

# Preface

Twenty-five years ago, Earl R. Stadtman, PhD discovered that specific enzymes regulating metabolism can be inactivated by oxidation [1]. He later showed that age-related oxidative modification contributes, at least in part, to age-related loss of function of the enzymes [2, 3]. Dr. Stadtman broke the ground for a new field of study to discover how oxidative stress contributes in significant ways to age-related cellular dysfunction and protein accumulation and that oxidation in the aging brain influences Alzheimer's disease, ischemia-reperfusion injury, amyotrophic lateral sclerosis, and lifespan [4–6]. Today, his research and mentorship have positively influenced the work of hundreds of scientists in this field. We dedicate this book to Dr. Earl R. Stadtman (1912–2008), in celebration of his passion for science and his superior collaborative and mentorship skills.

This book is comprised of three sections. The first describes the valuable roles reactive oxygen species (ROS) and reactive nitrogen species (RNS) play in cellular biology. The second section provides an overview of redox imbalance injury with effects on mitochondria, signaling, endoplasmic reticular function, and on aging in general. The third section takes these mechanisms to neurodegenerative disorders and provides a state-of-the-art look at the roles redox imbalances play in age-related susceptibility to disease and in the disease processes.

In the first section we attempt to answer a question posed by Dr. Stadtman, “Why have cells selected reactive oxygen species to regulate cell signaling events” [7]. It is imperative that we understand the biochemistry and the physiological significance of these molecules, in an effort to protect vital ROS/RNS functions in the cell and organism, as we attempt to minimize redox injury. As highly reactive molecules, ROS/RNS are expected to provide very rapid and focal signaling. In Chapter “Reactive Oxygen Species, Synaptic Plasticity and Memory”, this concept and the newly identified mechanisms of ROS involvement in synaptic are discussed in detail. There are indeed significant recent breakthroughs to better address Dr. Stadtman's question, including discovery of NADPH oxidase as a major source of ROS in long-term plasticity. This identification has led to substantiation of the roles reactive oxygen species play in memory and delineates neural groups involved in NADPH oxidase-dependent plasticity. As a new discovery, future directions

to further delineate the specific redox modifications resulting in long-term plasticity are described. Reactive nitrogen species also play important roles in cellular homeostasis and plasticity [8]. Chapter “Nitric Oxide Biochemistry: Pathophysiology of Nitric Oxide-Mediated Protein Modifications” makes sense of the elaborate biochemistry of nitric oxide species, describing the roles of specific reactive nitrogen species in learning and signaling, their sources and the relevance of their interactions with metals, thiols, and oxides in health and disease. In light of the pathological roles reactive oxygen and nitrogen species play in aging and many age-related neurodegenerative processes, the molecules must serve, in turn, extremely vital processes.

The following three chapters focus on redox pathophysiology in neural tissue. The common theme in these chapters is that while redox imbalance contributes to neural injury, there are important crosstalk mechanisms with the endoplasmic reticulum and mitochondria, and it is the combined interactions between endoplasmic reticulum, mitochondria and redox balance that determine susceptibility to injury. Thus, we describe how redox imbalance can perturb specific cellular functions, focusing on organelles implicated in neurodegenerative processes: the endoplasmic reticulum and mitochondria. Chapter “Redox Imbalance in the Endoplasmic Reticulum” describes a bidirectional influence between redox imbalance and endoplasmic reticulum function. As the protein-folding center, the endoplasmic reticulum lumen is a highly oxidative environment. Despite this, the endoplasmic reticulum lumen cannot handle further increases in oxidative stress. With meager reducing capacity, redox imbalance in the lumen can lead to significant oxidative folding modifications in lumen proteins sufficient to trigger an unfolded protein response. Small redox alterations can be addressed effectively by the endoplasmic reticulum by slowing protein synthesis, increasing degradation of poorly folded proteins, and increasing anti-oxidant enzymes and glutathione. Significant redox alterations initiate an executioner response with transcription and translation of pro-apoptotic factors. Endoplasmic reticulum stress and protein misfolding have been shown for most neurodegenerative processes. Thus, an understanding of the molecular mechanisms underlying redox homeostasis and dyshomeostasis in the endoplasmic reticulum is essential to understand toward the development of therapies for neurodegenerative processes. Mitochondrial function is impaired early on in many neurodegenerative processes. Chapter “Exocytosis, Mitochondrial Injury and Oxidative Stress in Neurodegenerative Diseases” describes specifically how mitochondrial injury and dysfunction can lead to neurobehavioral impairments. Here a major point is made that neurobehavioral impairments are the consequence not only of neuronal loss but also of impaired signaling in remaining neurons. This impaired signaling occurs when energy stores decline with early mitochondrial dysfunction. A model of how mitochondrial dysfunction would impact upon neuronal signaling in each of the major neurodegenerative diseases is provided. Understanding the early dysfunction of neurons in addition to mechanisms of cell loss is critical to identifying the most effective preventative therapies for

