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Role of Mitochondrial Homeostasis and Dynamics in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease that affects a staggering percentage of the aging population and causes memory loss and cognitive decline. Mitochondrial abnormalities can be observed systemically and in brains of patients suffering from AD, and may account for part of the disease phenotype. In this review, we summarize some of the key findings that indicate mitochondrial dysfunction is present in AD-affected subjects, including cytochrome oxidase deficiency, endophenotype data, and altered mitochondrial morphology. Special attention is given to recently described perturbations in mitochondrial autophagy, fission-fusion dynamics, and biogenesis. We also briefly discuss how mitochondrial dysfunction may influence amyloidosis in Alzheimer's disease, why mitochondria are a valid therapeutic target, and strategies for addressing AD-specific mitochondrial dysfunction.

Keywords

Alzheimer's disease; autophagy; bioenergetics; biogenesis; fission; mitochondria; mitochondrial DNA; mitochondrial dysfunction; mitochondrial medicine

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized clinically by cognitive decline and memory loss. It is estimated that approximately 5.4 million Americans suffer from AD (Thies and Bleiler, 2011). One in eight individuals over 65 have AD, and 40–50% of those over 85 years of age are affected (Evans et al., 1989).

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Mutations in the amyloid precursor protein (APP) gene and in two genes that encode proteins that participate in, among other things, APP processing associate with rare, autosomal dominant, pre-senile AD cases (Goate et al., 1991; Levy-Lahad et al., 1995; Sherrington et al., 1995; Wolfe et al., 1999). The vast majority of AD, however, occurs in individuals over the age of 65, and both prevalence and incidence increase with advancing age. This suggests that age-related physiologic changes play a critical role in the vast majority of those affected with AD (Corrada et al., 2008; Corrada et al., 2010).

Although much remains to be learned about both AD etiology and pathogenesis, it is clear that mitochondrial function in the brains of AD subjects differs from those of non-AD subjects. Equally interesting, and perhaps pertinent to the issue of AD etiology, is the fact that mitochondrial function in the non-brain tissues of AD subjects also differs from that of control subjects. This review will discuss mitochondrial dysfunction and its potential role in AD, and will emphasize data that show bioenergetic homeostasis is perturbed in AD.

Is sporadic Alzheimer's disease a primary or secondary amyloidosis?

In 1906, Alois Alzheimer described a 55-year old patient with severe dementia. Post-mortem evaluation revealed extensive amyloid plaques in this patient's cerebral cortex (Alzheimer, 1907; Verhey, 2009). In the 1970s, Katzman and colleagues extended the term "Alzheimer's disease" to include senile dementia, a condition not previously thought to critically overlap with the pre-senile dementia disorder described by Alzheimer. This was accomplished by using the presence of amyloid plaques and neurofibrillary tangles to argue the existence of a common etiology, and infer that all tangle and plaque dementias were a single disease (Katzman, 1976). The identification of deterministic mutations within the APP gene, from which beta amyloid ($A\beta$) derives (Goate et al., 1991), subsequently gave rise to the amyloid cascade hypothesis (Hardy and Allsop, 1991; Hardy and Higgins, 1992). This hypothesis has profoundly influenced AD conceptual thinking. Most investigators in the AD field currently assume that pre-senile, autosomal dominant cases of AD with APP mutations are instigated through abnormal amyloid processing, although the possibility that disease arises as a consequence of perturbed APP function has not been fully excluded (Galvan et al., 2006).

Problems arise when using the amyloid cascade hypothesis to explain the pathophysiology of senile, sporadic forms of AD. For example, unlike in autosomal dominant forms, no apparent mutations exist in APP or processing proteins. Even genetic polymorphisms in APP seem to have little or no effect on sporadic AD risk (Guyant-Marechal et al., 2007). Amyloid levels in the brain can exist in the absence of clinical symptoms, and elevated $A\beta$ levels preclude biochemical and clinical signs of neurodegeneration by years. Also, it is well recognized that elevated brain parenchyma $A\beta$ does not necessarily associate with clinical dementia (Berlau et al., 2009; Sperling et al., 2011). If amyloidosis were sufficient to cause disease, it seems unlikely that individuals with elevated $A\beta$ could remain asymptomatic for so long.

A key point to keep in mind, though, is that even if all AD cases include brain amyloidosis, the question of whether particular forms of AD represent primary or secondary amyloidoses must still be considered. The extremely rare APP mutation cases have the highest likelihood of being primary amyloidoses. In the absence of deterministic mutations, other physiologic events may be required to induce amyloidosis. If this presumption is correct then these cases are secondary amyloidoses. Recently, it has become abundantly clear that APP metabolism is an exquisitely regulated process, and bioenergetic status or states indeed regulate APP metabolism (Gabuzda et al., 1994; Gasparini et al., 1997; Khan et al., 2000; Webster et al., 1998).

Mitochondria in AD

Mitochondrial structural and functional perturbations in AD have been recognized for some time. For example, in 1985 the morphology of mitochondria in degenerating dendrites from brains of AD patients was noted to be abnormal, and postulated to perhaps even precede dendritic degeneration (Saraiva et al., 1985). One year later, Peterson et al. described altered calcium homeostasis in AD patient fibroblasts, a finding potentially consistent with the presence of a systemic bioenergetic defect (Peterson and Goldman, 1986). The activities of several mitochondria-localized enzymes, including α -ketoglutarate dehydrogenase complex and pyruvate dehydrogenase complex, are reduced in AD, and this observation encouraged some to propose AD is a disease of perturbed brain energy metabolism (Blass et al., 2002; Gibson et al., 1998; Gibson et al., 1988; Sorbi et al., 1983).

