The Role of Astrocyte Mitochondria in Differential Regional Susceptibility to Environmental Neurotoxicants: Tools for Understanding Neurodegeneration

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ABSTRACT

In recent decades, there has been a significant expansion in our understanding of the role of astrocytes in neuroprotection, including spatial buffering of extracellular ions, secretion of metabolic coenzymes, and synaptic regulation. Astrocytic neuroprotective functions require energy, and therefore require a network of functional mitochondria. Disturbances to astrocytic mitochondrial homeostasis and their ability to produce ATP can negatively impact neural function. Perturbations in astrocyte mitochondrial function may accrue as the result of physiological aging processes or as a consequence of neurotoxicant exposure. Hydrophobic environmental neurotoxicants, such as 1,3-dinitrobenzene and α-chlorohydrin, cause regionally specific spongiform lesions mimicking energy deprivation syndromes. Astrocyte involvement includes mitochondrial damage that either precedes or is accompanied by neuronal damage. Similarly, environmental neurotoxicants that are implicated in the etiology of age-related neurodegenerative conditions cause regionally specific damage in the brain. Based on the regioselective nature of age-related neurodegenerative conditions, it is reasonable to suggest that regioselective lesions targeting astrocyte mitochondria may provide insight into age-related susceptibilities in astrocyte mitochondria. Most of the available research to date focuses on neuronal damage in cases of age-related neurodegeneration; however, there is a body of evidence that supports a central mechanistic role for astrocyte mitochondria in the expression of neural injury. Regional susceptibility to neuronal damage induced by aging by exposure to neurotoxicants may be a reflection of highly variable regional energy requirements. This review identifies region-specific vulnerabilities in astrocyte mitochondria in examples of exposure to neurotoxicants and in age-related neurodegeneration.

Key words: Neurotoxicology, Astrocytes, Mitochondria, Aging, Regional Susceptibility
injury, there is a small but growing body of evidence that astrocytes may play a pivotal role in the initiation and progression of neurotoxic states in the CNS.

Astrocyte function is primarily focused on the preservation of neural environments including maintenance of the extracellular milieu (Suzuki et al., 2011), buffering of neurotransmitters (Ota et al., 2013) and ions (Lian and Stringer, 2004). These functions require energy and are therefore reliant on the presence of functional mitochondria in the astrocyte (Voloboueva et al., 2007). Perturbations in astrocyte mitochondrial functions, therefore, may adversely impact neuroprotective services provided by the astrocyte. For example, loss of astrocyte mitochondrial function precedes neuronal glutamate excitotoxicity and is likely related to an inability of astrocytes to convert glutamate to glutamine, a process that requires ammonia and ATP (Voloboueva et al., 2007). Despite the demonstrated importance of astrocyte mitochondria on provision of energetic substrates, metabolic demand is not necessarily higher in regions where lesions appear than in unaffected regions. Thus, energy demand alone cannot explain regional vulnerability to chemicals that interrupt energy production. Similarly, the aging process itself correlates with global reductions in the capacity of brain to respond to injury, with observed age-related global increases in oxidative load [reviewed by Poon et al. (2004)], reductions in mitochondrial derived energy production (Vancova et al., 2010) and related declines in neuronal function (Parihar and Brewer, 2007).

Despite the presence of global age-related declines in neural function, pathologies caused by chemical exposures in the aged animal are commonly localized to a specific anatomic region. In turn, regional differences in astrocytic responses to neurotoxically induced fluctuations in the composition of the extracellular space may account for the development of regiospecific lesions in the aged brain. Evidence for the pivotal role of astrocytes in providing metabolic and physical support for the adjacent neuron can be found in studies that show bolstered neuroprotection in age-related morbidities such as memory impairment (Gibbs et al., 2009) and stroke (Diekman et al., 2013; Zheng et al., 2010), which is at least in part due to increases in astrocytic metabolism. Regiospecific decrements in astrocytic mitochondrial function induced by neurotoxicant exposure in older animals point to either intrinsic (ie within the mitochondrion itself) or extrinsic (cellular and/or regional) factors that render a small, but important, population of mitochondria increasingly sensitive to environmental chemicals as a function of time.

