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Review

Mitochondria and Antioxidant Targeted Therapeutic Strategies for Alzheimer's Disease

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Abstract. Oxidative stress and mitochondrial dysfunction are important features present in Alzheimer's disease (AD). They appear early and contribute to disease progression, both in human postmortem AD brains as well as in transgenic AD mouse brains. For this reason, targeting oxidative stress and mitochondria in AD may lead to the development of promising therapeutic strategies. Several exogenous antioxidant compounds have been tested and found beneficial in transgenic AD mice, such as vitamins and spices. However, their efficacy was much more modest in human trials. More recently, new strategies have been elaborated to promote endogenous antioxidant systems. Different pathways involved in oxidative stress response have been identified. Compounds able to upregulate these pathways are being generated and tested in animal models of AD and in human patients. Upregulation of antioxidant gene expression was beneficial in mice, giving hope for future avenues in the treatment of AD and other neurodegenerative disorders.

Keywords: Alzheimer's disease, antioxidants, mitochondria, oxidative stress, therapeutic strategies, transgenic mice

OXIDATIVE STRESS AND MITOCHONDRIAL DYSFUNCTION IN ALZHEIMER'S DISEASE

Increased oxidative stress

Alzheimer's disease (AD) pathogenesis includes elevated oxidative damage. In human AD brains, DNA, RNA, lipid and protein oxidation are increased in the cortex and the hippocampus. For example, levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) [1] and nitrotyrosine [2] are markedly augmented in AD patients compared to normal control patients. Oxidative stress markers have been considered as biomarkers for disease progression. Studies reported that levels of F_2-isoprostane in the cerebrospinal fluid (CSF) of AD patients were consistently increased compared to normal control patients [3–5]. Increased oxidative stress occurs at early stages of amyloid deposition [2]. Similarly, patients with mild cognitive impairment (MCI) have elevated DNA [6], RNA [7], and protein oxidation [8], as well as lipid peroxidation [9,10]. MCI is an intermediate state between normal aging and AD, in which there is cognitive impairment not yet severe enough to impair normal daily functioning [11]. MCI is a heterogeneous state [12], but most cases likely represent very early stages of AD, since the risk of progression to AD is increased compared to those without any cognitive impairment [13], and since the pathology in many cases is that of mild AD [14]. Both AD and MCI data strongly suggest that oxidative stress is involved early in the disease pathogenesis.

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In transgenic mouse models of AD, markers of protein oxidation and lipid peroxidation were also increased in cortex and hippocampus. This was observed prior to the appearance of amyloid plaques [15,16] and neurofibrillary tangles [17]. There is also evidence that oxidative stress can exacerbate AD pathogenesis. In human neuroblastoma cells expressing the human wild-type amyloid-β protein precursor (AβPP) transgene, administration of both peroxynitrite and $FeCl_2$, two potent oxidative stress inducers, augmented the secretion of $A\beta_{1-42}$ and the expression of β-site AβPP-cleaving enzyme (BACE) [18].

Impaired mitochondrial functions

Mitochondria play a key role in the viability and functionality of cells by generating and scavenging free radicals. In AD, mitochondrial function is impaired [19]. Hirai and colleagues found that in AD brains, neurons with increased oxidative damage had altered mitochondrial DNA and cytochrome oxidase levels [20]. In addition, expression of several proteins involved in mitochondrial fission and fusion were affected in postmortem AD brains, leading to abnormal redistribution of mitochondria [21,22]. Wang and colleagues replicated this phenomenon in both M17 human neuroblastoma cells and primary neuronal cells by manipulation of proteins such as dynamin related protein 1 (Drp1) [22]. Mitochondria are particularly important at synapses. They actively participate in synapse formation and function. Considering that loss of synapses is the best correlate of dementia in AD [23], it is crucial to understand by which mechanisms mitochondria are involved. Li and colleagues reported that after manipulations of Drp1 and optic atrophy 1 (OPA1), reducing dendritic mitochondria content caused synaptic loss. Conversely, increasing dendritic mitochondrial content or mitochondrial activity increased the number and plasticity of spines and synapses [24].