Cytochrome oxidase activity is systemically reduced in AD

Cytochrome oxidase (COX) is the final enzyme in the mitochondrial respiratory electron transport chain (ETC). It receives electrons from cytochrome c. Mammalian COX exists as a dimer with 13 protein subunits per monomer. Ten are encoded by nuclear and three by mitochondrial DNA (mtDNA) genes. In addition to its protein moiety, COX contains two redox active hemes and two redox active copper centers.

In 1990, Parker et al. reported that AD patients have a non-brain limited reduction in COX activity, as the COX defect in this study was observed in AD subject platelet mitochondria (Parker et al., 1990). This observation was subsequently confirmed in brains of AD patients (Kish et al., 1992). Since then, other studies and investigators have documented that COX activity is systemically altered in AD subjects (Bosetti et al., 2002; Cardoso et al., 2004a; Curti et al., 1997; Mutisya et al., 1994; Parker et al., 1994; Parker and Parks, 1995; Swerdlow, 2011b; Wong-Riley et al., 1997). COX reduction has also been reported to occur at the mild cognitive impairment (MCI) stage of AD (Valla et al., 2006).

Animal studies suggest COX dysfunction may represent an early manifestation of A β toxicity. In AD mouse models, A β co-localizes with mitochondria, and A β also appears to co-localize with mitochondria in human AD brains (Caspersen et al., 2005; Crouch et al., 2005; Hansson Petersen et al., 2008; Lustbader et al., 2004; Manczak et al., 2006). APP transgenic mice display early evidence of mitochondrial perturbation, as manifested by an increased expression of COX genes at only two months of age (Reddy et al., 2004).

The role of COX dysfunction in AD, whether genetically transmitted, somatically acquired, or induced through toxic insults such as A β has been debated (Farber et al., 2000; Parker et al., 1990; Swerdlow, 2011b; Swerdlow and Kish, 2002). In addition to A β , another candidate toxic insult derives from studies of metal and ion toxicity. It is known that Al³⁺, Fe³⁺ and Ca²⁺ are elevated in AD brains (Good et al., 1992; Huang et al., 2004; Ito et al., 1994). Alleyne and colleagues (Alleyne et al., 2011), using a rabbit model (Klatzo et al., 1965), evaluated the impact of elevated metal ions on brain COX catalytic activity ($V_{\max}$) and substrate binding ability (K_m). They reported that 10 days after intra-cerebral injection of 1.4% solutions of AlCl₃, FeCl₃, CaCl₂, or MgCl₂, the isolated brain mitochondria showed significantly decreased COX $V_{\max}$ activities. The increased metal ion content that developed within the mitochondria enhanced the ionic strength of the inter-membrane space, which slowed the interaction between COX and its substrate, cytochrome c. One immediate consequence of this included excess oxygen radical production, which damaged the enzyme itself, damaged surrounding structures, and decreased ATP synthesis.

AD mitochondrial dysfunction is perpetuated in cybrid cell lines

Experimental data exist that suggest COX impairment is a downstream consequence, and not an initiating cause, of AD pathology. In the study by Fukui et al., it was found that the brains of mice expressing mutant APP and mutant presenilin 1 in a neuron-specific COX-deficient background exhibited significantly fewer amyloid plaques, a reduction in A β 42 levels, and reduced oxidative changes as compared to COX-competent transgenic mice (Fukui et al., 2007). The authors of this study concluded that COX impairment may not be responsible for A β accumulation in the AD brain.

Other data though, argue that the systemic AD COX defect can drive a number of disease-typical pathologic phenomena. Much of these data derive from studies of cytoplasmic hybrid (cybrid) cell lines; cybrid studies further suggest mtDNA is also at least partly responsible for reduced COX activity in AD patients (Swerdlow et al., 1997). When platelet mtDNA from AD patients is expressed within neuronal cell lines grown in culture, the resulting cybrid cell lines manifest a reduction in COX activity (Figure 1). This specific biochemical defect persists over time in the AD cybrid lines (Swerdlow, 2007; Swerdlow, 2011b; Swerdlow et al., 1997). It has further been observed that cybrid lines containing AD subject mitochondria/mtDNA overproduce oxygen radicals, accumulate A β , and have decreased ATP levels compared to control cybrid lines containing mtDNA from unaffected individuals (Cardoso et al., 2004b; Khan et al., 2000; Swerdlow, 2007). Since three of the 13 COX subunits are encoded by mtDNA, this phenomenon suggests mtDNA differs between AD patients and control subjects, and supports the view that mtDNA contributes to the AD-associated COX activity reduction. Taken together, these results support hypotheses which place mitochondrial dysfunction at the center of AD pathogenesis (Swerdlow et al., 2010; Swerdlow and Khan, 2004; Swerdlow and Khan, 2009; Swerdlow et al., 1997).