Age is the primary risk factor for the development of neurodegenerative disease in human populations. Estimates from the 2010 census indicate that nearly 630,000 people in the United States had Parkinson’s disease (PD), with projected disease burden to increase 2-fold by 2040 (Kowal et al., 2015). National statistics from the same year estimate that 4,700,000 people over the age of 65 years have Alzheimer’s disease dementia, with projected disease burden to increase to 13.8 million by 2050 (Hebert et al., 2013). Age-related sensory losses in hearing and balance are also prevalent in the elderly population in the United States (Lin et al., 2011; Rubenstein, 2006). The overall burden of age-related neurodegenerative diseases is likely to continue increasing unless mechanism-based strategies for mitigating age-related neural declines are discovered and exploited for prevention or therapy. The role of astrocytes (as both a cellular target and as a secondary participant) in regiospecific neurotoxicant exposure and in the etiology of neurodegenerative disease has been gaining traction in recent years. However, our understanding of astrocytic mitochondrial mechanisms in response to regiospecific neurotoxicant exposures and during aging is incomplete relative to our understanding of neuronal mitochondrial mechanisms (Table 1). This review highlights the role of astrocyte mitochondria in the development of region-specific lesions, both chemically induced and age-related, in the vestibulocochlear sensory pathway, the hippocampus, and substantia nigra (briefly summarized in Table 2).

### VESTIBULOCOCHLEAR SENSORY PATHWAY

The vestibulocochlear nerve (VIIIth cranial nerve) relays sensory information from the inner ear to the brain and coordinates the senses of balance and hearing. The ascending sensory tract contains specific populations of neurons (superior olivary nuclei, vestibular nuclei, cerebellar roof nuclei, inferior colliculi) supported by surrounding macroglia. Damage to these brain regions can manifest as hearing loss (Pearson and Barber, 1973), postural instabilities (Mbongo et al., 2009), and ataxia (Horn et al., 2013). Deficiencies in glial neuroprotection in the audiovestibular system potentially contribute to the onset and progression of these conditions. Conversely, glial neuroprotection can be enhanced during injury: astrocyte proliferation stimulated by GABA_A receptor antagonism shortens recovery time from unilateral vestibular neuroectomy (Duthieil et al., 2013). The balance between regional astrocytic functions in maintenance of audiovestibular neuroprotection and their role in precipitating specific neuroanatomical responses to neurotoxicant

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**Table 1: PubMed Search Results Comparing Number of Primary Research Articles on Neuron Mitochondria and Astrocyte Mitochondria**

<table>
<thead>
<tr>
<th>Search term</th>
<th>Number of publications in PubMed</th>
<th>Publications (astrocyte/neuron) (%)</th>
<th>Number of publications 2009–2014</th>
<th>Total publications in last 5 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuron mitochondria</td>
<td>11,400</td>
<td>—</td>
<td>2,774</td>
<td>24.3</td>
</tr>
<tr>
<td>Astrocyte mitochondria</td>
<td>1,214</td>
<td>10.6</td>
<td>300</td>
<td>24.7</td>
</tr>
<tr>
<td>Neuron mitochondria + Alzheimer’s disease</td>
<td>775</td>
<td>—</td>
<td>376</td>
<td>48.5</td>
</tr>
<tr>
<td>Astrocyte mitochondria + Alzheimer’s disease</td>
<td>78</td>
<td>10.1</td>
<td>25</td>
<td>32.1</td>
</tr>
<tr>
<td>Neuron mitochondria + PD</td>
<td>10,38</td>
<td>4.7</td>
<td>532</td>
<td>51.3</td>
</tr>
<tr>
<td>Astrocyte mitochondria + PD</td>
<td>49</td>
<td>—</td>
<td>20</td>
<td>40.8</td>
</tr>
</tbody>
</table>

Search terms were input on August 27, 2014; review articles were excluded from the list of results. Percent of publications were calculated based on number of publications for astrocytes divided by the number of publications for an identical search on neurons. Column data on proportion of publications in the last 5 years calculated as a percent of total number of publication results in PubMed for that search term. Article types included in the search results: Government Publications, Journal Articles, and Technical Reports.
TABLE 2. Age-Related Changes in the Brain during Aging

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Chemical exposure</th>
<th>Mitochondria-specific responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory Pathway</td>
<td>DNB-induced cytochrome c oxidase activity decrease (Tjalkens et al., 2003)</td>
<td>Decreased glutathione and aging increase susceptibility to DNB-induced neurotoxicity (Hu et al., 1999)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Glial mitochondria inhibition by fluoracetate associated with disrupted synaptic transmission (Canals et al., 2008)</td>
<td>Age-related clasmatodendrosis linked to mitochondrial inhibition (Hu et al., 2001)</td>
</tr>
<tr>
<td>Substantia Nigra</td>
<td>MPTP-induced inhibition of mitochondrial enzymes (Sundar Boyalla et al., 2011)</td>
<td>Mitochondria-specific iron accumulation in astrocytes (Schipper et al., 1998)</td>
</tr>
</tbody>
</table>

Age-specific global changes in the brain and global declines in brain mitochondrial function (shaded). Mitochondria-specific responses to neurotoxicant exposure and age-related mitochondrial toxicity in astrocytes in the vestibulocochlear sensory pathway, hippocampus, and substantia nigra are summarized as well.

