Treatment advances in Alzheimer’s disease based on the oxidative stress model

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Abstract
Effective therapy for Alzheimer’s disease (AD), up to this point, has been hampered by our inability to diagnose the disease in its early stages, before the occurrence of significant neurodegeneration and clinical symptoms. Because AD historically has been defined by neuropathologic criteria, treatment strategies have been aimed at diminishing the pathologic end result of the disease process, namely neurodegenerative changes associated with extracellular amyloid-beta-containing plaques, as well as intracellular neurofibrillary tangles of the hyper-phosphorylated microtubule protein, tau. While these avenues continue to be pursued, results thus far have been disappointing. It is now understood that oxidative stress plays a key role in the shared pathophysiology of neurodegenerative diseases and aging. For experimental treatment of AD, the focus of research and development efforts is increasingly shifting to target mechanisms of oxidative stress. Most recently, dimebon, whose mechanism of action relates to improved mitochondrial function, has emerged as a promising candidate for experimental treatment of AD.

Introduction and context
While Alzheimer’s disease (AD) has been defined largely through molecular mechanisms of neuronal dysfunction, there is growing evidence indicating that oxidative stress and reactive oxygen species (ROS) contribute to dementia. Oxidative stress refers to cellular damage mediated by toxic ROS, the formation of which is due to an imbalance between ROS production and the capacity for removing ROS. ROS normally are produced as part of well-characterized metabolic pathways of oxidative phosphorylation during cellular respiration. Free radicals, generally unstable and highly reactive, are removed by specific detoxifying enzymes. With age, increased metabolic demand, and diseases (including AD), there is increased oxidative insult, heightened superoxide radical formation, and increased superoxide dismutase levels which may cause $\text{H}_2\text{O}_2$ to diffuse through the mitochondrial membrane to the cytoplasm. Most free radicals are produced by mitochondria, and mitochondrial abnormalities in AD have been associated with deficiencies of the enzymes of the Krebs cycle, which may either increase free-radical production or alter
the mechanism for their clearance [1-5]. Redox-active transition metals aberrantly accumulate in AD-susceptible neurons [6], and increased cytoplasmic H$_2$O$_2$, in the presence of redox-active metals and amyloid-beta (A$_3$), may cause localized increased ROS concentration [7-9]. Increased ROS results in oxidation of lipids and RNA.

Studies suggest that there are multiple mechanisms by which oxidative stress may accumulate and create dysfunctional neuronal responses in AD and that development of the AD phenotype requires multiple insults [10-12]. Ischemia, inflammation, and aging are all pro-oxidant conditions. The brain, with its high oxygen use and a consumption of approximately 10% of cardiac output, depends on a number of cellular and tissue-specific antioxidant mechanisms for removal of the resultant by-product of ROS. When these mechanisms are ineffective or dysregulated, there is characteristic cellular injury.

The blood-brain barrier (BBB), critical to normal neuronal function (including synaptic transmission, remodeling, angiogenesis, and neurogenesis [13]), is also substantially compromised in a subpopulation of AD patients [14]. This may be a consequence of endothelial cell injury and dysfunction. One result may be impaired A$_3$ transport to and from the brain via the receptor for advanced glycation endproducts (RAGE) and transcytosis of A$_3$ into the brain parenchyma, where it binds to neurons and may enhance formation of toxic ROS.

**Current treatment options**

The current drugs approved by the US Food and Drug Administration (FDA) to treat AD are the acetylcholinesterase (AChE) inhibitors, such as donepezil, and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine. These drugs are aimed at symptomatic improvement in cognitive ability and are marginally effective [15,16]. The AChE inhibitors are designed to enhance cholinergic neurotransmission by reducing breakdown of acetylcholine (ACh) in the synaptic cleft. The benefit of AChE inhibitors is thought to relate to the role of ACh in memory and the prominent degeneration of basal forebrain cholinergic neurons in AD [17]. Despite its limited clinical efficacy, AChE inhibition has been successful for over 20 years as the best available treatment strategy for AD. More recently, memantine has been FDA-approved for treating AD. Memantine is the first in a class of NMDA receptor antagonists that influence neurotransmission to provide marginal improvement in memory formation and cognitive function in AD [18].