Mitochondrial cascade hypothesis

The apparent importance of mitochondria in AD and the inability of A β protein accumulation to fully account for the epidemiology and pathology of sporadic AD, as well as systemic biochemical perturbations in AD subjects, led Swerdlow and Khan to propose the mitochondrial cascade hypothesis (Swerdlow and Khan, 2004). Briefly, this hypothesis proposes that inherited mutations in mtDNA determine the basal functional ability of mitochondria and their ability to respond to and recover from stress signaling that is mediated by molecules such as reactive oxygen species (ROS). At the point at which a critical threshold of mitochondrial dysfunction is reached, the histopathology of AD develops, and includes neuronal apoptosis, β -amyloid deposition, and neurofibrillary tangles (Figure 2).

Maternal transmission of AD

Although gene mutations have been identified in the early onset familial forms of AD, and some risk factor genes have been uncovered in the far more common late-onset forms (Corder et al., 1993), the genetic factors that influence sporadic AD risk are overall less clear-cut. Other such factors likely exist, though, since for cognitively normal individuals of advanced age having a first-degree family history of late-onset AD constitutes a robust risk factor (Farrer et al., 1997; Silverman et al., 1994). First-degree relatives of affected probands have a four to tenfold higher risk of developing AD than the general population, with some variability depending on which family members are affected (Cupples et al., 2004; Green et al., 2002; Silverman et al., 2005).

The possibility that maternally inherited mtDNA may influence disease risk and pathology has been considered. While several studies conclude there is no evidence of a unique maternally-inherited AD risk factor or even that there is predominant paternal transmission

(Ehrenkrantz et al., 1999; Payami and Hoffbuhr, 1993), other epidemiological studies find maternal inheritance strongly influences AD risk (Duara et al., 1993; Edland et al., 1996). Among AD patients with one affected parent, the ratio of mothers to fathers affected is 3:1. For cases in which affected proband relations include one affected parent and at least one sibling, the mother to father ratio increases to 9:1 (Edland et al., 1996).

Brain imaging techniques also provide evidence of a unique maternal genetic contribution. Positron emission tomography (PET) imaging, when using 2-[¹⁸F] fluoro-2-deoxy-D-glucose (FDG) as the ligand, can be used to determine the cerebral metabolic rate of glucose (CMR_{glc}). It has been demonstrated that in AD patients, CMR_{glc} is reduced in several neuroanatomic areas including the parietotemporal, posterior cingulate, and to a lesser extent frontal cortex and medial temporal lobe regions (Mosconi, 2005). These reductions occur years before AD symptom onset (Jack et al., 2010). One FDG-PET study reported that cognitively normal subjects (aged from 46–80) with AD mothers but not AD fathers had AD-like patterns of CMR_{glc} reduction even after accounting for other possible AD risk factors including age, gender, education, apolipoprotein E (APOE) genotype, and subjective memory complaints (Mosconi et al., 2007).

In a related study, COX activity was determined in platelet mitochondria from 36 cognitively normal individuals with or without a family history of late-onset AD. It was found that the subjects with an AD-affected mother had 30% lower COX activity when compared to subjects with a paternal history or no family history. No differences were found between the latter two groups (Mosconi et al., 2011). This result remained significant even after controlling for age, gender, education, and APOE genotype.

Other studies report evidence of a maternally-inherited AD endophenotype. These studies include demonstrations of increased brain amyloid deposition in the cognitively intact children of AD mothers, increased isoprostanes and AD-like Aβ₄₂ changes in cerebrospinal fluid from cognitively intact children of AD mothers, increased degrees and rates of brain atrophy in cognitively intact children of AD mothers, and a potential relative softening of memory test performance in cognitively intact children of AD mothers (Berti et al., 2011; Debette et al., 2009; Honea et al., 2011; Honea et al., 2010; Mosconi et al., 2010a; Mosconi et al., 2009; Mosconi et al., 2010b).

AD endophenotype and some epidemiologic studies, therefore, infer that although maternal and paternal inheritance influences AD risk, maternal inheritance has a bigger impact. These studies, though, cannot directly prove that mtDNA represents the responsible genetic factor, although reduced COX activity in the children of AD mothers, as well as AD cybrid data, indicate mtDNA should be strongly suspect. The rules of mitochondrial genetics, which deviate from those of Mendelian genetics, also make mtDNA a particularly attractive candidate. Indeed, a hypothesis of mtDNA-mediated sporadic disease inheritance was previously proposed by Parker (Parker, 1990). This hypothesis stresses that, due to factors such as maternal inheritance, heteroplasmy, threshold, and mitotic segregation, mtDNA inheritance may not only give rise to matrilineal patterns of disease transmission, but also to apparent sporadic disease transmission.

Heteroplasmy refers to the fact that not all mtDNA molecules within a cell are equivalent. Different distributions of a heteroplasmic mutation may allow the sparing versus impairment of different brain regions, and also mtDNA variation between oocytes. Thus, as individual mitochondria segregate during embryonic development, major regional differences in mtDNA may result (Parker et al., 1990; Swerdlow and Khan, 2004).

Mitochondrial function affects A β processing

Accumulating data indicate mitochondrial bioenergetics, bioenergetic homeostasis, and probably brain metabolism in general affect APP processing (Brody et al., 2008; Gabuzda et al., 1994; Gasparini et al., 1997; Kang et al., 2009; Khan et al., 2000; Webster et al., 1998). To better understand this phenomenon, it is worth considering how mitochondrial function impacts certain cell signaling pathways.

