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Review Article

Oxidative stress, neurodegeneration, and the balance of protein degradation and protein synthesis

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ABSTRACT

Oxidative stress occurs in a variety of disease settings and is strongly linked to the development of neuron death and neuronal dysfunction. Cells are equipped with numerous pathways to prevent the genesis, as well as the consequences, of oxidative stress in the brain. In this review we discuss the various forms and sources of oxidative stress in the brain and briefly discuss some of the complexities in detecting the presence of oxidative stress. We then focus the review on the interplay between the diverse cellular proteolytic pathways and their roles in regulating oxidative stress in the brain. Additionally, we discuss the involvement of protein synthesis in regulating the downstream effects of oxidative stress. Together, these components of the review demonstrate that the removal of damaged proteins by effective proteolysis and the synthesis of new and protective proteins are vital in the preservation of brain homeostasis during periods of increased levels of reactive oxygen species. Last, studies from our laboratory and others have demonstrated that protein synthesis is intricately linked to the rates of protein degradation, with impairment of protein degradation sufficient to decrease the rates of protein synthesis, which has important implications for successfully responding to periods of oxidative stress. Specific neurodegenerative diseases, including Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, and stroke, are discussed in this context. Taken together, these findings add to our understanding of how oxidative stress is effectively managed in the healthy brain and help elucidate how impairments in proteolysis and/or protein synthesis contribute to the development of neurodegeneration and neuronal dysfunction in a variety of clinical settings.

Contents

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Oxidative stress

Redox homeostasis is maintained in an organism as equilibrium between antioxidant and oxidant levels. Imbalance between intracellular levels of pro-oxidants and antioxidants, in favor of the former, results in oxidative stress [1]. All cells of the brain have various antioxidant defense mechanisms designed to maintain homeostasis in response to oxidative stressors. ROS (reactive oxygen species) and RNS (reactive nitrogen species) represent a broad range of chemically defined molecules that are derived from enzymatic and nonenzymatic processes in all cells (Table 1). ROS and RNS play vital roles in many biological processes, including cell growth, cell signaling, smooth muscle relaxation, immune responses, synthesis of biological molecules, and blood pressure modulation [2–5]. ROS and RNS vary in their level of reactivity and represent a broad group of molecules (Table 2). Oxidative stress results in the modification of the biomolecules such as proteins, lipids, DNA, and sugars [6,7] (Fig. 1). ROS and RNS have been found to play roles in the development of many pathophysiological conditions and a diverse array of diseases including cancer, diabetes, atherosclerosis, obesity, cardiovascular disease, and neurodegenerative conditions (reviewed in [7–9]). Interest in ROS and RNS in each of these conditions is highlighted because of the strong implications that oxidative stress may be not only a by-product of each of these diseases, but actually a central mediator of toxicity in each of these conditions (Fig. 1).

Table 1
Sources of reactive species.

Exogenous	Endogenous
Chemotherapy	Macrophages
Drugs (antibiotics)	Mitochondria
Hydrogen peroxide	NADPH oxidase
Hypochlorous acid	Neutrophils
Infectious agents	Nitric oxide synthases
Radiation (UV light)	Xanthine oxidase
Stress	Peroxisomes
Toxic elements	Cyclooxygenases
Xenobiotics	Lipoxygenase
Immune cells	Plasma membrane
Ionizing radiation	

Table 2
List of ROS and RNS.

Name	Symbol
Superoxide ion	$O_2^{\bullet -}$
Hydrogen peroxide	H_2O_2
Hydroxyl	$HO^{\bullet}$
Peroxyl radical	$ROO^{\bullet}$
Singlet oxygen	$O_2^1\Delta_g$
Nitric oxide	$NO^{\bullet}$
Peroxynitrite	$ONOO^-$
Nitroxyl	HNO
Nitrite	NO_2^-
Nitrate	NO_3^-
S-nitrosothiol	RSNO
Carbon monoxide	CO

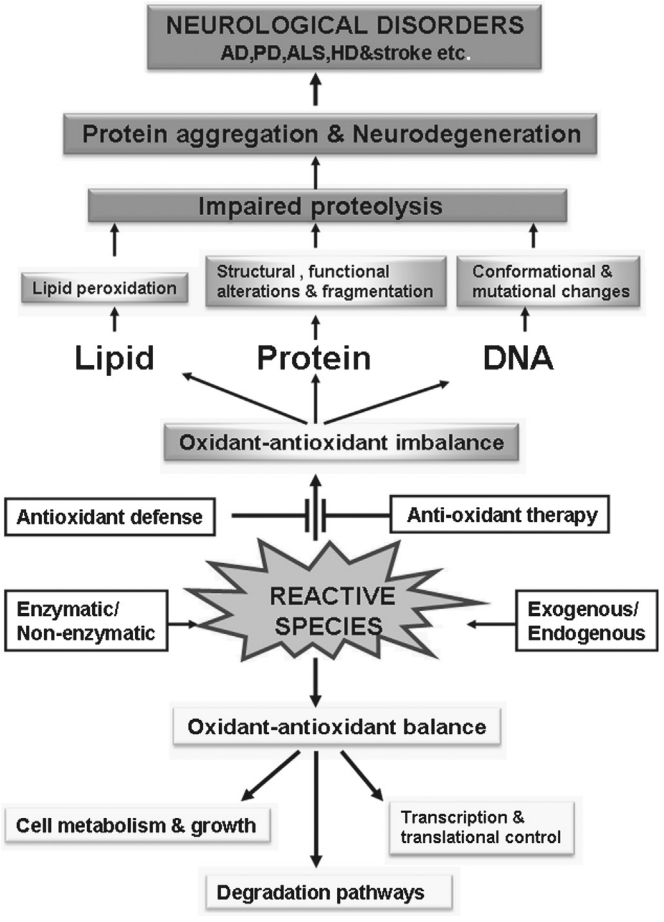

Fig. 1. Sources of ROS/RNS and their cellular effects.