Other psychotropic medications are also used to treat AD patients symptomatically. With moderate to advanced AD, patients frequently become agitated or develop psychotic symptoms such as paranoid ideation and auditory hallucinations. These symptoms often are improved with psychotropic medications, including atypical antipsychotics [19,20] such as risperidone and olanzapine, and typical antipsychotics such as haloperidol [19-21]. These antipsychotic medications, though often helpful, unfortunately carry the risk of precipitating cerebrovascular accidents in older people [22]. Similar to the AChE inhibitors and NMDA receptor antagonists, the antipsychotic agents do not retard progression of the neurodegenerative process. Benzodiazepines sometimes are used, particularly in the acute setting, to treat agitated patients with AD and are also sometimes prescribed for insomnia, as circadian rhythms are frequently disrupted in AD. Although the benzodiazepines are sometimes helpful due to their anxiolytic and sedating properties, it is usually best to avoid using them because they can exacerbate cognitive impairment [23,24].

**Recent advances**

**Redox-active compounds**

The advances in the molecular and pathogenetic mechanisms that evolve into the final pathologic picture of AD provide enormous insight into possible targets for newer, and hopefully more effective, therapy. Extracts of Ginkgo biloba show antioxidant properties with reduced superoxide release in polymorphonuclear leukocytes [25]. Ginkgo constituents may act as scavengers of free radicals [26] and increase cholinergic transmission in the brain by inhibiting AChE [27], both of which may be beneficial in AD. However, clinical studies of Ginkgo have not consistently yielded positive results.

A randomized placebo-controlled trial using antioxidant therapies alpha-tocopherol, selegiline, and combination therapy showed significant delays in time to death, placement in a nursing home, development of severe dementia, or a defined severity of impairment of activities of daily living [28]. Antioxidants may ablate cognitive decline [29,30], suggesting that these strategies are beneficial in reducing the risk for developing AD. On the other hand, the beneficial effects of alpha-tocopherol and selegiline and other antioxidants have not always been reproduced in clinical trials [31]. It is possible that the oxidative stress pathophysiology in AD is so severe that conventional antioxidants have marginal or insufficient power to buffer against pathophysiologic redox metabolism. At the present time, antioxidant therapy is not recommended in AD, although patients frequently are advised by physicians to take over-the-counter antioxidant supplements, partly
due to the low probability that these compounds will have adverse effects.

Iron chelation
Chelation therapy offers another strategy for reducing oxidative stress. Formation of the toxic hydroxyl radical from H₂O₂ requires electron donation from Cu²⁺ or Fe³⁺, the latter being much more prevalent in the labile pools of cytosolic redox-active metals. In the context of AD, the Aβ peptide is considered a strong redox-active agent that is capable of reducing transition metals in the cytoplasm and allowing the conversion of molecular oxygen to H₂O₂ [9,32,33]. The metal ion dyshomeostasis in AD, with high levels of redox-active metals (particularly iron) being found in the affected areas of the brain, suggests chelation as a reasonable form of therapy. The use of covalent conjugation of nanoparticles with iron chelators [34] has been proposed to help overcome the limitation to chelation therapy imposed by BBB permeability. This unique approach would enable transport of chelators and chelator-metal complexes in both directions across the BBB.

Non-redox-active compounds
Numerous other compounds under development for experimental treatment of AD do not directly quench ROS through redox activity but are known to have downstream antioxidant effects. There is epidemiologic evidence that homocysteine is an independent risk factor for the development of dementia [35], with a plasma level of greater than 14 μM causing a twofold increased risk of AD. A number of studies, however, show that the central nervous system (CNS) is acutely sensitive to homocysteine, which is also an NMDA receptor agonist that stimulates calcium influx and promotes glutamate excitotoxicity, and causes oxidative stress and DNA damage. With its redox-active thiol residues, homocysteine can also impair the antioxidant activities of glutathione. In addition, with its ability to coordinate copper, homocysteine can promote one-electron transfer reactions with H₂O₂, resulting in the formation of the toxic hydroxyl radical. Elevated plasma homocysteine and low folate may be risk factors for the development of dementia and AD, spurring controlled studies on the efficacy of folate supplementation and reduction of homocysteine levels on dementia and AD [36,37].

