

Redox imbalance and oxidative modifications of macromolecules in brain during aging and neurodegenerative diseases

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Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most common age-related neurodegenerative disorders affecting millions of people worldwide. Although the exact underlying mechanisms contributing to degenerative changes in AD and PD are multifactorial, oxidative stress induced damage to cellular macromolecules is widely considered to play an important and central role in the pathophysiology and progression of AD and PD.^{1,2} The purpose of this article is to highlight the oxidative stress-induced damages to macromolecules in brain during aging and neurodegenerative disorders.

1. Oxidative stress in the brain during aging

Reactive oxygen species (ROS), as well as reactive nitrogen species (RNS), are products of normal cellular metabolism. Aging is associated with accumulation of these oxidative-induced damages in brain, owing to an imbalance between antioxidant defenses and intracellular generation of ROS. The overall rationale of oxidative stress in aging brain is based on the following premise: (a) the brain contains high levels of unsaturated fatty acids which are vulnerable to oxidation (particularly high in 20:4 and 22:6 fatty acids); b) the brain consumes high amounts of oxygen (about 20% of the total amount used in the body); and c) the brain contains high concentrations of transition metals such as iron (Fe^{2+}) that are key catalysts of oxidative-induced damages³ For scavenging these free radicals, cells have an extensive antioxidant system

in place comprising both enzymatic and nonenzymatic substances, which is differentially distributed within various cellular compartments. Endogenous enzymes including superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), catalase, peroxiredoxins, and thioredoxins can scavenge ROS, thereby mitigating their toxicity. A decline in the antioxidant enzymes with aging may compromise cellular redox homeostasis resulting in high concentrations of ROS and RNS.⁴ This may further ►

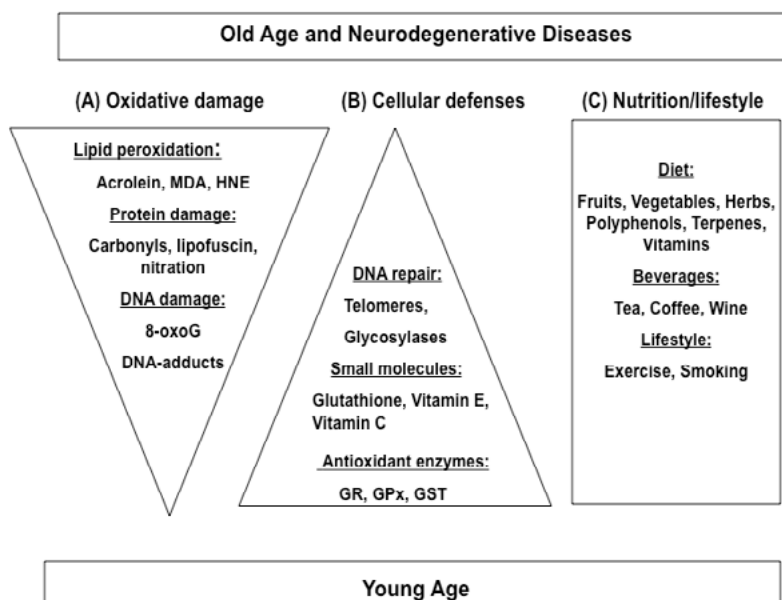


Figure 1 Interplay between cellular ROS levels, antioxidant system during aging and their modulation by nutrition and lifestyle changes. Oxidative damage increases with age, while cellular defenses decrease. An antioxidant rich diet and exercise have been shown to protect against age-related neurodegenerative diseases.

disrupt cellular redox circuits and induce damage to nucleic acids, lipids and proteins in the brain, thereby contributing to AD or PD. Although the magnitude of modifications of multiple biomolecules by oxidative damages and age-related functional losses is not a linear one, these changes are exacerbated in AD and PD as shown in Figure 1.