NAD⁺/NADH ratio and the cell redox status

Mitochondria oxidize reduced NADH to NAD⁺. This activity is integrated into other cell bioenergetics-related pathways, such as glycolysis, which requires the presence of NAD⁺ to proceed. The primary role of complex I (NADH:ubiquinone oxidoreductase) in the ETC is to accept high energy electrons from NADH, which is produced during glycolysis, the tricarboxylic acid cycle, or other specific redox reactions. A malate-aspartate shuttle allows the transfer of NADH reducing equivalents from the cytosol and into the mitochondrial matrix. When mitochondria are inhibited experimentally or functioning suboptimally, the ratio of NAD⁺/NADH within the cell can substantially decrease (Braidy et al., 2011; Schuchmann et al., 2001; Stefanatos and Sanz, 2011). Conversely, cells with relatively healthy mitochondria may have a high NAD⁺/NADH ratio. NAD⁺ is utilized by and activates other enzymes, including the sirtuin (silent mating type information regulation two homolog) family of proteins. Sirtuins are increasingly believed to play roles in neuroprotection and longevity, and sirtuins may represent AD therapeutic targets (Guarente, 2011; Lombard et al., 2011; Rahman and Islam, 2011; Zhang et al., 2011a; Zhang et al., 2011b).

Recently, sirtuin 1 protein, which is encoded by the gene SIRT1, has been shown to play a potential role in APP processing. In 2010, Donmez et al. showed that sirtuin 1 upregulates expression of ADAM10, which encodes an α -secretase (Donmez et al., 2010). Specifically, the authors showed that in a transgenic mouse model of AD, co-transgenic overexpression of SIRT1 resulted in a significant reduction of amyloid plaques and A β 42 levels. Brain-specific deletion of SIRT1 induced significant mortality at age 3–5 months in mice transgenic for mutant human APP and presenilin transgenes. It was further demonstrated that SIRT1 overexpression resulted in significantly higher α -secretase protein levels, which coincided with increased levels of α -secretase cleavage products. From a mechanistic perspective, sirtuin 1 seemed to interact with and deacetylate the retinoic acid receptor β (RAR β) to increase ADAM10 transcription, as the ADAM10 promoter contains a retinoic acid receptor element (Figure 3).

By shifting the cell NAD⁺/NADH redox balance towards a more reduced state, mitochondrial dysfunction could reduce the amount of NAD⁺ that is available to sirtuin 1. This in turn could reduce α -secretase levels and divert APP processing towards its β -secretase derived A β product.

Oxidative stress

Oxidative stress is believed to represent an early manifestation of AD pathology (Nunomura et al., 2001). Numerous studies indicate that AD brains have oxidized RNA, nuclear and mtDNA, lipids, and proteins (Gabbita et al., 1998; Mecocci et al., 1994; Nunomura et al., 1999; Sayre et al., 1997; Smith et al., 1991). It has long been held that mitochondria are the primary source of intracellular ROS, and that elevated ROS may correlate with mitochondrial dysfunction (Shigenaga et al., 1994). Depending on cell type and intracellular localization, ROS can have a vast array of functions, some beneficial and necessary, others detrimental and pathological (Finkel, 2011). Considerable data perhaps implicate a

mechanistically relevant role for ROS in AD. In particular, evidence suggests elevated ROS upregulate A β production (Tamagno et al., 2002).

Studies in COS, PC12, and neuroglioma cell lines indicate that perturbation of mitochondrial function with sodium azide, oligomycin, or carbonyl cyanide m-chlorophenylhydrazone shifts APP processing away from its α -secretase cleavage, thus decreasing soluble APP derivatives and likely promoting the amyloidogenic beta secretase-mediated cleavage of APP (Gabuzda et al., 1994; Gasparini et al., 1997; Webster et al., 1998). In one study, glutathione supplementation restored soluble APP processing, suggesting oxidative stress was to some degree responsible for diverting APP processing away from the α -secretase cut (Gasparini et al., 1997).

The identification of signaling molecules sensitive to ROS has helped to further implicate a role for ROS in driving amyloidosis (Figure 4). For example, a 1998 report by Saitoh et al. reported the redox homeostatic protein thioredoxin binds to and inactivates the mitogen activator protein kinase kinase kinase (MAPKKK) ASK1 (apoptosis signal-regulating kinase) (Saitoh et al., 1998). ROS can directly oxidize thioredoxin, and when this occurs thioredoxin dissociates from ASK1 (Finkel, 2011; Gotoh and Cooper, 1998; Saitoh et al., 1998; Shen and Liu, 2006). Free ASK1 can undergo phosphorylation, and subsequently activate its downstream targets. One of these targets includes c-Jun N-terminal kinase (JNK) (Filomeni et al., 2003; Filomeni et al., 2005).

In addition to its upregulation by ASK1, ROS may activate JNK through other mechanisms (Figure 4). Adler et al. showed that glutathione S-transferase (GST) associates with and inhibits JNK (Adler et al., 1999a; Adler et al., 1999b). This may partly explain why, in the absence of oxidative stress, JNK activity tends to remain low. In the presence of oxidative stress, however, GST is oxidized. Oxidized GST no longer binds JNK, thus preventing GST-mediated JNK inhibition.