At a young age and prior to the appearance of amyloid deposition, transgenic AD mice displayed increased levels of H_2O_2 and decreased levels of cytochrome oxidase [25]. Another group reported that in young transgenic AD mice, there was a reduction of mitochondrial membrane potential and of ATP levels [26]. In this study, mitochondrial dysfunction was associated with increased production of reactive oxygen species (ROS) [26]. Recently, Yao and colleagues confirmed that deficits in mitochondrial bioenergetics precede amyloid deposition, as evidenced by decreased mitochondrial respiration and pyruvate dehydrogenase levels and activity in transgenic mice with human AβPP, presenilin 1 (PS1), and tau mutations [27]. Taken together, these data strongly suggest that mitochondrial dysfunction occurs early in disease pathogenesis.

Several other mitochondrial key enzymes have been studied in the context of AD. In this review, we will focus our discussion on the α-ketoglutarate dehydrogenase complex (α-KGDHC) and the manganese superoxide dismutase (MnSOD). First, activity of α-KGDHC is reduced in human postmortem AD brain [28–31]. Furthermore, levels of its subunits α-ketoglutarate dehydrogenase (E1; EC 1.2.4.2) and dihydrolipoyl succinyltransferase (E2; EC 2.3.1.61 or DLST) are also diminished in brains of patients bearing the Swedish AβPP mutation KM670/671NL [32]. Recently, our group reported that both thiamine deficiency [33] and dihydrolipoyl succinyltransferase deficiency [34] exacerbated oxidative stress and increased amyloid plaque deposition in transgenic AD mice. In addition, deficiency of dihydrolipoyl succinyltransferase induced spatial memory deficits in young transgenic AD animals [34].

MnSOD is another important mitochondrial enzyme. It catalyzes the dismutation of superoxide to H_2O_2, which is then decomposed to water via catalase or glutathione peroxidase. In transgenic AD mice, partial deficiency of MnSOD increased amyloid plaque deposition [35] and tau phosphorylation [36]. It also accelerated the onset of behavioral abnormalities in transgenic AD mice [37]. Conversely, overexpression of MnSOD is protective. We showed that MnSOD overexpression in transgenic AβPP mice reduced protein oxidation, amyloid plaque deposition, and microgliosis. It also rescued memory impairment and synaptic protein levels [38]. Our data were recently confirmed by Massaad and colleagues, who found that in another transgenic AD mouse, MnSOD overexpression decreased hippocampal superoxide levels and amyloid plaques and improved memory deficit at various ages [39].

Other studies have also provided evidence to demonstrate the importance of mitochondria in AD pathogenesis. For example, Cyclophilin D (CypD), a matrix component of the mitochondrial permeability transition pore, has been recently examined. Deficiency of CypD reduced mitochondrial, cognitive, and synaptic dysfunction but did not affect amyloid deposition in transgenic AD mice [40,41].

EXOGENOUS ANTIOXIDANT DRUGS AS THERAPEUTIC STRATEGIES IN ALZHEIMER'S DISEASE

Transgenic mouse models

One well known therapeutic approach related to oxidative stress is the administration of direct antioxidant drugs. Supplementation with vitamin E was used in transgenic AD mice for its ability to reduce ROS. Authors found that vitamin E reduced lipid peroxidation in both young and aged mice, but reduced plaque burden only when the drug was administered at early ages [42]. In combination with vitamin C, vitamin E reduced memory deficits but did not affect amyloid deposition in transgenic mice with both AβPP and PS1 mutations [43]. Interestingly, genetic depletion in vitamin E in transgenic AD mice resulted in increased lipid peroxidation, and amyloid deposition and oligomerization by affecting Aβ clearance [44].