2. Overview of cellular macromolecule damages in the brain during aging, AD and PD

A) Protein oxidation

The most frequent oxidative modification in proteins is the formation of carbonyl groups, which may lead to inactivation, proteolysis, or formation of intra-/intermolecular cross-links. Oxidative-induced damage to proteins can affect virtually all amino acids, with sulfur-containing amino acids and aromatic amino acids being the most susceptible.⁵ Protein oxidation may be considered to be the most important functionally, because proteins act as cellular receptors, transporters, enzymes, and transcription factors. In fact, the difference in oxidized proteins was found to be nearly two- and four-fold greater between young and elderly humans and rats, respectively.⁶ Several carbonylated proteins have been identified in the brains of AD and PD patients. Some of these oxidized proteins such as SOD, DJ-1, and heme oxygenase-1 (HO-1) are the important components of cellular antioxidant system, and oxidation of these key proteins may compromise their functional integrity.^{1,2}

B) Lipid peroxidation

Lipid peroxidation is another consequence of decreased antioxidant mechanisms with aging. Reaction of ROS in the presence of redox active metals with the double bond of polyunsaturated fatty acids (PUFAs) produces oxidized lipids which may further result in a large number of reactive electrophilic aldehydes including malondialdehyde (MDA), 4-hydroxy-nonenal (4-HNE), 4-oxo-2-nonenal (4-ONE) and acrolein.⁷ Lipid peroxidation has been reported to be elevated in the brain with age. MDA was increased in the cytoplasm of neurons and astrocytes in normal aging, but was barely detected in normal young subjects.⁸ All of the biologically active aldehydes e.g. acrolein, 4-HNE and 4-ONE are capable of depleting reduced glutathione (GSH), and activating DNA damage and apoptosis in human neuroblastoma cells.^{9,10} Amongst the α , β -unsaturated aldehydes, acrolein and 4-HNE have increasingly been implicated in the pathogenesis of AD and PD.^{11,12}

C) Oxidative DNA damage

In normal tissues, 10,000 oxidative interactions occur between DNA and endogenously generated free radicals per human cell per day,¹³ resulting in damaged nucleotides and strand breaks. These oxidative DNA lesions can block genome replication if not repaired properly. One of the most common lesions is 8-oxo-7, 8-dihydroguanine (8-oxoG); a hydroxyl radical-induced modification of guanine and its level is elevated four times in old brains compared to young brains.¹⁴ Mitochondrial DNA (mtDNA) is more susceptible to oxidative stress than nuclear DNA (nDNA) owing to its close proximity to the ROS generating site and the lack of protective histones combined with a lower capacity for DNA repair. The rate of increase in the 8-oxoG levels was 10 times more in mtDNA than in the nDNA in the cerebral cortex and cerebellum from humans with age.¹⁵ An increase in nuclear and mitochondrial DNA oxidation products have been observed in AD and PD patients.^{1,16}

3. The healthy brain during aging: dietary and lifestyle factors

Recently epidemiological studies have also identified dietary factors associated with the decreased risk of AD and PD. Among these, a higher adherence to a Mediterranean diet (MediD) could be associated with slower cognitive decline and reduced risk of AD.¹⁷ Several plant based foods i.e. vegetables, fruits, legumes, cereals and olive along with wine are important components of MediD. These foods are enriched in polyphenols antioxidants that are able to protect neuronal cells in various *in vitro* and *in vivo* models of AD and PD through different intracellular targets.¹⁸ Polyphenols may simultaneously modulate multiple oxidative stress-induced disease-modifying mechanisms involved in AD and PD progression.¹⁸ These findings from epidemiological studies may be further useful in determining the dietary interventions needed for promoting healthy brain aging.

In conclusion, accumulating evidence supports a role of oxidative stress-induced increase in lipid peroxidation, protein oxidation, and DNA damage in the neuronal degeneration and death during aging, AD and PD. Furthermore, there is considerable evidence that dietary antioxidant especially, polyphenols, have neuroprotective effects on preventing or reversing oxidative stress induced -changes of cognitive and motor functions in normal aging, AD and PD and, as such, should be included in intervention strategies for the prevention of AD and PD. ■

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Manjeet Singh completed his PhD in Biology at the INRS-Institut Armand Frappier, Laval in February 2013. He is currently a postdoc fellow at Health Canada, Ottawa. His PhD project was focussed on the neuroprotective mechanisms of some Indian medicinal plants in in vitro models of Alzheimer's and Parkinson's diseases. His research interests include understanding the role of various environmental chemicals in the onset and progression of various neurodevelopmental disorders and neurodegenerative diseases. He aspires to become a researcher focusing on using natural health products as treatment/preventive measures for neurodevelopmental disorders and neurodegenerative diseases.