While toxicological concerns surrounding 3-chloropropanediol (3-CPD), found in food products, are focused on renal and testicular effects [reviewed by Bakhiya et al. (2011)], 3-CPD also causes glial-specific neurotoxicity in brainstem nuclei confined within the VIIIth cranial nerve (Cavanagh et al., 1993). Thus, it has been used as a neurotoxicological tool to investigate the relationship between neurons and astrocytes in regionspecific, astrocyte-targeting chemical challenge. 3-Chloropropanediol exposure results in focal astrocytic loss in inferior colliculi, preceded by an inability of astrocytes to appropriately maintain glutamate levels in response to ammonia challenge (Brown et al., 2011). This ultimately correlates with loss of function, as measured by a lack of auditory response in inferior colliculi (Brown et al., 2011). Region-specific glial dysfunction caused by 3-CPD exposure is likely rooted in differential astrocytic susceptibility to oxidative stress, as 3-CPD inhibits glutathione-S-transferase in inferior colliculus, but not in other regions (Skamarožkas et al., 2007). Further, 3-CPD exposure causes astrocytic mitochondrial membrane potential to decrease in concert with increased mitochondrial oxidative stress, similar to what is observed in DNB exposure (Steiner et al., 2013).

In the examples of DNB and 3-CPD exposure, metabolic dysfunction in specific sub-populations of astrocytes precedes...
pathological involvement of neurons in brainstem nuclei (Philbert et al., 1987; Willis et al., 2013). This discrepancy in cellular vulnerability occurs despite neurons having a higher resting metabolic demand compared to astrocytes (Howarth et al., 2012). Thus, these regioselective neurotoxins do not exclusively target mitochondria based solely on cellular energetic demand. Increased neuronal energy demand may exacerbate astrogliosis, as observed in the case of DNB exposure (Holton et al., 1997). Involvement of mitochondria in astrogliosis is likely related to astrocytic metabolic output in the case of DNB exposure due to the accumulation of astrocyte-derived extracellular adenosine; the ensuing mixed inhibition of extracellular adenosine deaminase by DNB contributes to the accumulation of extracellular adenosine (Wang et al., 2012).

**Age-Related Alterations to Astrocytic Mitochondria within the Vestibulocochlear Sensory Pathway**

The available epidemiological evidence supports an inverse relationship between age and vestibulocochlear function. Coincident with the decline in neural function, the incidence of falls and loss of hearing increases with age in the U.S. population (Lin et al., 2011; Rubenstein, 2006). The aging process itself alters not only the number of astrocytes within the vestibulocochlear pathway, but also modifies their spatial distribution within the region, resulting in fewer and larger astrocytes (Jalenques et al., 1997). Morphological changes to astrocytes can ultimately change the distribution of mitochondria. Hence, the position of mitochondria in astrocytes can determine their ability to respond to focal changes in the extracellular environment (Jackson et al., 2014), potentially dampening the neuroprotective response in the aged astrocyte. Severity of focal DNB-induced lesions in the vestibulocochlear pathway increases with the age of the animal and is influenced by glutathione concentrations (Hu et al., 1999). Age-related disparate concentrations of glutathione in astrocyte populations could be a factor in regional susceptibility to DNB-induced lesions, as could differences in mitochondrial glutathione in vestibulocochlear astrocyte populations. Despite evidence of age-related audiovestibular dysfunction and age-related alterations to astrocytic mitochondria (Lin et al., 2007), much remains to be discovered with respect to mechanistic relationships between aging astrocyte and neuronal mitochondria, the role of intrinsic cellular factors and extrinsic neural and non-neural signals, the relative contribution of dietary and xenobiotic modulators of neural function and energetics within the audiovestibular region.