Other compounds that have antioxidant effects and that have been tested for efficacy in treating cognitive decline include estrogen replacement, which was shown not to be effective in treating post-menopausal AD. In experimental studies, leuprolide, a selective gonadotropin-releasing hormone agonist that markedly reduces secretion of the gonadotropins, luteinizing hormone, and follicle-stimulating hormone, is thought to divert Aβ protein precursor and reduce brain amyloid and ROS formation [38]. Luteinizing hormone is found to be elevated in AD due to the negative feedback stimulation by low gonadal steroid levels. In clinical studies, female AD patients treated with leuprolide showed stabilization of cognitive impairment and activities of daily living.

Leptin is a centrally acting hormone that controls AMP kinase, maintains lipid levels, and regulates glycogen synthase kinase 3, which modulates tau phosphorylation. Leptin has been shown in vitro and in vivo to reduce extracellular Aβ and neuronal tau phosphorylation as well as improve cognitive performance of transgenic mouse models of AD. In humans, weight loss preceding the onset of AD dementia is inversely proportionate in severity to leptin levels, suggesting that leptin deficiency contributes to systemic and CNS abnormalities in AD and that this hormone may be a novel therapeutic agent in AD, with antioxidant effects through its modulation of intracellular signaling cascades [39].

Insight into the role of metabolic agents, which are influenced by underlying genetics, has emerged. There is a significant increased risk of developing AD in people who have the gene for apolipoprotein E4 (ApoE4), a protein that helps carry circulating cholesterol. A specific fragment formed rapidly from ApoE4 plays a role in oxidative stress by adversely affecting mitochondrial function. It is thought also that poor glucose use and insulin resistance, as seen in type 2 diabetes mellitus, play a role in AD [40,41]. Preliminary results with the oral hypoglycemic agent rosiglitazone in patients with mild to moderate AD show that patients who do not carry the ApoE4 gene show improvement whereas patients with ApoE4 do not respond [42].

We are cautiously optimistic about the potential therapeutic value of dimebon, a new candidate therapeutic agent for AD. Dimebon has been shown to inhibit degeneration of neurons and works through a novel mechanism of action, improving mitochondrial function. In a phase II randomized double-blind placebo-controlled trial with mild to moderate AD, dimebon-treated patients showed statistically significant improvement in cognition, activities of daily living, behavior, and overall function [43]. It was found to have a positive impact on caregiver stress, reducing the amount of time they needed to spend assisting patients. It also showed a favorable side-effect profile. Larger scale clinical trials of dimebon are clearly warranted.

Implications for clinical practice
While cholinesterase inhibitor and NMDA receptor antagonists such as memantine, alone or in
combination, continue to be prescribed for patients with AD along with the promotion of proper nutrition and occupational health [44], we feel we are on the threshold of a new era in AD therapy in which therapies will slow the rate of disease progression. Even for those who still believe that the aim of therapy should be to reduce the pathologic end result that characterizes the disease, the hormone leptin shows promise in reducing extracellular Aβ, and the use of covalently conjugated nanoparticles with iron chelators to solubilize Aβ may overcome the limitations of chelation therapy posed by the BBB. Leuprolide therapy, and especially its temporal relationship to menopause, may prove to be the treatment of choice in preventing AD in women. Most of all, the relationship between vascular and cognitive health and the role played by the presence of glucose intolerance on first one and then the other are yielding a new and exciting approach to AD therapy, which may be mechanistically based in oxidative stress. With improved understanding of AD pathogenesis, there is little doubt that the focus of AD therapy will shift to target what appears to be a key player in disease evolution, namely oxidative stress. In this respect, promising compounds like dimembon warrant further development.

We have come a long way in our treatment strategies for AD. Acknowledging that it is the molecular mechanisms instrumental in the evolution of the disease, not the final pathologic result [45], that should be the target is a very big step in a promising direction. This is a very exciting time for the field of Alzheimer’s research and should prove fruitful.

Abbreviations
Aβ, amyloid-beta; ACh, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer’s disease; ApoE4, apolipoprotein E4; BBB, blood-brain barrier; CNS, central nervous system; FDA, US Food and Drug Administration; NMDA, N-methyl-D-aspartate; RAGE, receptor for advanced glycation endproducts; ROS, reactive oxygen species.

Competing interests
MAS is a paid consultant and/or receives lecture fees from Anavex Life Sciences Corp (Geneva, Switzerland), Medivation (San Francisco, CA, USA), and Neurozet (Bridgewater, NJ, USA).

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