Melatonin is another potent antioxidant drug used in transgenic AD animal models [45]. Melatonin receptors affect mechanisms of learning and memory in mice, especially electrophysiological processes such as long-term potentiation [46]. In transgenic AD mice, administration of melatonin reduced oxidative stress and pro-apoptotic markers. It also elevated levels of SOD and glutathione, two mitochondrial enzymes involved in free radical scavenging [47]. Long term administration of melatonin improved cognitive performance and reduced amyloid deposition in transgenic AD mice [48]. Another study showed that melatonin treatment in mice injected with Aβ protofibrils reduced ROS and intracellular calcium levels [49].

Spices are other sources of antioxidants. Curcumin in particular has been widely used to reduce oxidative stress. In transgenic AD mice, low and high doses of curcumin decreased oxidized proteins, soluble and insoluble Aβ, as well as amyloid plaques [50]. *In vitro* and *in vivo*, curcumin also reduced Aβ aggregation [51]. As a possible mechanism for plaque clearance, curcumin can bind Aβ and increase Aβ uptake from macrophages [52]. Interestingly, short term administration of curcumin partially restored distorted neurites in transgenic AD mice [53]. Several other natural antioxidants have been studied in the context of AD therapy, such as blueberry [54] and red grape [55–57], particularly for their content of resveratrol. Fruit extracts and resveratrol itself have shown beneficial effects including lowering plaque burden and improving behavioral deficits in transgenic AD mice [58] possibly via AMP-activated protein kinase activation pathway [59].

Human patients

We turn now to a selective discussion of exogenous antioxidant drugs in human trials to treat or prevent AD or MCI. It should be noted at the outset that as yet no therapy, antioxidant or otherwise, has been shown to reverse, arrest, or even change the slope of decline in human trials.

One of the best studied antioxidants in AD is vitamin E (α-tocopherol). In 1997, the Alzheimer's Disease Cooperative Study (ADCS) published a double-blind, placebo-controlled, randomized, multicenter trial of deprenyl and vitamin E [60]. Deprenyl inhibits the free-radical generating degradation of catecholamines by monoamine oxidase B. A total of 341 patients with AD of moderate severity were assigned to placebo, deprenyl, vitamin E, or both, and followed for an average of 2 years. Unfortunately, the randomization failed, and at baseline the placebo group was significantly better cognitively than the other groups. No benefit of either deprenyl or vitamin E was seen without adjusting for this baseline difference. Beneficial delays in disease progression with vitamin E or deprenyl were seen when analyses were adjusted for baseline cognition, but the need for statistical adjustment leaves some doubt. This trial was similar to the earlier DATATOP (deprenyl and tocopherol antioxidative therapy of Parkinson's) trial, in which 800 subjects with Parkinson's disease were randomized to the same treatments, and the time to disability requiring L-dopa therapy was measured [61]. No motor benefit was seen for vitamin E, and it remains unclear whether the benefit seen with deprenyl was due to augmentation of dopamine rather than an antioxidant effect. There was no effect of either deprenyl or vitamin E on cognitive performance in early PD [62]. A subsequent ADCS trial of vitamin E in MCI showed no benefit on risk of progression to AD [63]. A total of 769 subjects randomly received vitamin E, the cholinesterase inhibitor donepezil, or placebo, and were followed for 3 years. Donepezil reduced the risk of AD for 1 year in all patients, and for all 3 years in subjects with an apolipoprotein E ε4 allele, with a trend toward slowing of hippocampal atrophy [64]. In contrast, there were no significant differences in rate of progression to AD between the vitamin E and placebo groups at any time point, either among all patients or among apolipoprotein E ε4 carriers.

It is possible that vitamin E did not have an effect in AD or MCI because of kinetic issues. For an antioxidant to be effective, it must react with oxidants faster than the oxidants react with endogenous targets. The

second order rate constant for the reaction of vitamin E with most oxidants is not robustly greater than the rate constant of the oxidants with their targets, which is typically greater than 10^6 M^{-1} s^{-1}. In addition, it is not known whether supplementation with vitamin E significantly increases brain levels, although levels in CSF are increased [65].

