Neuropharmacology xxx (2010) 1–5

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Oxidative stress in Alzheimer disease: A possibility for prevention

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ARTICLE INFO

Article history:
Received 1 December 2009
Received in revised form
18 March 2010
Accepted 7 April 2010

Keywords:
Alzheimer disease
Antioxidants
Coenzyme Q
Dimebon
Mitochondrial antioxidants
MitoQ
Oxidative stress
Reactive oxidative species

ABSTRACT

Oxidative stress is at the forefront of Alzheimer disease (AD) research. While its implications in the characteristic neurodegeneration of AD are vast, the most important aspect is that it seems increasingly apparent that oxidative stress is in fact a primary progenitor of the disease, and not merely an epiphenomenon. Moreover, evidence indicates that a long "dormant period" of gradual oxidative damage accumulation precedes and actually leads to the seemingly sudden appearance of clinical and pathological AD symptoms, including amyloid-β deposition, neurofibrillary tangle formation, metabolic dysfunction, and cognitive decline. These findings provide important insights into the development of potential treatment regimens and even allude to the possibility of a preventative cure. In this review, we elaborate on the dynamic role of oxidative stress in AD and present corresponding treatment strategies that are currently under investigation.

1. Introduction

Despite continued efforts, the development of an effective treatment for Alzheimer disease (AD) remains elusive. Current therapeutic strategies are limited to those that attenuate AD symptomology without deterring the progress of the disease itself, and thus only postpone the inevitable deterioration of the affected individual. As the population of AD cases is growing faster than ever (Ballenger, 2006; Jellinger, 2006), the demand for an adequate method of treatment is also on the rise. Notably, as oxidative stress is perhaps the earliest feature of an AD brain (Nunomura et al., 2001; Zhu et al., 2001, 2004, 2007), the successful neuronal protection from oxidative damage will potentially prevent the disease altogether, if appropriately administered. In this regard, efforts focused on the sequestration of reactive oxidative species (ROS) that cause oxidative stress within the cell have yielded significant results and will hopefully succeed through clinical trials for efficacy. That withstanding, further improvement requires an elucidation of the molecular mechanisms involved in the oxidative stress of AD.

2. Oxidative stress in Alzheimer disease

Within any functional, aerobic cell, the processes involved in respiration inevitably generate ROS (Petersen et al., 2007). In particular, the oxidation–reduction reactions necessary for the generation of ATP (via the establishment of a proton gradient in oxidative phosphorylation) produce free radical intermediates as electrons are transferred from one molecule to another. Despite the resident sequestration mechanisms present within the cell that prevent the potentially harmful dispersion of the free radical intermediates, a substantial amount of ROS manage to escape daily, free to wreak havoc on macromolecules. In fact, in a specialized cell with high metabolic activity, such as a neuron, the number of such free radicals produced is estimated by some to be 10^{11} ROS/cell/day (Petersen et al., 2007).

This damaging effect is most notable in AD. That is, oxidative damage marked by lipid peroxidation, nitration, reactive carbonyls, and nucleic acid oxidation is increased in vulnerable neurons in AD, relative to unaffected patients, whether or not they contain any other corresponding pathology (i.e., neurofibrillary tangles (NFTs), etc.) (Castellani et al., 2001; Nunomura et al., 1999, 2001). Furthermore, reduced metabolic activity, deemed the result of oxidative damage to vital mitochondrial components, has been

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0028-3908/$ – see front matter © 2010 Published by Elsevier Ltd.
doi:10.1016/j.neuropharm.2010.04.005

demonstrated in AD (Aksenov et al., 1998; Aliev et al., 2003a; Anderson et al., 1994; Hirai et al., 2001). Specifically, cytochrome oxidase, the pyruvate dehydrogenase complex, and the α-ketoglutarate dehydrogenase complex show reduced activity as a result of oxidative damage (Aliev et al., 2003a; Atzori et al., 2001; Behl et al., 1992, 1994; Bozyczko-Coyne et al., 2001; Butterfield et al., 2001; Castegna et al., 2002a).