**HIPPOCAMPUS**

The hippocampus actively participates in the formation and sorting of memory functions and is facilitated by long-term potentiation, while relying heavily on proper synaptic transmission within the hippocampus. Known disruption of mechanisms contributing to memory formation in the hippocampus includes disturbances in synaptic transmission, accumulation of neurofibrillary tangles, and abnormal accumulation of proteins such as amyloid-β (Reitz et al., 2009). Alzheimer’s disease, the most prevalent neurodegenerative disease in the United States (Hebert et al., 2013), is characterized by these neurodegenerative changes. Interestingly, hippocampus-specific neuronal glutamate excitotoxicity, accumulation of neurofibrillary tangles, and abnormal buildup of proteins such as amyloid-β are tempered by adjacent glia, namely astrocytes (Choi et al., 2014; Ota et al., 2013; Penkowa et al., 2005; Pihlaja et al., 2008; Yang et al., 2014). Thus, neurotoxicant-induced and age-related hippocampal degeneration manifesting overtly as neuronal damage may have origins in astrocyte-related dysfunction in neuroprotective mechanisms.

**Astrocyte Mitochondria Modulate Hippocampal Synaptic Transmission**

Recent contributions to the understanding of hippocampal cellular dynamics point to the integral role of astrocytes in the propagation and maintenance of synaptic transmission (Amiri et al., 2013; Bernardinelli et al., 2011; Heja et al., 2012). Glutamate transporter-1 (GLT-1), a highly expressed astrocytic glutamate transporter responsible for the removal of excitotoxic glutamate, “co-compartmentalizes” with astrocyte mitochondria in hippocampal sections (Genda et al., 2011). This observed congregation of astrocytic mitochondria near GLT-1 sites seems also to be regulated by adjacent neuronal activity: increased neuronal activity correlated with an increased number of stationary astrocytic mitochondria near GLT-1, whereas inhibition of astrocytic glutamate uptake increased the rate of mobile mitochondria 3-fold (Jackson et al., 2014). Because extracellular glutamate levels regulate synaptic transmission, this indicates that astrocyte mitochondria play a direct role in glutamate-mediated synaptic transmission in the hippocampus. Chemical exposure specifically targeting glial mitochondria in the hippocampus has been shown to disrupt synaptic transmission: Canals et al. (2008) reported that synaptic transmission in hippocampal pyramidal neurons is impaired when adjacent glial mitochondria are inhibited by fluorocacetate, likely mediated by glial adenosine release. Chemically induced neuroprotective mechanisms imparted by hippocampal astrocytes are observed during organophosphate exposure, whereby astrocytes restore and promote neurite outgrowth in hippocampal neurons exposed to diazinon (Pizzurro et al., 2014). Hippocampal astrocytes have recently been discovered to further contribute to neuroprotection by conditioning the extracellular environment by releasing ATP to promote long-term depression (Chen et al., 2013) and in potassium-induced transmission between astrocytes (Wang et al., 2013).

**Astrocyte Mitochondria in the Aging Hippocampus: Emerging Roles in Alzheimer’s Disease Pathology**

While reactive gliosis is often observed as a factor in the progression of Alzheimer’s disease, it is typically observed in later stages of the disease, found in areas beyond the hippocampus (cortex, cerebellum, thalamus, and brainstem) and is likely reflective of factors beyond plaque-related astrogliosis (Delacourte, 1990). Recent evidence indicates that susceptibility to region-specific plaque-related astrogliosis in Alzheimer’s brain depends on distinctive glial fibrillary acidic protein (GFAP) isoform expression identifying significantly longer astrocyte processes (Kamphuis et al., 2014). Because observed changes in GFAP expression were not found to be exclusively linked to age or astrogliosis (Kamphuis et al., 2012), longer astrocyte processes observed in Alzheimer’s disease brains as a result of plaque-related GFAP expression likely identifies a unique, disease-specific population of astrocytes. Astrocytic proliferation, as measured by increases in GFAP, requires significant mitochondrial energetic output. However, degradation of astrocyte processes, also known as clasmatodendrosis, has previously been attributed to decreased mitochondrial function in hippocampal astrocytes (Hulse et al., 2001). Thus, astrocytic mitochondrial function and energetics within the hippocampus are critical for neuroprotection.
heterogeneity within brain regions may prove to be just as significant as astrocytic mitochondrial heterogeneity between regions in neurotoxicant- and disease-related regioselectivity. Recent findings indicate that intrahippocampal astrocytic mitochondrial heterogeneity may contribute to progression of mild cognitive impairment (often preceding the onset of Alzheimer’s disease) through upregulation of heme oxygenase-1 and association of astrocytic mitochondria with age-related protein inclusions (Song et al., 2014). Additionally, astrocytic mitochondria are targeted by molecular hallmarks of Alzheimer’s disease, such as β-amyloid and amyloid precursor protein, in the hippocampus (Sarkar et al., 2014; Schmidt et al., 2008).