Another reason that vitamin E may not have had an effect in AD or MCI could be that oxidative stress may be most important early in disease pathogenesis. As noted above, vitamin E reduces amyloid levels and amyloid deposition in transgenic AD mice when started before plaque deposition, but not when started after plaques appear [42]. Even in clinically very mild AD (Clinical Dementia Rating 0.5), there are already sufficiently many plaques and tangles for a neuropathologic diagnosis of AD, and 50% decreases in entorhinal cortex layer II neurons [66,67]. This may be too late for antioxidants to be effective. Based on this hypothesis, antioxidants would be most efficacious in prevention.

In support of this hypothesis, several epidemiologic studies of antioxidant vitamin supplements suggest decreased risk of AD or dementia. In a prospective, population-based observational study of vitamin E and vitamin C use in 633 subjects [68], baseline use of any vitamins was determined for the preceding two weeks. After an average of 4.3 years, there were 91 incident cases of AD, none of which occurred in the 27 subjects who took vitamin E at baseline or the 23 subjects who took vitamin C at baseline. In the Honolulu-Asia Aging Study [69], vitamin E and vitamin C use was determined in 3385 Japanese American men, and 3–10 years later cognitive status was classified as AD, vascular dementia, mixed/other dementia, low test scores without dementia, or cognitively intact. There was a significant protective effect of combined vitamin E and vitamin C for non-AD dementias but not for AD. However, among those without dementia, use of either vitamin E or vitamin C alone was associated with better cognitive performance. Similar results were found in the Canadian Study of Health and Aging [70].

In the Rotterdam study [71], dietary intake of vitamin E, vitamin C, β-carotene, and flavonoids from food sources was assessed in 5395 non-demented subjects who were then followed for an average of 6 years. The rate of incident AD was decreased by a factor of 0.82 for each 1 standard deviation increase in intake of vitamin C or vitamin E. Among current smokers, there were also significant protective effects for β-carotene and flavonoids. In the Nurses' Health Study [72], long term current users (14968 community-dwelling women) of vitamin E with vitamin C had significantly better global cognitive test scores than subjects who had never used either. In the Cache County study [73], vitamin E and vitamin C supplement use was determined in 4408 subjects, of whom 200 had prevalent AD, and in whom 104 incident AD cases were identified during follow-up. Combined use of vitamin E and vitamin C was associated with reduced AD prevalence and incidence. In follow-up from this study, increasing quartiles of vitamin C intake combined with vitamin E was associated with higher baseline Modified Mini-Mental State exam (3MS) scores, and the effect was stronger for food sources than for supplements [74].

Not all epidemiologic studies have shown positive results, though in general these studies have been smaller (< 1000 subjects). In the Monongahela Valley Independent Elders Survey of 1059 subjects [75], intake of antioxidant supplements (vitamins A, C, E, β-carotene, zinc, and selenium) was initially associated with better cognitive performance in univariate analyses. However, women and persons with higher levels of education were more likely to take antioxidants, and in multivariate analyses including age, gender, and education, there were no significant differences between antioxidant users and nonusers. In a prospective, community-based study of 815 non-demented subjects [76], vitamin E from food, but not from supplements, was associated with decreased incidence of AD in the highest quintile of vitamin E intake, a protective effect seen only among subjects not carrying an apolipoprotein E $\varepsilon 4$ allele. In the Washington Heights-Inwood Columbia Aging study of 980 non-demented subjects [77], intake of vitamin C and carotenes, or vitamin E in supplemental or dietary (nonsupplemental) forms, was not associated with decreased incidence of AD. In the Age-Related Eye Disease Study, participants were randomly assigned to receive daily antioxidants (vitamin C, vitamin E, β-carotene), zinc and copper, antioxidants plus zinc and copper, or placebo, and a cognitive battery was administered to 2166 elderly subjects after a median of 6.9 years of treatment [78]. There were no differences among the treatment groups in any of the cognitive tests. In the Women's Health Study [79], a double-blind, randomized, placebo-controlled trial of vitamin E in 39876 healthy women, 6377 women 65 years or older participated in a cognitive sub-study. There were no differences between treatment groups in global composite scores at the first or last time points or in mean cognitive change over time.