Notably, these changes precede any other such characteristics of AD (Nunomura et al., 2000, 2001; Perry and Smith, 1998; Pratico et al., 2001). The aforementioned presence of oxidation markers (i.e., lipid peroxidation and the like), for example, is evident even in these vulnerable neurons not yet showing other signs of disease (Nunomura et al., 1999, 2001). This indicates that oxidative stress in fact precedes these other hallmarks. Moreover, the accumulation of oxidative active modification products, such as 8-hydroxyguanosine (8-OHG) and nitrotyrosine in the cytoplasm of cerebral neurons from Down's syndrome patients, temporally precede amyloid-β (Aβ) deposition—a feature of the majority of these same patients in their teens and twenties (Nunomura et al., 2000; Odetti et al., 1998). Notably, these oxidative-stress markers appear decades prior to Aβ deposition in these patients (Nunomura et al., 2000; Odetti et al., 1998). Amyloid-β protein precursor (AβPP) transgenic mouse models of AD (Tg2576 AβPP mutants) similarly demonstrate the primary presence of oxidative stress in the disease, appearing before Aβ deposition (Pratico et al., 2001; Smith et al., 1998). Relatedly, increased levels of isoprostanes, products of polyunsaturated fatty acid oxidation, are found in living patients diagnosed with the predromal stage of AD, mild cognitive impairment (MCI) (Pratico et al., 1998, 2000, 2002). Furthermore, MCI individuals show increased levels of lipid peroxidation and nucleic acid oxidation in post-mortem brain tissues, cerebrospinal fluid, plasma, urine, and peripheral leukocytes, as well as decreased levels of antioxidants and total plasma antioxidant capacity (Butterfield et al., 2006a, 2006b; Keller et al., 2005). Another sensitive marker of oxidative stress, heme oxygenase-1, is also increased in post-mortem brain tissue of individuals with both AD and MCI (Schipper et al., 2006; Smith et al., 1994a).

Altogether, the evidence for the primary occurrence of oxidative stress in AD is overwhelming. As such, the perspective on the mechanistic etiology of AD has shifted away from the Aβ cascade hypothesis over the last few years. Although Aβ and its aggregated, senile-plaque form (one of the hallmark pathologies of AD) are undoubtedly involved in the neurodegeneration typical of the disease, the chronology of its presence is now deemed secondary by many (Castellani et al., 2006; Zhu et al., 2001, 2004, 2007). Even more, evidence suggests that the secretion and deposition of Aβ within vulnerable AD neurons are actually compensatory measures taken by cells in an effort to protect themselves against damage due to oxidative stress (Hayashi et al., 2007; Nakamura et al., 2007; Smith et al., 2002). For instance, Aβ has not only been demonstrated to follow the appearance of oxidative-stress markers in AD (Petersen et al., 2007), but it has also been shown to have antioxidant capacities in cerebrospinal fluid and plasma, protecting lipoproteins from oxidation (Atwood et al., 1998, 2003; Cuajungco et al., 2000; Kontush et al., 2001). Zhu and colleagues have proposed a "Two-Hit" hypothesis whereby the early and progressive oxidative damage to neurons elicits a compensatory response such that the cell can exist in the overly oxidizing environment (Zhu et al., 2001, 2004, 2007). This "oxidative steady state," while initially instituted for protection, eventually makes the cell vulnerable to additional insults, such as Aβ deposition, NFT formation, cell cycle aberration, etc. (Zhu et al., 2001, 2004, 2007).