Recently, Guo et al. showed that anisomycin-induced JNK activation significantly increased A β production in SH-SY5Y neuroblastoma cells (Guo et al., 2011). These investigators further showed that activation of JNK caused upregulation of APP, β -site APP cleaving enzyme 1 (BACE1), and the presenilin 1 gene through demethylation of their respective promoters and histone deacetylation. These effects would collectively be expected to increase A β production. Studies such as these provide additional insight into how a primary mitochondrial defect might drive amyloidosis.

Mitochondrial biomass and homeostasis in AD

Because of their high energy demands, neurons are especially dependent on mitochondrial dynamics, and tightly control their mitochondrial mass (Santos et al., 2010). When neurons accumulate dysfunctional mitochondria or experience increased metabolic or bioenergetic demands, they must pursue one or a combination of several strategies to ensure sustained function. One response includes autophagy, an important mechanism through which abnormal mitochondria are decommissioned and eliminated. Fusion and fission events help traffic abnormal mitochondria toward autophagic processing, and help maintain normal mitochondrial numbers throughout the neuron. Biogenesis produces new mitochondria and increases mitochondrial mass. Evidence suggests that cells tightly regulate mitochondrial fission, fusion, autophagy, and biogenesis in order to maintain a healthy mitochondrial population (Twig et al., 2008b).

Mitochondrial autophagy in AD

Autophagy helps cells eliminate unnecessary cytoplasmic contents via phagosome formation and lysosomal degradation (Yang and Klionsky, 2011; Youle and Narendra, 2011). In hepatic cells, inhibition of mitochondria by the antiretroviral drug efavirenz significantly upregulates mitochondrial autophagy, and ultimately appears to have a protective effect (Apostolova et al., 2011a; Apostolova et al., 2011b). Findings like these support the view that autophagic elimination of dysfunctional mitochondria under some conditions could prove physiologically advantageous. This may have important implications for AD, since AD is characterized by the presence of dysfunctional mitochondria.

In 2001, Hirai et al. reported that when mtDNA contained within phagocytized mitochondria are specifically accounted for, AD subject hippocampal neurons can actually contain elevated levels of mtDNA (Hirai et al., 2001). This finding suggests that mitochondrial autophagy rates are increased in AD. It has also been shown that in AD brains other mitochondrial components such as COX and lipoic acid, a cofactor utilized by pyruvate dehydrogenase and α -ketoglutarate dehydrogenase, concentrate within autophagosomes (Hirai et al., 2001; Moreira et al., 2007b). Ultrastructural analysis of dystrophic neurites in AD brains indicates that most organelles present are autophagosomes, further supporting the view that autophagy is increased in AD neurites (Nixon et al., 2005). In healthy neurons, by contrast, autophagosome accumulation is rarely observed (Boland et al., 2008; Nixon and Yang, 2011).

Some studies find that autophagic fluxes are impaired in AD (Cataldo et al., 1995; Nixon and Yang, 2011), which could potentially account for increased numbers of autophagosomes in AD neurons. Whether increased mitochondrial autophagy in AD is due to a break-down in autophagy pathways or increased flux through functioning autophagy pathways remains to be seen. The need to dispose of elevated numbers of dysfunctional mitochondria could conceivably lead to either or both possibilities.

Several pathways that monitor cell energy status link mitochondria with autophagy and permit mitochondrial function to regulate autophagy activity. Nutrient deprivation and decreased bioenergetic capacity of cells have been shown to inhibit cytosolic mammalian target of rapamycin (mTOR) signaling (Noda and Ohsumi, 1998; Scott et al., 2004; Tee et al., 2005). Inhibition of mTOR allows the initiation of autophagosome formation (Crespo et al., 2005), thus promoting autophagy. Decreased mitochondrial function can also increase cell AMP/ATP ratios. Elevating AMP relative to ATP activates AMP kinase (AMPK), which modifies a wide range of cellular functions in order to maintain energy homeostasis (Carling et al., 1994; Hardie and Hawley, 2001; Mihaylova and Shaw, 2011). Interestingly, AMPK can inhibit the mTOR signaling pathway, and thus upregulate autophagy (Meley et al., 2006), suggesting that high cellular AMP levels due to mitochondrial dysfunction may activate autophagic clearance of mitochondria. Indeed, one study found that in AD patients, lymphocyte mTOR levels directly correlate with cognitive decline (Paccalin et al., 2006). This study is consistent with the view that systemic mitochondrial deficits occur in AD, and further suggests a potential role for perturbed mTOR signaling-autophagy relationships in AD.

Mitochondrial fission and fusion

Mitochondrial fission and fusion are necessary for proper mitochondrial function (Santos et al., 2010). For example, inhibition of fusion by genetic knockout of mitofusin 2 (Mfn2) causes severe mitochondrial dysfunction that drives neuronal degeneration (Chen et al., 2007).

Impaired fission also interferes with the cell's ability to target dysfunctional mitochondria for autophagic removal. It is believed that fission divides a dysfunctional mitochondrion into two unequal daughter mitochondria, one with seemingly normal mitochondrial markers and the other with dysfunctional markers. The dysfunctional daughter unit is then packaged for autophagy, while the healthy unit is free to undergo fusion (Twig et al., 2008a).