SUBSTANTIA NIGRA

The substantia nigra is a major coordinating center of muscle movement in the brain. It is the region in which lesions appear in PD, characterized by loss of dopaminergic neurons, resulting in tremor, rigidity, and loss of motor control that are distinguishing features of the disease. Both aging and environmental factors have been implicated in PD progression. Neurotoxicants known to induce damage to the substantia nigra have thus far typically been characterized by neuron-specific effects, most notably loss of dopaminergic neurons, resulting from exposure to paraquat (Izumi et al., 2014; McCormack et al., 2002), manganese (Zhang et al., 2013), rotenone (Cannon et al., 2009; Sherer et al., 2003), and heptachlor (Hong et al., 2014). Perhaps, the most widely studied neurotoxicant that induces pathology parallel to PD is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), used to reliably induce degeneration to dopaminergic neurons in the nigrostriatal pathway [reviewed by Langston and Irwin (1986)]. The onset of reactive astrogliosis is implicated as a causative factor in neuronal degradation in substantia nigra in PD. However, reactive astrocyte-specific inflammatory signaling cascades in animal models of PD can result in either neuronal death or in neuroprotection [reviewed by Episcopo et al. (2013)]. There is a growing body of evidence in support of additional neuroprotective and neurodegenerative mechanisms governing neuronal function in the substantia nigra (Bajo-Graneras et al., 2011; L’Episcopo et al., 2011; Michael et al., 2011). Thus, functional consequences of astrocytic dysregulation in substantia nigra are likely a combination of upregulation of astrocytically mediated neuroinflammation and a disruption to native astrocytically mediated neuroprotective mechanisms, of which the boundary remains unclear.

Role of Astrocyte Mitochondria in Neurotoxicant-Induced Focal Damage within Substantia Nigra

While the classes of neurotoxicants that cause injury mimicking or associated with PD-like lesions are fundamentally divergent (metals, pesticides, and synthetic drugs), evidence suggesting astrocytic mitochondrial dysfunction is emerging as a common mechanistic feature of neurotoxicant-induced lesion development within the substantia nigra. In the case of MPTP toxicity, astrocytes convert MPTP into its toxic metabolite, MPP+ (Ransom et al., 1987) which is released into the extracellular space (Di Monte et al., 1992). It is then directly taken up by neighboring dopaminergic neurons through the dopamine transporter (Pflü et al., 1993). This suggests that regioselectivity is governed largely by neuronal dopamine transporter expression. While the defining cytotoxic event in MPTP exposure is dopaminergic neurodegeneration, MPTP and MPP+ both exert mitochondrial toxicity in astrocytes that contribute to dopaminergic neurodegeneration. Direct inhibition of astrocyte mitochondrial enzymes in substantia nigra is documented in MPTP exposure (Sundar Boyalla et al., 2011). The mechanism of MPTP toxicity may also be linked to regiospecific decreases in mitochondrial membrane potential and resultant decreases in astrocytic ATP, as MPP+ reduces mitochondrial membrane potential in a glioma cell line (Badisa et al., 2010). Blocking ATP-sensitive potassium channels on primary astrocytes from whole brain protected them from MPP+-induced mitochondria-mediated apoptosis and maintained astrocytic ATP levels (Zhang et al., 2009). Additionally, MPTP-induced activation of ATP-sensitive potassium channels causes dopaminergic neuronal death in substantia nigra (Liss et al., 2005). However, the mitochondrial-specific astrocytic effects observed by Zhang et al. may not be defining characteristics of regioselectivity of lesion development per se; the primary astrocytes were derived from whole brain and were observed in culture without neurons—thus, the neuroprotective contribution of suppression of astrocytic versus neuronal ATP-sensitive potassium channels within the affected region is unknown.

Selective vulnerability to neurotoxicant-induced lesion development in the substantia nigra may be due in part to the activity of a cytoprotective protein, DJ-1, whose downregulation inhibits mitochondrial activity in rotenone-exposed astrocytes (Mullett and Hinkle, 2011), resulting in weakened astrocyte-mediated neuroprotection during rotenone exposure (Larsen et al., 2011). Manganese exposure studies reveal that astrocyte mitochondria may also contribute to lesion formation in substantia nigra through caspase-3 activation (Yin et al., 2008), or dampening of astrocytic ATP-dependent calcium wave propagation caused by mitochondrial calcium sequestration (Tjalkens et al., 2006).