neurodegenerative processes. Chapter “Neuronal Vulnerability to Oxidative Damage in Aging” adds consideration of calcium dysregulation in oxidative neural injury and places these interactions into the context of aging: a vicious cycle of cellular dyshomeostasis.

The third section begins to explore in greater depth specific conditions of neural injury. We begin in Chapter “Ischemia-Reperfusion Induces ROS Production from Three Distinct Sources” with ischemia-reperfusion injury. Neurodegenerative processes are typically insidious and redox imbalance is examined late in the course of injury. Ischemia-reperfusion affords a unique opportunity to examine the acute pattern of oxidative stress with high temporal resolution. Sources of ROS differ across this temporal course, and thus addressing each source will be important to identify optimal therapies for ischemia-reperfusion redox injury. The next three chapters detail oxidative injury in Alzheimer’s disease. Chapter “Alzheimer Disease: Oxidative Stress and Compensatory Responses” describes anti-oxidant responses of  $\beta$ -amyloid and hyperphosphorylated tau to counter mitochondrial and metal abnormalities early on in Alzheimer’s pathophysiology. Chapter “Oxidative Stress Associated Signal Transduction Cascades in Alzheimer Disease” delves further into specific enzyme abnormalities in mitochondrial dysfunction early on in Alzheimer’s and how the neurons respond to the oxidative challenge. Here enters a second vicious cycle through the stress-activated protein kinase pathway upregulating  $\beta$ -amyloid and an initiation pathway for apoptosis. Chapter “Nitrated Proteins in the Progression of Alzheimer’s Disease: A Proteomics Comparison of Mild Cognitive Impairment and Alzheimer’s Disease Brain” complements the previous two chapters with molecules involved in nitrative injury. Nitrosative stress occurs early in Alzheimer’s and is present in mild cognitive impairment. Proteomics has identified nitrated proteins in mid cognitive impairment that may be classified by biological function to provide insight into pathophysiology of nitrosative stress in mild cognitive impairment and in Alzheimer’s disease, with involvement of energy, dendritic, signaling, and detoxification proteins. Differences between proteins nitrated in mild cognitive impairment versus Alzheimer’s suggest early and late nitrosative stress effects.

The last three chapters focus on oxidative and nitrosative stress in neuronal injury and loss in Parkinson’s disease. Chapter “Parkinson Disease: An Overview of Pathogenesis” provides an overview of genetic and environmental modifiers of Parkinson’s disease, describes the strengths and weaknesses of each animal model of Parkinson’s disease, and then places oxidative stress in the context of pathophysiology. The latter concept is elaborated upon in Chapter “Protein Oxidation Triggers the Unfolded Protein Response and Neuronal Injury in Chemically Induced Parkinson Disease”, where protein oxidation is linked to endoplasmic reticulum stress and the unfolded protein response. This book ends on a positive note with Chapter “Treating Oxidative Neural Injury: Methionine Sulfoxide Reductase Therapy for Parkinson Disease” describing an effective approach for reducing oxidative stress and slowing Parkinson’s symptoms in both the mouse and fly models.

It is anticipated that continued comprehensive exploration of early and late interactions between mitochondrial and endoplasmic reticulum function and redox imbalance are required to identify the most promising targets for preventing age-related neural injury and neurodegenerative processes. The true test for effectiveness should come back to Dr. Stadtman's earlier work with testing the functionality of perturbed metabolic enzymes.

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