In AD, fission seems to be particularly perturbed (Manczak et al., 2011; Wang et al., 2008a; Wang et al., 2009; Wang et al., 2008b). This phenomenon is not brain limited, but appears to also apply to fibroblasts from sporadic AD subjects (Wang et al., 2008a). Wang et al. reported that in 19% of fibroblasts from AD patients, mitochondria were excessively localized to the perinuclear region and were dramatically elongated. Additionally, it was found that dynamin-related protein 1 (Drp1), a protein that plays a major role in mitochondrial fission, was significantly decreased and that experimental over-expression of Drp1 in these cells rescued the abnormal mitochondrial morphology. In this study, the exaggerated mitochondrial perinuclear distribution further emphasizes that fission-fusion dynamics influence mitochondrial transport, since abnormally sized mitochondria may distribute throughout the cell differently than normal mitochondria.

In possible contrast to the Wang et al. study, Manczak et al. more recently reported Drp1 mRNA and protein were increased in AD subject autopsy brains (Manczak et al., 2011). However, this group also described a significant increase in Fis1, a mitochondrial fission protein, and a decrease in the Mfn1 and Mfn2 fusion proteins. These findings further support the case that mitochondrial fission and fusion are disrupted in AD.

Mitochondrial biogenesis

Mitochondrial biogenesis is the process by which cells generate new mitochondria and, if necessary, increase mitochondrial mass. This process involves coordinated expression of proteins encoded by nuclear and mitochondrial DNA. To accomplish this, peroxisome proliferator-activated receptor γ coactivator 1 α (PGC1 α) coordinates mitochondrial biogenesis in at least some tissues such as muscle, heart, liver, and pancreas via co-activation of various transcription factors (Finck et al., 2006; Finck and Kelly, 2006; Lehman et al., 2000; Lin et al., 2002; Onyango et al., 2010; Rhee et al., 2003).

PGC1 α is regulated by several metabolism-responsive elements. Sirtuin 1, which is activated by NAD⁺, de-acetylates PGC1 α . This is an activating de-acetylation that helps to increase mitochondrial biogenesis (Lagouge et al., 2006; Nemoto et al., 2005). AMP kinase (AMPK), which is activated by elevated AMP/ATP ratios, can phosphorylate and thus directly activate PGC1 α (Jager et al., 2007; Reznick and Shulman, 2006). For example, AMPK activation of PGC1 α in rat visual cortical neurons increases mitochondrial mass (Yu and Yang, 2010). AMPK can also modulate the activities of other proteins, such as mTOR and forkhead box containing protein O (FOXO), to further affect PGC1 α activity (Cunningham et al., 2007; Daitoku et al., 2003; Greer et al., 2009; Nakae et al., 2008a; Nakae et al., 2008b).

It was recently shown that PGC1 α mRNA and protein levels are reduced in AD subject brains (Qin et al., 2009; Sheng et al., in press; Swerdlow, 2011a). Even if PGC1 α changes represent a consequence as opposed to cause of AD pathology, PGC1 α remains an attractive target for therapeutic intervention. Whether mitochondrial mass changes in AD constitute an upstream or downstream physiologic event, it is reasonable to postulate that increasing mitochondrial mass may alleviate bioenergetics-related stress in the AD brain.

Mitochondrial transport

Evidence suggests that mitochondria can be rapidly transported to areas of high bioenergetic demand as required by the neuron (Hollenbeck and Saxton, 2005; MacAskill et al., 2010). This mitochondrial transport appears to be important for the development, stability, and function of synapses and dendritic spines (Li et al., 2004; Mattson et al., 2008), and impaired mitochondrial trafficking has been implicated in a number of neurodegenerative disorders such as Huntington's disease (Reddy and Shirendeb, 2011), Parkinson's disease (Sterky et al., 2011), and amyotrophic lateral sclerosis (De Vos et al., 2007). Altered mitochondrial transport may also play a role in AD (Wang et al., 2008a). One study found that mitochondrial transport in AD patient brains was decreased compared to control brains (Dai et al., 2002). Trimmer and Borland showed that the transport of fluorescently-labeled mitochondria in cybrids generated from AD patients is significantly reduced compared to control cybrids, suggesting that mitochondrial transport may be impaired in AD (Trimmer and Borland, 2005). Mitochondrial transport may also be altered in mouse models of AD (Calkins et al., 2011; Massaad et al., 2010; Pigino et al., 2003) and in cell cultures treated with A β (Calkins and Reddy, 2011). These studies together argue that impaired mitochondrial transport impacts the pathogenesis of AD.

Mitochondria as an AD therapeutic target

Data discussed thus far suggest that abnormal mitochondrial dynamics and function play an important role in AD neurodysfunction and neurodegeneration. Certainly, if anti-amyloid treatments are found to inadequately benefit AD patients (Herrmann et al., 2011), alternative targets such as mitochondrial function will prove increasingly important.

