

## Forum Editorial

# Oxidative Stress in Neurodegenerative Disorders

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### INTRODUCTION AND OVERVIEW

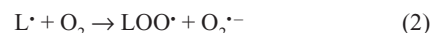
OXYGEN IS ESSENTIAL TO NORMAL BRAIN FUNCTION, but sometimes, like Kentucky bourbon, too much of a good thing is detrimental. In particular, reactive oxygen species (ROS) and reactive nitrogen species (RNS), although important in neuronal signaling and physiology at low levels, can, at higher levels, lead to neuronal dysfunction and death (4). Some aspects of free radical chemistry applicable to brain are discussed here and in the contributions of this Forum that follow. It is the opinion of this Forum Editor that this collection of comprehensive and thought-provoking reviews and primary data articles will be of immense value to scientists and physicians involved in research in and/or care of persons with neurodegenerative disorders. Principles outlined here may be applicable to other neurodegenerative disorders not discussed in this forum. As Forum Editor, I take responsibility for the choice of persons invited to participate and topics covered in this Forum but credit for only the research in my own Forum Review article. I am truly grateful to the outstanding scientists and physicians who have contributed to this exceptional collection of articles.

### OXIDATIVE STRESS: CAUSES AND CONSEQUENCES

Free radicals can arise from numerous sources, including but not limited to redox metal ion-catalyzed reactions, enzymatic reactions, mitochondrial-resident electron transport chain function, and advanced glycation end products (4, 11). However, other sources of oxidative stress in brain are emerging from recent research, among which is the unique chemistry associated with protein deposits in several neurodegenerative disorders (3). Oxidative stress (nitrosative stress derived from RNS is likewise critically important in brain dysfunction but is not explicitly discussed in this editorial) arises when the production of free radicals is not balanced equivalently by their scavenging or conversion to non-free radical products. Oxidative stress is manifested by excess free radical production, protein oxidation, lipid peroxidation,

DNA/RNA oxidation, loss of reductive potential of cells, and other markers (4, 11). Common markers for oxidative stress include those for protein oxidation (protein carbonyls; 3-nitrotyrosine; protein glutathionylation; and others), lipid peroxidation [free and protein-bound reactive alkenals such as 4-hydroxy-2-nonenal (HNE) and 2-propen-1-al (acrolein); isoprostanes and neuroprostanes derived from peroxidation of arachidonic acid and docosahexanoic acid, respectively; and thiobarbituric acid reactive substances, a less specific index of lipid peroxidation], DNA oxidation (8-hydroxy-2-deoxyguanosine), and advanced glycation end products (formed via Amadori chemistry of initially formed reaction products of reducing sugars with amines) (4, 11). In nearly every case, oxidative modification of proteins leads to their dysfunction (4, 22, 23, 26).

The brain is particularly susceptible to oxidative damage, because this 1,300-gram organ consumes about one third of the inspired oxygen in humans, is rich in polyunsaturated fatty acids with their allylic hydrogens highly vulnerable to free radical attack, and has a relatively high abundance of redox-capable transition metal ions coupled with a relatively low abundance of antioxidant defense systems (4). For example, protein oxidation and lipid peroxidation are abundant in the aging brain (4, 11). A series of reactions characteristic of chain reactions is thought to occur:



Radical reaction with allylic hydrogens on lipid acyl chains results in formation of lipid-centered carbon radicals that immediately bind paramagnetic oxygen (which due to its zero dipole moment is highly soluble in the hydrophobic lipid domain of membranes) to form lipid peroxyl radicals. These

latter radicals, in turn, react with other lipid-resident allylic hydrogen atoms to form lipid hydroperoxides and additional carbon-centered lipid radicals, propagating the chain reaction. Lipid hydroperoxides can undergo decomposition to HNE, acrolein, isoprostanes, and other molecules. Reactive alkenals (HNE; acrolein) react with protein-resident cysteine, histidine, and lysine residues by Michael addition (4, 8) to form covalent adducts that affect the structure (25) and function (13) of modified brain proteins.

Oxidative stress also leads to loss of the reducing environment of cells, primarily loss of glutathione (GSH) and thioredoxin (TRX) levels to form the respective oxidative products. Changes in redox environment of cells lead to cellular stress responses, some of which are restorative (21) and some of which are detrimental to the cell (18). For example, a decreased ratio of GSH to GSSG triggers liberation of the transcription factor Nrf2 from Keap1, permitting translocation of Nrf2 from the cytoplasm to the nucleus, where it binds to the antioxidant response element (ARE) of DNA (6, 15). This, in turn, leads to increased production of antioxidant-related enzymes, including those necessary to increase GSH production. In contrast, changes in the redox status of neurons can trigger death signals, resulting in apoptotic processes and death of neurons (18).

