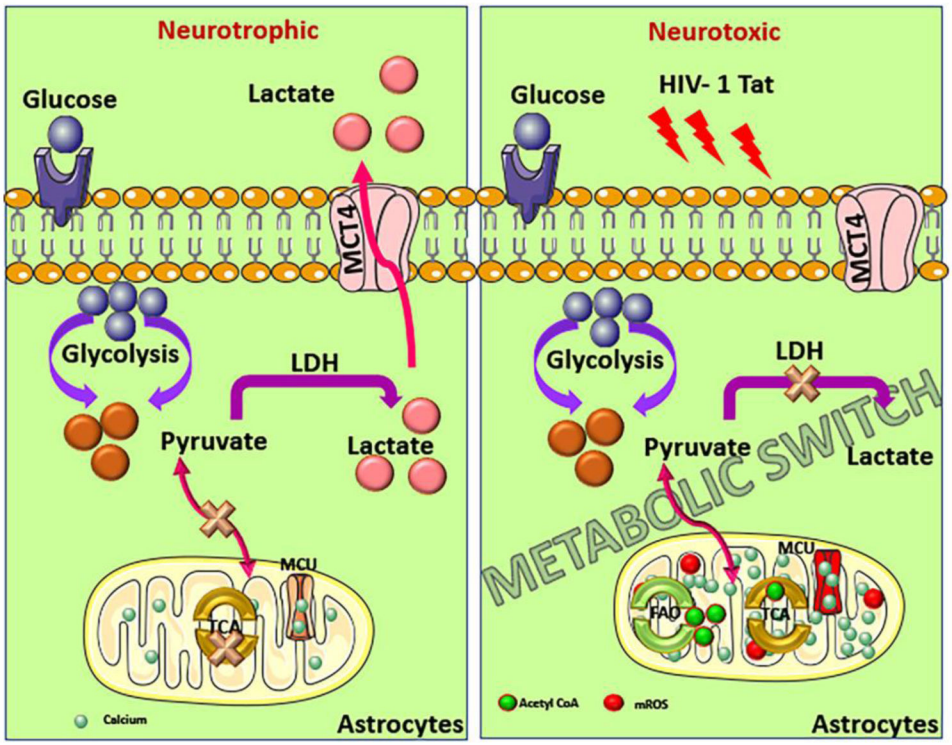

Figure 2. HIV-Tat increases beta-oxidation in human primary astrocytes.

Astrocytes were exposed to 50 ng/ml recombinant HIV-1 Tat for 48h and assessed by immunofluorescence for and GFAP (red) and carnitine palmitoyltransferase 1 (CPT1) (green), a rate limiting enzyme for beta-oxidation. Reprinted with permission from Natarajanseenivasan *et al.*, *Cell Death & Disease*, 9: 415, 2018, http://creativecommons.org/licenses/by/4.0/.

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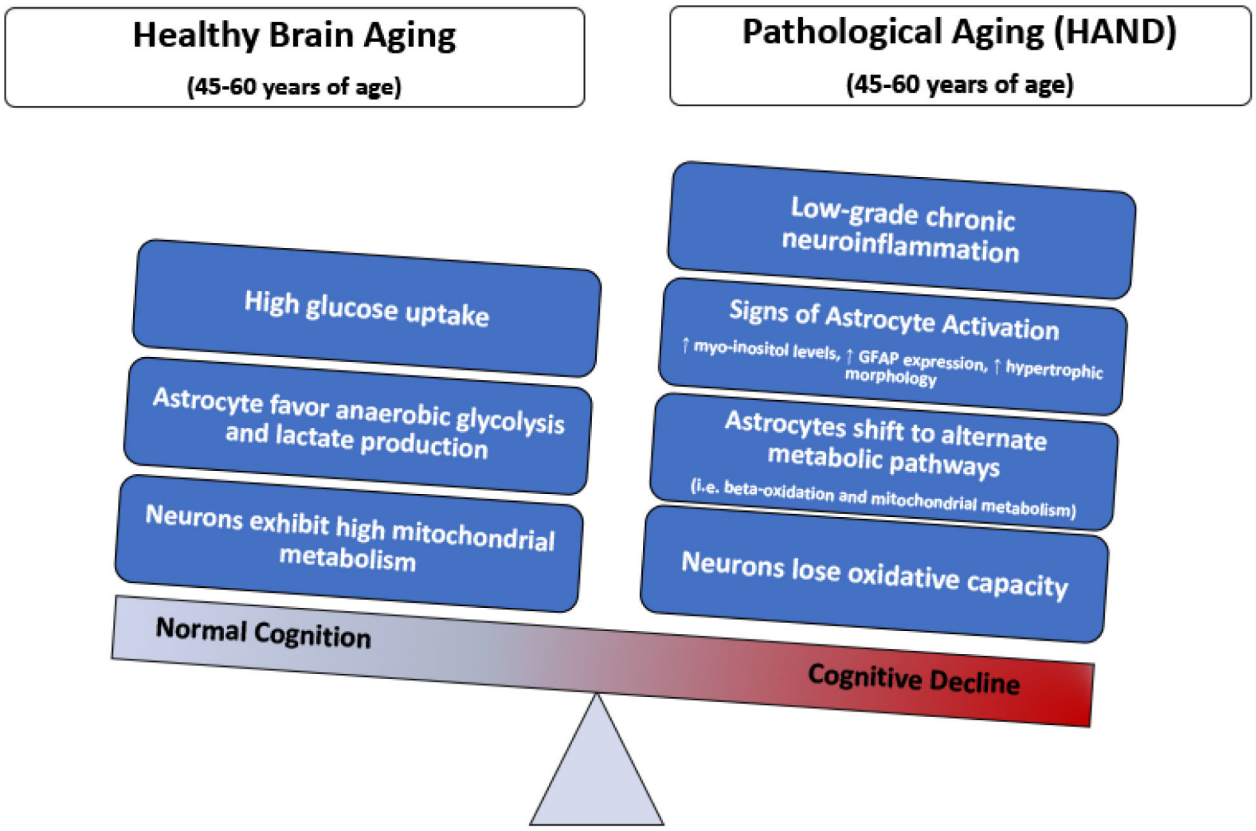

Figure 3.

The shifts in the balance of neuroinflammation and brain energy homeostasis can contribute to cognitive decline observed in PWH.