Antioxidants

To date, a variety of compounds with free radical scavenging properties have been evaluated in AD subjects or AD models. Lipoic acid, a coenzyme of mitochondrial pyruvate dehydrogenase and α -ketoglutarate dehydrogenase, is an antioxidant that readily penetrates the blood-brain barrier. It can chelate redox-active transition metals, reduce inflammation, and increase levels of acetylcholine, a neurotransmitter which is severely reduced in some AD structures (Bielarczyk et al., 2006). It can also recycle other antioxidants such as vitamin C, vitamin E, and glutathione (Su et al., 2010). Lipoic acid treatment has been shown to improve cognition and AD-related pathology in Tg2576 mice that express a mutant human APP transgene (Quinn et al., 2007). A cell-culture based study has also demonstrated that lipoic acid with or without N-acetyl cysteine decreases oxidative stress and apoptotic markers in AD subject fibroblasts (Moreira et al., 2007a). A clinical study of 43 AD patients reported that over the course of approximately one year, taking 600 mg per day of lipoic acid appeared to slow disease progression as measured by neuropsychological tests (Hager et al., 2007). This study, though, was not placebo-controlled, double-blinded, or randomized and therefore more conclusive studies are needed.

Coenzyme Q10 (CoQ10), which participates in ETC electron transfer, also functions as an endogenous antioxidant. In the ETC, CoQ10 accepts electrons from complex I and II. Animal studies using aged APP/presenilin 1 transgenic mice report oral CoQ10 attenuates oxidative stress, tau-related pathology, intracellular A β levels, and amyloid plaque deposition (Yang et al., 2010; Yang et al., 2008). Idebenone, a water-soluble, synthetic variant of CoQ10, has also been tested in AD patients. Two randomized, double-blind, placebo-controlled studies with over 300 mild-to-moderate AD patients reported that idebenone (90 mg three times daily) for either one year (Gutzmann and Hadler, 1998; Weyer et al., 1997) benefited cognitive outcome measures. A third idebenone trial tested three different idebenone doses (120, 240, or 360 mg) in 536 AD subject. Although each

individual dose failed to demonstrate clinical benefits, when all three idebenone groups were combined, cognitive decline overall appeared to slow in the idebenone-treated subjects (Thal et al., 2003).

When it comes to designing potential antioxidant approaches, cell compartmentalization issues require consideration. Antioxidants that only access the cytosol may have a limited impact on mitochondrial ROS (Su et al., 2010). To address this concern, a mitochondrial-targeted antioxidant, MitoQ, has been produced by conjugation of the lipophilic triphenylphosphonium cation to coenzyme Q (Murphy and Smith, 2000). This molecule's cationic properties allow it to concentrate within negatively charged mitochondrial matrices.

Studies have shown that in N2a neuroblastoma cells and primary neurons from Tg2576 mice, MitoQ treatment mitigates the effects of A β exposure, which include altered peroxiredoxin expression, altered mitochondrial structural gene expression, mitochondrial oxidative stress, reduced COX activity, and reduced ATP levels (Manczak et al., 2010). Another study reported that MitoQ prevents A β -induced long-term potentiation impairments in hippocampal slices from transgenic mice (Ma et al., 2011). These results suggest mitochondrial antioxidant targeting may confer more robust physiologic effects than non-targeted antioxidants. This is important because antioxidant trials in AD have to date yielded disappointing results.

PGC1 α

As discussed above, PGC1 α is a key regulator of mitochondrial biogenesis and respiration. In the first reported study of AD brain PGC1 α levels, Qin et al. analyzed postmortem brain samples and found that relative to control brains PGC1 α mRNA expression and protein levels were decreased (Qin et al., 2009). PGC1 α expression was negatively associated with both AD-type neuritic plaque pathology and total A β levels, suggesting that either A β interferes with PGC1 α , or that reduced amyloidosis is a downstream effect of sustained PGC1 α expression. This study went on to show that viral-mediated PGC1 α expression in primary Tg2576 cortico-hippocampal neurons reversed glucose-induced A β peptide production.

Overexpression of PGC1 α also protects neurons from degeneration induced by oxidative stress or mutant huntingtin, and increases neurite mitochondrial density (Cui et al., 2006; St-Pierre et al., 2006; Wareski et al., 2009). Overall, data suggest reversing the AD PGC1 α deficit, or otherwise enhancing PGC1 α activity or expression, constitutes a reasonable AD therapeutic target.

Exercise

Exercise has been shown to decrease ROS production rates in different organs, including the brain (Molteni et al., 2004; Ogonovszky et al., 2005; Radak et al., 2001). Given that there are abnormal levels of oxidative stress in AD brains, exercise may help to mitigate this phenomenon. In one pertinent study that used 13-month old NSE/APPsw transgenic mice, a 16-week treadmill running intervention (13.2m/min, 60min/day, 5 days/week) improved spatial learning and memory, significantly decreased A β 42 protein levels, and increased brain superoxide dismutase-1 and catalase expression (Cho et al., 2010). These data are consistent with data from studies of TgCRND8 and 3xTg AD mice that found voluntary wheel running reduced plaque formation (Adlard et al., 2005; Garcia-Mesa et al., 2011).

Since physical exercise most likely indirectly affects the brain, exercise's brain effects are presumably mediated by reducing some factor that is normally within the brain, or else by adding a factor. Regarding the latter possibility, one candidate that has not previously been considered is lactate. Lactate is generated through sustained or repetitive muscle contraction.