The level of protein oxidation in cells is a consequence of the interplay of the formation and removal of such oxidatively modified proteins. For example, enzymes such as methionine sulfoxide reductase, carbonyl reductase, and aldehyde reductase convert oxidatively modified proteins back to their native states (4, 11). Moreover, degradation of oxidatively modified or aggregated proteins is mostly accomplished via action of the complex machinery of the proteasome (10). As elegantly discussed in this issue by Halliwell, when the proteasome itself is compromised, neurodegeneration can occur, in part because of the effects of oxidative stress (10).

## OXIDATIVE STRESS AND NEURODEGENERATIVE DISORDERS

Oxidative damage to the central nervous system is observed in a variety of neurodegenerative disorders, often, but not always, associated with deposition of one or more proteins in the brain (3). For example, amyloid  $\beta$ -peptide,  $\alpha$ -synuclein, huntingtin, and superoxide dismutase are deposited (sometimes with other proteins in addition) in Alzheimer's disease (AD), Parkinson disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), respectively. Among these oxidative stress-related neurodegenerative disorders, some are consequences of genetic mutations (HD and rarely AD, PD, and ALS), whereas others may have susceptibility factors that are genetic in origin (e.g., apolipoprotein E, allele 4 in AD). By far the largest proportion of most neurodegenerative disorders results from nongenetic factors, mostly unknown. However, viruses, particularly the human immunodeficiency virus (HIV), can lead to dementia, and is the single largest contributor to dementia in persons younger than 35 years (20, 24). Multiple sclerosis (MS) is arguably associated with viruses and is usually mani-

fested by recurrent demyelination of axons with consequent deficits in motor function. However, other aspects of the nervous system, including cognitive deficits, are known in MS patients (9).

Complete coverage of every oxidative stress-related neurodegenerative disorder in this Forum on Oxidative Stress and Neurodegeneration is simply not possible. Moreover, oxidative stress-related studies in less common neurodegenerative disorders is often complicated by the scarcity of human tissue obtained in a timely manner. Consequently, investigators have often resorted to animal models of these disorders. In this Forum, models of ALS and MS are presented in insightful articles by Hensley and co-workers and Lev and colleagues, respectively (12, 16). In contrast, 22 million persons worldwide may be currently diagnosed with AD, the single largest dementia-associated human condition known (13). Consequently, studies on tissue obtained from AD patients is more likely. In this Forum, studies on AD are represented extensively (1, 5, 17, 27). For example, studies related to nitrosative stress and thiol homeostasis in AD are presented by Calabrese and colleagues (5). Martins and co-workers (1) present a provocative review on the role of reproductive hormones and oxidative stress in AD, whereas Markesbery and Lovell (17) give an excellent review of DNA oxidation and its consequences in AD brain. Butterfield and co-workers (27) review protein oxidation and lipid peroxidation in brains of subjects with AD and mild cognitive impairment (MCI), arguably the earliest form of AD. These researchers also review their redox proteomics studies relevant to AD and MCI. In addition, studies relevant to HD brain and brain in persons with HIV are presented in elegant articles by Browne and Beal (2) and Nath and colleagues (24), respectively. Although it is clear that PD also is associated with oxidative stress in brain, this subject has been reviewed recently (19).

Mattson (18) and Halliwell (10) present intriguing reviews of processes that may be relevant to many, if not all, oxidative stress-related neurodegenerative disorders. Mattson reviews signaling mechanisms relative to life-and-death decisions made by neurons in response to various stresses, including oxidative stress (18). Halliwell posits that proteasomal dysfunction may be a common feature of neurodegenerative disorders and that environmental sources of proteasome inhibition may be involved to greater or lesser extents in nongenetic mechanisms of neurodegeneration (10).

## FUTURE STUDIES

That in brain of subjects with MCI, strong evidence of oxidative stress exists, suggests that oxidative stress in AD may be associated with the progression of this dementing disorder and not simply a consequence of this disorder. It is my opinion that similar conclusions will be reached for other neurodegenerative disorders as well: that oxidative stress, uniquely sourced in particular neurodegenerative disorders, will be determined to be of fundamental importance in each disease and not simply consequent to the disorder. If this opinion is correct, then it is my view that new and emerging "omic" approaches to investigation of oxidative stress in neurodegenerative disorders are going to gain prominence in the future. For example, redox proteomics

(7), lipidomics (29), and metabolomics and newer genomic approaches (28) will play an increasingly important role in the investigation of these disorders. Likewise, a prediction of this opinion of the fundamental role of oxidative stress in neurodegenerative disorders is the emergence of new therapeutic strategies based on restoration of the natural, endogenous redox balance of neurons, perhaps coupled with multifunctional, brain-accessible exogenous antioxidant compounds that target specific organelles within neurons.

Understanding the causes and consequences of oxidative stress in neurodegenerative disorders is, in my opinion, paramount to the better treatment and, one day, prevention of these devastating diseases. This Forum is a good beginning in this worthwhile endeavor.

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