Chapter 3
Free Radicals in Oxidative Stress, Aging, and Neurodegenerative Disorders

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ABSTRACT

Free radicals are intricately woven into the fabric of oxidative stress and are significant in the development of neurodegenerative disorders (NDs). This chapter examines free radicals in the context of neurodegeneration and provides overview of the multiple roles they play in the pathophysiology and clinical progression of varying NDs including Pick's disease (PiD), Parkinson's disease (PD), Alzheimer's disease (AD), prion diseases (PrD), traumatic brain injury, and aging. The molecular mechanisms of degeneration in Huntington's disease (HD) are also examined with respect to free radicals. Different antioxidant systems and their mechanisms of action are briefly reviewed in addition to the role of diet in aging. The effectiveness of selected synthetic drugs and natural products used in oxidative stress is also reviewed. Lastly, the chapter examines challenges associated with the use of antioxidants and how promising future directions like the endocannabinoid system is being pursued in the race to effectively manage NDs.

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INTRODUCTION

Since Moses Gomberg's first description of triphenylmethyl radical in literature in 1900, free radicals have remained an important subject of discussion owing to their numerous physiological effects (Gomberg, 1900). Initially they were not believed to be present in biological systems due its excessive reactivity. However, by the end of the second half of the 20th century, the scientific world had come to terms with the fact that free radicals are found in biological systems and contribute to several pathologies as well as aging (Lushchak, 2014). Today it is recognized that free radicals instigate oxidative stress and propagate neuronal injury thus playing a major role in NDs like AD, PD, amyotrophic disorders, PrD and several others (Khan et al., 2016). It is important to note that free radicals are not always deleterious such as the generation of nitric oxide in neurotransmission and the production of superoxide anion ($O_2^{\bullet}$) by activated microglia. There is a focus on free radicals in the central nervous system (CNS) and mechanisms involving free radicals in selected NDs. Free radicals are reviewed as potential targets of drug action in the management of NDs. Thus this chapter will evaluate what free radicals are and review their contribution to oxidative stress induced neurodegenerative disorders as well as aging. It is expected that at the end of this chapter further knowledge on the mechanisms of free-radical induced neurodegeneration in some NDs would have been gained in addition to an understanding of the prospects of novel therapeutic approaches. Overall, this chapter examines the interplay of free radicals and oxidative stress in the development and progression of several NDs.

BACKGROUND

Free radicals are exceptionally reactive atoms or molecules with one or more unpaired electrons and capable of independent existence (Halliwell, 1992). In some instances, free radicals have been used interchangeably with reactive oxygen species (ROS). While this may be correct sometimes, not all ROS are free radicals. Although both generate oxidative stress, ROS are chemically reactive species that contain oxygen and may or may not necessarily be a radical. For example, whereas hydrogen peroxide (H_2O_2) is a reactive oxygen species, it is not a free radical. Other examples include lipid, protein and nucleic acid peroxides. There are also reactive species that are not oxygen species such as reactive species of nitrogen (peroxynitrite ($ONOO^{\bullet}$) and nitric oxide ($^{\bullet}NO$)), carbon and sulfur.

However, the common denominator in all these terminologies is oxidative stress. Oxidative stress is a chemical process resulting from excessive free radical production due to an insufficiency of the counteracting antioxidant response system (Birben, Sahiner, Sackesen, Erzurum, & Kalayci, 2012). Free radicals and reactive species of oxygen or otherwise participate in chain reactions that culminate in oxidative stress. Normally in aerobic organisms, molecular oxygen is reduced to water via intermediate steps of oxygen reduction that forms $O_2^{\bullet}$, $H_2O_2$and the hydroxyl radical ($^{\bullet}OH$) (Halliwell & Gutteridge, 1990). Free radicals and other reactive species' production in the body is approximately balanced by antioxidant mechanisms needed to mop up these reactive species. However NDs as well as aging, the production of free radical is higher than antioxidant defense. Antioxidants are molecules which at minimal concentrations compared with that of an oxidizable substrate, appreciably slows or stops oxidation of that substrate (Halliwell & Gutteridge, 1990). These enzymatic or non-enzymatic antioxidants, reduce the potential damage of the reactive species thus only minor reactive species induced-damage occurs. Therefore, oxidative stress arises in the event of a significant disparity between the production of free