To complicate matters, there have recently been several large meta-analyses suggesting that high dose an-

tioxidant vitamin supplementation may be associated with a slight increase in all-cause mortality. One such analysis, focused on vitamin E, combined 19 clinical trials (135967 participants) [80]. They found that in high dose vitamin E ($>$ 400 IU/day) trials, the pooled all cause mortality risk difference was 39 per 10000 persons, whereas in low dose ($\leqslant$ 400 IU/day) trials, the risk difference was -16 per 10000. The Cochrane Hepato-Biliary Group [81,82] attempted to analyze all randomized trials in adults involving β-carotene, vitamin A, vitamin C, vitamin E, and selenium. When all qualified randomized trials were included (68 trials, 232606 participants), there was no significant effect on mortality. However, in "low-bias" trials (180938 participants), antioxidant supplementation was associated with a slight ($\sim$5%) but statistically significant increase in mortality. Specifically, there were slight but statistically significant increases in all-cause mortality with β-carotene ($\sim$7% increase), vitamin A ($\sim$16% increase), and vitamin E ($\sim$4% increase).

One potential explanation for a slight increase in mortality might be that antioxidants may also act as pro-oxidants under the right circumstances. For example, vitamin C combined with ferrous iron is a standard free-radical generating system. An additional consideration is that antioxidant systems normally form a complex network. High dose supplementation with a single antioxidant vitamin in isolation could disrupt the balance of the network. The studies reviewed above, suggesting that antioxidant intake from food is superior to vitamin supplements, support the idea that the entire antioxidant network is important.

Several other antioxidant compounds have been examined in human AD trials with varying results. Idebenone is a water-soluble analog of ubiquinone. Early double-blind, placebo-controlled, randomized trials of idebenone in mild to moderate AD involved 92–450 subjects [83–85], and suggested dose-dependent, beneficial effects on cognition and slowing of disease progression for up to 2 years. Idebenone was better tolerated and associated with less deterioration than the cholinesterase inhibitor tacrine [86]. In contrast, the ADCS trial found no significant effect in 536 subjects randomized to placebo or 3 doses of idebenone [87]. There was a benefit in cognition when all 3 idebenone groups were combined, but this effect was deemed too small to be clinically significant.

Aggregation of Aβ and Aβ-induced free radicals are dependent in part on binding of Cu and Zn ions. In a pilot Phase 2 clinical trial, 36 subjects with moderate AD were randomized to placebo or clioquinol, which inhibits Cu and Zn ions from binding to Aβ [88]. Subjects more severely affected at baseline experienced significant worsening in the placebo group, compared with minimal deterioration in the clioquinol group. A subsequent trial of a second generation metal-binding compound, PBT2, involved 78 subjects with mild AD randomized to placebo or two doses of PBT2 [89]. Compared to placebo, the higher dose was associated with decreased CSF Aβ_{42} levels and improved performance in two tests of executive function.

The curry spice curcumin has antioxidant [50], anti-inflammatory [90], and amyloid-disaggregating properties [51] *in vitro* and in animal studies. In a small 6-month pilot trial [91], 34 subjects with AD were randomized to placebo or two doses of curcumin. There was no cognitive decline in the placebo group, and no improvement was observed with curcumin.

