

Alzheimer's Disease: When Free Radicals Run Amok



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Alzheimer's disease (AD) is an age-related, progressive, dementing disorder that currently affects 4 million to 5 million Americans. Because of the large Baby Boomer bubble in the US population, 14 million Americans are predicted to have the disease in just a few decades. The current approximately \$100 billion spent annually on care and treatment of AD will expand to become an enormous percentage of the US gross domestic product in 2050, making AD, in the view of many, a public health crisis. Effective means of delaying, or even stopping, disease onset are necessary but not yet available. In order to develop these means, understanding the molecular basis of the disorder is essential.

Amyloid- β peptide ($A\beta$), which is derived from amyloid precursor protein by proteolytic processing that involves at least two proteases, consists of 39 to 43 amino acids and is thought by many to be central to the pathogenesis of AD. The central core of senile (neuritic) plaques, one of the hallmarks of AD, is composed of $A\beta$. Persons inheriting AD invariably have excess $A\beta$ production. Transgenic animals overexpressing mutations in human genes that lead to AD also exhibit deposits of $A\beta$, although these rodent models have been criticized for lack of neuronal death. Transgenic mice expressing mutations in human genes that lead to deposits of both $A\beta$ and the cytoskeletal protein tau (another pathological feature of AD) express $A\beta$ deposits prior to tau deposits. In AD, dementia ratings correlate with the levels of soluble $A\beta$, likely the toxic species of this peptide.

The AD brain is also characterized by extensive oxidative stress, indexed by protein oxidation, lipid peroxidation, DNA/RNA oxidation, and advanced glycation end products, among other biomarkers. The centrality of $A\beta$ to the oxidative stress observed in AD brain has been united in a framework in which the focus is oxidative stress associated with $A\beta$. Consistent with this model, $A\beta$ —in ways that are inhibited by free-radical scavengers—induces brain protein oxidation, lipid peroxidation, free radical formation, activation of microglia with its proinflammatory cytokines, inducible nitric oxide synthase, mitochondrial dysfunction, among

other indices of oxidative stress, and causes the death of neurons.

What do these observations mean for drug discovery in AD? Clinical trials of various antioxidants have not been impressive, but often have involved patients late in the disease with significant irreversible neuronal loss. Ongoing trials—sponsored by the National Institutes of Health, Bethesda, Md.—in mild cognitive impairment, which some researchers believe is the earliest form of AD, may provide a better patient cohort to determine if antioxidant therapy is a viable strategy in treating AD. In addition, agents that empower the patient's own antioxidant defense system to become more engaged in combating the oxidative stress in AD are likely to become more important as a therapeutic strategy.

Nutraceuticals may play an increasingly important role in neurodegenerative disorders associated with oxidative stress, such as AD. For example, curcumin, from turmeric spice, activates the gene *heme oxygenase-1*, which in turn produces biliverdin that is quickly converted to bilirubin, a highly efficient antioxidant. Other heat shock proteins, such as HSP 60 or HSP 70/72 that bind to misfolded, aggregated, or oxidized proteins (thereby apparently directing these proteins for recycling via the proteasome), can be activated by caloric restriction and other means. The field of nutrition in neurodegenerative disorders, which is only in its infancy, offers new areas of drug development.

An additional approach to defining potentially new therapeutic targets for AD may be proteomics. Identification of proteins with differential post-translational modifications (e.g., protein carbonyls, 3-nitrotyrosine, others) has suggested new protein therapeutic targets related to energy use, excitotoxicity, degradation of damaged proteins via the proteasome, and communication between neurons, all of which are reportedly altered in the AD brain.

Slowing or stopping AD is a daunting challenge, as is finding drugs that enhance exogenous or endogenous antioxidant action in this disorder. However, given the immense number of current (and future) AD patients, it is imperative that effective therapies be found that are based on underlying sound scientific observations of this devastating dementia disorder.