Age-Related Susceptibility to Astrocytic Mitochondrial Damage within Substantia Nigra

Age is positively correlated with the deposition of iron in astrocyte mitochondria within the substantia nigra (Schipper et al., 1998); thus, astrocytes within this region in the aged brain are inherently prone to disturbances in metal redox homeostasis. Additionally, manganese exposure can further exacerbate imbalances in iron-related oxidative mechanisms in aged astrocytes, as it has been shown to inhibit mitochondrial aconitase (Zheng et al., 1998). Oxidative inactivation of aconitase in astrocytes causes an increase in ferrous iron and hydrogen peroxide, resulting in death to proximal neurons (Cantu et al., 2009). Hence, age-related and neurotoxicant-induced contributions to Fenton chemistry in astrocyte mitochondria are plausible components of lesion development in substantia nigra.

FUTURE DIRECTIONS

Astrocyte mitochondria provide metabolic substrates necessary for proper neural function throughout the brain and have been the focus of increased recent investigations. Concurrent with the effort toward a greater understanding the mitochondrial mechanisms contributing to both neurological health and disease, there have been promising new discoveries in the treatment of neurodegenerative disease.

Whether or not there are intrinsic fundamental mitochondrial mechanisms/processes in specific regional subpopulations of astrocytes that account for differences in regional vulnerability to neurotoxicants and the development of lesions in age-related neurodegenerative disease remains to be determined. Such astrocytic mitochondrial mechanisms may include (but are
likely not limited to) regional differences in mitochondrial anti-
oxidant capacity, mitochondrial biogenesis, the capability of mi-
 tochondria to properly buffer calcium, and others. Examination of
these potentially key functional differences will aid in under-
standing the observed differential regional susceptibilities of as-
trocyte mitochondria—an essential step toward developing new
therapeutic strategies for reducing the impacts of environmental
impacts on accelerated regional aging in brain.

**Targeted Gene Therapy in Region-Specific Lesion Treatment: Potential Roles for Astrocyte Mitochondria**

Gene therapy refers to delivering potentially therapeutic DNA to
tissues to ameliorate disease sequelae. Gene therapies overex-
pressing glial-derived neurotrophic factor (GDNF) using viral
transfection and miniosmotic pumps have yielded positive re-
results in animal models of PD (Sterky et al., 2013; Tereshchenko
et al., 2014). Despite observed benefits, global delivery of GDNF
eventually involves off-target exposures with as yet undeter-
dined side-effects (Drinkut et al., 2012). Astrocyte-specific over-
expression of growth factors has proven to be both localized and
effective, as in the cases of recombinant lentiviral GDNF
overexpression in hippocampal astrocytes in an AD mouse model
(Revilla et al., 2014) and in GDNF overexpression in astro-
cytes in a PD mouse model (Drinkut et al., 2012). Overexpression
of vascular endothelial growth factor (VEGF) or GDNF in neuro-
toxicant-induced PD animal models shows a positive correla-
tion between VEGF and GDNF expression and expression of
nuclear-encoded mitochondrial genes (Yue et al., 2014), lending
further credence to the potential therapeutic significance of ast-
trocyte mitochondria in vulnerable brain regions. Additionally,
transmembrane tyrosine-specific protein kinase TrkB (a recep-
tor for BDNF) colocalizes with mitochondria in astrocytes
(Wiedemann et al., 2006), suggesting that astrocyte mitochon-
dria have the potential to directly interact with neurotrophic
factors introduced by gene therapy. While it remains to be de-
determined which treatments may be most effective in truncating
neurodegenerative disease progression, these studies suggest
that regionally targeted, astrocyte-specific delivery of gene ther-
apies provide a novel component to current methods, with the
potential for reducing unforeseen off-target effects of contem-
porary gene therapy.

Prior to the development of any potential therapeutic strate-
gy for the attenuation of regional functional neurological defi-
cits, much remains to be discovered regarding the nexus among
environmental, nutritional and genetic (genomic and mitochon-
drial) contributors to differential aging and vulnerability of spe-
cific neural pathways. The development of new therapeutic
strategies will also require a better understanding of the poten-
tial for adverse interactions with emerging targeted therapeutic

technologies [reviewed by Cicchetti and Barker (2014)].

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