Perhaps more importantly, the cycle of neuronal damage self-propagates, as many of the above-mentioned secondary hallmarks are themselves the sources of oxidative stress. The overall effect is one of positive feedback. For example, the excessive iron and copper deposits extensively reported in AD (Castellani et al., 2007; Sayre et al., 2000; Smith et al., 1994b, 2010) catalyze the formation of •OH from H_2O_2 as well as the formation of advanced glycation end products (Castellani et al., 2001; Smith et al., 1994b). Similarly, activated microglia, such as those that surround senile plaques (Cras et al., 1990), elicit nitric oxide and superoxide (O_2^{-}•) *in vivo* (Colton and Gilbert, 1987), which react to form peroxynitrate (Good et al., 1996; Smith et al., 1997). Activation of microglial NADPH oxidase in the brain also generates ROS and results in significant neuronal death (Park et al., 2009). Aβ itself has also been directly implicated in ROS formation via peptidyl radicals (Butterfield et al., 1994; Hensley et al., 1994) or metal-associations (Rottkamp et al., 2001; Sayre et al., 1997); it also indirectly stimulates ROS formation through its activation of microglia (Wang et al., 2008a, 2008b). Advanced glycation end products can undergo redox cycling in the presence of transition metals to produce ROS (Yan et al., 1994, 1995). Notably, the glycation end products can activate receptors (as does Aβ) to increase ROS production. Specifically, the receptor for advanced glycation end products and the class A scavenger-receptors are involved (El Khoury et al., 1996; Yan et al., 1996). Abnormalities in proteosomal function/protein degradation systems also foster ROS production (Zhu et al., 2001).

Lastly, mitochondrial abnormalities, initially caused by gradual oxidative disturbances, are an enormous contributor of ROS to the cell (Bonda et al., 2010b). Briefly, as mitochondria are the centers of metabolic activity and are the initial sources of oxidative stress, any oxidative perturbance in their operations creates damaged metabolic capacity (Wang et al., 2009). That is, oxidative damage to an electron transport chain complex, for example, would prevent the complex from effectively transferring electrons during oxidative phosphorylation, thus generating excessive ROS. The overall effect is a vicious positive feedback cycle where ROS produce oxidative stress that eventually yields more ROS, along with other cellular detriments. Because AD is the ultimate manifestation of this cycle, and because age is the primary risk factor for AD (Katzman, 1986), we propose it is such an "age-induced oxidative cascade of neurodegeneration" that is the culprit for the etiology of AD. Although somewhat simplified, the cascade is essentially as follows:

The ROS inevitably produced in a respiring cell incur damage upon vital macromolecules (i.e., DNA, mitochondrial DNA, phospholipids, proteins, etc) despite the best efforts of the built-in antioxidant machinery (Petersen et al., 2007). This damage, though majorly shunted by mitochondrial dynamic processes and the like (Bonda et al., 2010b), gradually accumulate in the cell over many years. Eventually, as oxidative damage due to free radicals itself causes further oxidative free radical generation, a threshold is reached whereby the cell can no longer control the debilitating cyclic propagation. The cell then begins to initiate a compensatory "steady state" such that it can regain control of its environment and continue to exist (Zhu et al., 2001, 2004, 2007). However, it is the oxidative steady state intended to prolong the cell's life that makes it vulnerable to additional insults. Specifically, a secretion of Aβ (to sequester ROS) eventually leads to a destruction of cellular integrity; the peptide itself becomes subject to oxidative damage that causes its oligomerization and aggregation (Wang et al., 2008a, 2008b), which in turn produces neuroinflammation, mitochondrial damage, and thus further ROS generation. Other consequences of cellular oxidative damage include cell cycle aberration and tau hyperphosphorylation, leading to the formation of NFTs (Castegna et al., 2002b, 2003; Lee et al., 2004a; Lee et al., 2005; Mark et al., 1997). Consequently, these cells, damaged beyond repair, succumb to cell degeneration, or otherwise exist in a much debilitated, very dysfunctional state, the ultimate manifestation of which is the cognitive decline and dementia descriptive of AD (Zhu et al., 2001, 2004, 2007).

