

## Chapter 2

# Oxidative Stress and Neurodegeneration

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### ABSTRACT

*Neurons are the building units of the nervous system and are therefore critical units for the health of the brain and the spinal cord. This is necessitated by their inability to be either replaced or reproduced once lost. Their losses are implicated in a number of conditions which have been elaborated in this chapter. Oxidative stress has been strongly implicated in neurodegeneration through blockade of neuroprotection by a number of mechanisms including inhibitory effect on insulin-like growth factor I (IGF-1) via stimulation of the transcription factor, Forkhead box O3 (FOXO3). This chapter elaborates on these two phenomena which cannot be decoupled.*

## **INTRODUCTION**

Neurodegenerative disorders (NDs) are a group of pathological disorders that primarily affect neurons and are associated with progressive loss of neuronal structure and function, and death (Khan et al, 2016). Neurodegeneration is manifested in a number of disorders including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), prion disease, ophthalmological diseases, etc (Khan et al, 2016; Tezel, 2006).

Neuronal loss is triggered by a number of mechanisms which include inflammation and oxidative stress (Harris, 2014; Barreto et al, 2011; Cabezas et al, 2012). Protein misfolding, compromised chronic oxidative stress response, excitotoxicity, altered calcium homeostasis, reduced cerebral blood flow and supply, impaired phosphorylation, loss of gene expression regulating ability, changes in proteases/inhibitors and environmental factors also play a role in neuronal loss (Khan et al, 2016; Sayre et al, 2001; Leszek et al, 2016).

Oxidative stress has also been implicated aetiologically in the development of neurodegeneration in other conditions such as HD, a trinucleotide CAG repeat expansion polyglutamate toxicity disorder (Hensley et al, 2006), and ALS (Polidori et al, 1999). Despite the huge hereditary and biochemical confirmation of increased oxidative stress in NDs, and also the established therapeutic benefits of antioxidants in animal models, there is no success with clinical use of antioxidants in human subjects. Accordingly, the role of oxidative stress in the pathogenesis of NDs stays disputable.

A number of causalities have been attributed to the development of neurodegeneration. Such factors include environmental and genetic causes; however, oxidative stress continues to be ascribed to play a focal pathogenic role in their development (Mark, 2004). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated in vivo as a result of oxidative stress and free radical generation. These two groups of reactive metabolites are believed to play a significant role in neurodegeneration (Emerit & Edeas, 2004). ROS are known to have significant impact on the neuronal biochemical composition. This is due to the high levels of unsaturated lipids in these neuronal biochemical molecules and their susceptibility to peroxidation and oxidative alterations (Uttara et al, 2009). Butterfield et al (2002) has also reported on the susceptibility of the double bonds in unsaturated fatty acids to free radical attack. This triggers a cascade of events that ultimately lead to the damage of neighbouring unsaturated fatty acids. Also, the brain tends not to have high levels of antioxidants to mop up free radicals when compared to other internal organs such as the liver (Uttara et al, 2009). Marklund et al (1982) has reported on the brain's reduced levels of catalase. This, coupled with the fact that the substantia nigra (SN) is enriched with iron and dopamine, both pro-oxidants, tend to increase the levels of reactive species in the brain (Zaleska et al, 1989). This chapter therefore discusses the relationship between oxidative stress and the development of NDs.

## **BACKGROUND**

The pathological signature of NDs is the gradual, progressive and selective loss of anatomically or physiologically related neural systems (Leszek et al, 2016). With the loss of neuronal architecture in these multiple circuits comes the altered integrity of neuronal tissues and irreversible loss of brain function. This is mostly seen as cognitive deficits, dementia, dyskinesia, behaviour deviations and psychological

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