The Russian antihistamine latrepirdine (Dimebon) initially showed promise in a double-blind, placebo-controlled, randomized trial conducted in Russia, involving 183 subjects with mild to moderate AD [92]. At 6 months and 1 year, subjects on latrepirdine were significantly better than those in the placebo group with respect to all key outcomes – cognition, activities of daily living, behavior, and overall function. Latrepirdine also improved MMSE scores in a trial of Huntington's disease [93]. The mechanism of these effects is obscure, but have been proposed to include interaction with glutamate receptors [94], blockade of voltage-dependent calcium channels [95], and inhibition of the mitochondrial permeability transition pore [96]. However, the more recent CONNECTION trial [97], based in the US, Europe, and South America, showed no benefit for latrepirdine in any parameter [98].

In summary, antioxidant/mitochondrial-based therapies have presented a mixed picture. Many have not proved significantly effective in treatment of AD or MCI, though a few show promise. Efficacy may be greater in prevention of AD and reducing risk of cognitive decline with aging. Based on the studies reviewed here, future trials of antioxidants are likely to be more successful if focused on prevention or on very early stages of disease, and if a broad increase in the entire network of antioxidant defense systems is targeted.

FACILITATION OF ENDOGENOUS ANTIOXIDANT SYSTEMS AS THERAPEUTIC STRATEGIES IN ALZHEIMER'S DISEASE

Another important avenue for the treatment of AD could be the facilitation of the endogenous antioxidant

systems. In this review, we focus on a particular pathway involved in antioxidant and anti-inflammatory response, the nuclear factor erythroid-related factor 2/antioxidant response element (Nrf2/ARE) pathway. Nrf2 is a transcription factor, which in humans is encoded by the *NFE2L2* gene [99]. Nrf2 is a master regulator of the antioxidant response [100,101]. Its activity is regulated in part by the actin-associated protein Keap1. Keap 1 binds to Nrf2 and sequesters it in the cytoplasm. With oxidative stress, the binding is disrupted and Nrf2 is released, allowing translocation into the nucleus [100, 101]. Nrf2 can then bind to promoters with AREs, inducing the expression of genes that coordinate a cytoprotective response [102]. Many of these genes encode for mitochondrial antioxidant enzymes.

Transgenic mouse models

In transgenic AD mice, expression of Nrf2 and Nrf2/ARE regulated genes are reduced as amyloid deposition progressed [103]. The same group reported that facilitation of Nrf2 expression by both *tert*-butylhydroquinone (tBHQ) and overexpression of Nrf2 through adenovirus-mediated gene delivery protected against Aβ_{1-42}-induced cell death in hippocampal cells *in vitro* [103]. This protection was associated with an increase of Nrf2/ARE regulated genes [103]. More recently, Kanninen and colleagues reported that intrahippocampal injection of a lentiviral vector expressing Nrf2 in AβPP/PS1 mice reduced spatial learning deficits, soluble Aβ, and astrogliosis. These mice also had uregulated mRNA levels of Nrf2 and heme oxygenase-1 [104]. Taken together, these data suggests that induction of endogenous antioxidant pathways could represent a promising therapeutic approach for AD [105].

Synthetic triterpenoids (TPs), derivatives of 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO), have been identified as potent pharmacological inducers of the Nrf2/ARE signaling pathway *in vitro* and *in vivo* [106,107]. TPs also suppress inflammatory stress [108]. It should be noted that inflammation is an important factor as it may exacerbate oxidative stress; activated microglia may be a source of ROS in addition to neurons. Induction of the Nrf2/ARE pathway by TPs is due to disruption of the binding between Nrf2 and Keap1, allowing Nrf2 to translocate to the nucleus [107]. For these reasons, we investigated the effect of triterpenoid CDDO-methylamide (CDDO-MA) in transgenic AD mice, and found that administration of CDDO-MA improved spatial memory retention. It also reduced plaque burden, levels of Aβ_{42}, inflammation, and oxidative stress [109]. Thus, the development of new drugs able to facilitate the Nrf2/ARE pathway represents a key approach for the treatment of AD.