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Ultimately, while this detrimental cycle is certainly uncontrollable once it takes full effect (i.e., once an "oxidative steady state" is established), it seems that early therapeutic intervention might yield beneficial results. That is, if sufficient antioxidant treatment could be appropriately administered, for instance early in the cycle and thus early in life, then the positive feedback loop of neurodegeneration and oxidative stress could be prevented. The affected cells would thus refrain from entering the ultimately fatal "steady state" and the AD phenotype would fail to manifest. As such, the antioxidant therapies under investigation merit discussion; those with the most potential are outlined below.

3. Antioxidants for Prevention

As stated above, an effective antioxidant treatment regimen could potentially buffer the effects of *in vivo* ROS such that cellular damage remains minimal. Consequently, several methods for antioxidant delivery become available. One option involves the use of naturally occurring antioxidants, and reports indeed indicate some corresponding potential. RRR-α-tocopherol (vitamin E), for example, has been demonstrated to be a lipid soluble, chain-breaking antioxidant, and randomized trials have shown the vitamin to effectively slow the progression of AD (Burton et al., 1982; Perrig et al., 1997; Zandi et al., 2004). Additionally, a recent epidemiological study demonstrated that vitamin E and ascorbic acid (Vitamin C) were associated with reduced prevalence and incidence of AD (Zandi et al., 2004). While these compounds are therapeutically appealing, however, their lack of specificity to neuronal mitochondria, where ROS production is most significant, leaves room for improvement.

As such, mitochondrial antioxidants provide greater potential for therapeutic benefit. As noted above, because mitochondria are ultimately the primary generators of ROS within the cell (Lee et al., 2004b), and because oxidative damage to mitochondrial components precedes that of any other cellular component (Aliev et al., 2003b; Ogawa et al., 2002; Zhu et al., 2004, 2006), a targeting of free radical damage to this organelle would significantly improve therapeutic efficacy. Indeed, several potential mitochondrial antioxidant therapies are under investigation. The first utilizes the electron carrier Coenzyme Q_{10} (CoQ_{10})-part of the electron transport chain (ETC)-as a protectant against oxidative stress. Functionally, CoQ_{10}, which naturally resides in the inner mitochondrial membrane, acts to carry the high energy electrons in the ETC from complex I to complex II during oxidative phosphorylation. Recent studies have shown the enzyme to be neuroprotective in AD through a nullification of oxidative damage and attenuation of mitochondrial dysfunction (Beal, 2004; Lee et al., 2009). Furthermore, a dose of 6.5 μM CoQ_{10} to MC65 neuroblastoma cells provided complete protection from neurotoxicity due to oxidative stress and suppressed H_2O_2 and O_2- production (the most prevalent free radicals produced in respiration) (Wadsworth et al., 2008). However, CoQ_{10} presents two major inadequacies in treatment. First, the functioning of the enzyme is entirely dependent on that of the ETC: its continuous operation directly requires the ETC to facilitate its redox cycling from its oxidized form (ubiquinone) to its reduced form (ubiquinol), and correspondingly, without the ETC, CoQ_{10} cannot sufficiently provide stress relief. This shortcoming becomes critical when oxidatively damaged mitochondria contain defective oxidative phosphorylation (OXPHOS) systems and ETCs, continually producing ROS and eliciting further cellular damages while simultaneously disabling the recycling of administered CoQ_{10}. At this point, essentially occurring just prior to the institution of the "oxidative steady state", CoQ_{10} becomes ineffective. Secondly, despite the apparent attenuation of oxidative damage to brain proteins following CoQ_{10} oral administration, brain tissue and mitochondrial levels of the protein were not increased (Kwong et al., 2002; Lass et al., 1999; Wadsworth et al., 2008). This lack of entry into the central nervous system indicates that CoQ_{10} is unable to breach the blood–brain barrier (BBB) to directly protect neurons from damage—a critical necessity for any effective treatment. Consequently, studies are focusing on a more soluble derivative of CoQ_{10} able to penetrate the BBB that does not require ETC functioning. One such derivative is MitoQ, a triphenylphosphonium-linked ubiquinone derivative (Murphy, 2001) that concentrates several hundred-fold in mitochondria due to the large mitochondrial membrane potential ($\Delta\psi m$) (Smith et al., 2004).