Several human studies using nuclear magnetic resonance spectroscopy techniques have shown blood lactate can constitute an important neuron energy fuel that is ultimately consumed and oxidized within mitochondria (Boumezbeur et al., 2010; Gallagher et al., 2009; Quistorff et al., 2008; van Hall et al., 2009; Wyss et al., 2011). Lactate generated via astrocyte glycolysis increasingly appears to serve as a key neuron energy fuel that is essential for long-term memory formation (Suzuki et al., 2011). Glucose and lactate are not functionally interchangeable, which suggests lactate may play a unique role in brain bioenergetic metabolism. Further studies are needed to explore whether exercise-produced lactate can specifically supplement a neuron's astrocyte-derived lactate supply.

Although cell and animal based studies suggest exercise training impacts brain mitochondria and A β accumulation at least in mice (Adlard et al., 2005; Boveris and Navarro, 2008), to date no studies have tested whether lactate contributes in any way to these effects. If lactate does play a role, it would have important implications for a commonly asked question: how much and what forms of exercise are likely to have the most robust impact on the brain?

Conclusions

It increasingly appears that mitochondria play an important role in AD pathogenesis. In AD subjects, mitochondrial dysfunction is not brain-localized, but rather appears to be systemic. By influencing cell bioenergetic states and fluxes, as well as the cell redox environment, mitochondria are in a position to influence brain amyloidosis. In this capacity it is conceivable that in the AD brain, mitochondrial dysfunction actually lies upstream of brain amyloidosis. Moreover, various aspects of mitochondrial function, maintenance, and homeostasis are perturbed in AD, and many of these disrupted physiologies could potentially serve as AD therapeutic targets.

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Abbreviations

Aβ	beta amyloid
AD	Alzheimer's disease
ADAM10	a disintegrin and metalloproteinase domain-containing protein 10
AMP	adenosine monophosphate
AMPK	AMP kinase
APOE	apolipoprotein E
APP	amyloid precursor protein
ASK1	apoptosis signal-regulating kinase
BACE	β -site APP cleaving enzyme 1
CMR_{glc}	cerebral metabolic rate of glucose
COX	cytochrome oxidase
Drp1	dynammin-related protein 1
EtBr	ethidium bromide

FDG	2-[¹⁸ F] fluoro-2-deoxy-D-glucose
Fis1	fission 1
FOXO	forkhead box containing protein O
GST	glutathione-S-transferase
JNK	c-Jun N-terminal kinase
Mfn	mitofusin
mtDNA	mitochondrial DNA
mTOR	mammalian target of rapamycin
NAD	nicotinamide adenine dinucleotide
PET	positron emission transmission
PGC1α	peroxisome proliferator-activated receptor- γ -coactivator 1 α
ROS	reactive oxygen species
SIRT	silent mating type information regulation two homolog

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Highlights

- Alzheimer's disease patients have systemic mitochondrial dysfunction
- Mitochondrial dysfunction in Alzheimer's disease may drive other pathologies
- Mitochondrial autophagy, fission, fusion, and biogenesis are altered in Alzheimer's
- Mitochondria represent a reasonable Alzheimer's disease therapeutic target

Figure 1.

Generation of cybrid cell lines. Tumor or immortalized cell lines are grown in the presence of ethidium bromide, which effectively eliminates functional mtDNA to result in a $\rho 0$ cell line. $\rho 0$ cells are then fused with a patient's platelets, which contain mitochondria but not nuclei. This creates cytoplasmic hybrid (cybrid) cells that can be isolated and expanded. The expanded cybrid cell cultures are biochemically analyzed. Differences in function between cell lines mostly likely arise through differences in their mtDNA.

Figure 2.

Mitochondrial cascade hypothesis. Bi-parental inheritance of genes required for mitochondrial function and maintenance, as well as the specific maternal inheritance of mitochondrial genes, determines intrinsic mitochondrial function and durability. Over time, mitochondrial injuries accumulate and these injuries perturb mitochondrial function. While these perturbations are initially compensated for, compensatory changes eventually prove inadequate and a critical point is reached where the neuron comes to favor anaerobic over aerobic bioenergetics. Activation of various cell stress pathways, combined with a shift from an aerobic to an anaerobic bioenergetic profile, gives rise to AD-typical histology changes including A β accumulation in the brain parenchyma, tau phosphorylation and neurofibrillary tangle formation in neurons, and synaptic degeneration,

Figure 3.

Role of NAD⁺/NADH in APP processing. In the mitochondria, NADH is oxidized to NAD⁺, which in turn increases cytosolic NAD⁺. Cytosolic NAD⁺ activates sirtuin 1, which leads to de-acetylation of retinoic acid receptor β. De-acetylation of retinoic acid receptor β allows it to interact with the α-secretase promoter and increase α-secretase expression. α-secretase-mediated APP cleavage prevents processing of APP to Aβ.

Figure 4.

Role of ROS in APP processing. (A) Excess ROS are produced by dysfunctional mitochondria. (B) ROS oxidizes thioredoxin, releasing it from ASK1. (C) ASK1 causes JNK activation. (D) Alternatively, ROS oxidizes GST, releasing JNK. (E) Activated JNK deacetylates histones and demethylates APP, BACE, and presenilin gene promoters, which leads to increased A β production.