Other endogenous pathways involved in mitochondrial function and oxidative stress have been investigated in the context of AD. In human postmortem AD brain, peroxisome proliferator-activated receptor-γ coactivator 1 alpha (PGC-1α) expression decreases as dementia progresses [110]. PGC-1α is an important transcription cofactor that specifically regulates genes involved in energy metabolism. Its activation is dependent on various insults including the generation of ROS. PGC-1α interacts with the nuclear receptor peroxisome proliferator-activated receptor-γ (PPAR-γ), which permits the interaction of this protein with multiple transcription factors. In addition, this transcription factor may influence AβPP-related gene transcription, such as BACE1 [111].

Thus, PPAR-γ agonists have been studied as potential therapeutics for AD treatment [112]. Pioglitazone and rosiglitazone, two thiazolidinediones (TZDs), selectively stimulate PPAR-γ. Rosiglitazone is also a selective ligand of PPAR-γ. Primarily used to treat diabetes, these drugs have now been administered to transgenic AD mice. After treating aged transgenic AD mice with pioglitazone, cerebrovascular functions were restored and oxidative stress was reduced [113]. Interestingly, rosiglitazone was found to simulate neuronal mitochondrial biogenesis in an apolipoprotein E isoform-independent manner, by inducing both mitochondrial DNA and estrogen-stimulated related receptor alpha mRNA [114]. More recently, it has been shown that chronic administration of rosiglitazone reduced memory deficit in transgenic AD mice [115].

Human patients

Considering the beneficial effects of PPAR-γ agonists in mouse models of AD, several human trials have been conducted. In a pilot trial, 30 subjects with MCI or early AD were randomized to rosiglitazone ($n = 20$) or placebo ($n = 10$), and at 4 and 6 months, subjects receiving rosiglitazone performed better on tests of delayed recall [116]. However, in a larger trial with 511 subjects with mild to moderate AD, no statistically significant difference was observed between placebo and any of 3 doses of rosiglitazone [117], though exploratory subgroup analyses suggested that apolipoprotein E ε4 noncarriers did improve on the highest dose of rosiglitazone. This is reminiscent of the apolipopro-

tein E isoform-independent induction of mitochondrial biogenesis in transgenic mice [114]. In a small, open-label, controlled trial, 32 subjects with mild to moderate AD and diabetes mellitus were randomized to receive pioglitazone or not, and followed for 6 months [118]. In the pioglitazone group, there were improvements in AD Assessment Scale-Cognitive subscale scores, as well as in Wechsler Memory Scale-Revised Logical Memory performance. Pioglitazone also improved regional cerebral blood flow in the parietal lobes [119], which are typically hypometabolic in AD.

These studies clearly require replication in larger trials, but facilitators of endogenous antioxidant systems hold promise. It is also clear that other new pathways should be investigated in order to promote a more robust endogenous antioxidant response that can counteract the early increased oxidative stress in AD.

CONCLUSION

The literature on the importance of mitochondria in neurodegenerative disorders is abundant. In AD, oxidative stress and mitochondrial dysfunction are present early in disease pathogenesis. They also contribute actively to disease progression. Mitochondria and antioxidant targeted therapeutic strategies have been heavily studied in AD mouse models as well as human trials. However, most direct antioxidant drugs beneficial in mouse models of AD have not proved as successful in human trials, though some show promise. There may be several reasons for this. First, it should be noted that most transgenic models of AD are in fact models of amyloid deposition, and do not capture all the complexity of the human disease. Second, antioxidant and mitochondrial-based therapies are likely to be most successful when used in very early stage disease, or even for prevention. Advances in this direction will require better identification of disease at earlier stages, ideally even before clinical symptoms. Third, use of single isolated antioxidant agents may not be sufficient to provide benefit, and could potentially even be deleterious. Recent studies suggest that facilitation of the entire endogenous antioxidant network may produce more robust effects.

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