The comparative benefits of MitoQ are two-fold: 1) As mentioned above, it selectively accumulates within neuronal mitochondria, and 2) it is effective in the absence of ETC functioning (Lu et al., 2008; Murphy and Smith, 2007). After systematic depletion of glutathione (a regulator of mitochondrial permeability transition), for instance, MitoQ effectively blocked ROS generation, protected mitochondrial protein redox status, preserved the integrity of mitochondrial structures, and blocked cell death (Lu et al., 2008). Importantly, these studies were performed in cell cultures of non-neuronal tissues (i.e., parental leukemic CEM cells), but their remarkable findings nonetheless indicate the potential benefits of MitoQ in the treatment of oxidative-stress related disease. In fact, the drug is currently in Phase II clinical trials for Parkinson's disease (etiologically similar to AD) as well as liver damage associated with HCV infection (Tauskela, 2007). The results of these studies will thus hopefully shed light on the use of MitoQ for AD treatment.

Additionally, there are two other mitochondrial antioxidants currently under investigation: acetyl-L-carnitine (ALCAR) and R-α-lipoic acid (LA). In recent reports, these agents reduced oxidative stress and mitochondrial abnormalities in rat parenchyma cells, as well as restored their cognitive functions (Aliev et al., 2009; Liu et al., 2002a, 2002b; Long et al., 2009). Overall cognitive ability in aged rats and dogs also resulted following the administration of ALCAR and LA (Ames and Liu, 2004; Liu et al., 2002c; Milgram et al., 2007). Perhaps most exciting, however, were the findings that ALCAR and LA administration, 0.5% and 0.2% respectively, greatly lowered damage to hippocampal mitochondria: neuronal cell bodies showed fewer giant mitochondria compared to age-matched controls; treated mitochondria lacked ultra-structural abnormalities and appeared intact with minimal damage; and statistically significant decreases in the prevalence of damaged mitochondria ($p < 0.001$), increases in normal mitochondria ($p < 0.02$), and improvements in the differences in damaged mitochondria between young and old rats followed ALCAR and LA administration (Aliev et al., 2009). These results provide substantial hope for the effectiveness of future therapies, as oxidative stress and mitochondrial disruptions are primarily responsible for the disease. Finally, the effects of the antihistamine Dimebon, currently under investigation as a possible therapeutic agent for AD (Doody et al., 2008), are believed to involve mitochondrial stabilization (Bonda et al., 2010a).

4. Conclusions

Ultimately, there is much potential on the horizon for AD therapeutics. If administered appropriately, a successfully developed mitochondrial antioxidant provides the vulnerable, aging neuron with a defensive shield against the oxidative cascade of neurodegeneration. Importantly, however, as effective as such therapies may be to those who have yet to enter the neurodegenerative cascade mentioned above, once significant amounts of oxidative damage accumulate within the cell such that the secondary pathologies of AD become apparent, any hope of reversing the

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course of the disease remains beyond the scope of simple antioxidant therapy. Therefore, while such a preventative treatment strategy is ideal for the young-to-middle aged population, its benefits do not extend to those who present the "oxidative steady state" within affected cells. At that point, secondary or symptomatic therapeutics must also be instituted.

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Please cite this article in press as: Bonda, D.J., et al., Oxidative stress in Alzheimer disease: A possibility for prevention, Neuropharmacology (2010), doi:10.1016/j.neuropharm.2010.04.005

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Please cite this article in press as: Bonda, D.J., et al., Oxidative stress in Alzheimer disease: A possibility for prevention, Neuropharmacology (2010), doi:10.1016/j.neuropharm.2010.04.005