Metals, oxidative stress and neurodegenerative disorders. K. Jomova, D. Vondrakova, M. Lawson, and M. Valko, *Mol. Cell. Biochem.*, **345**, 91–104 (2010).

The neurodegenerative diseases, Alzheimer's disease (AD) and Parkinson's disease (PD), are age-related disorders characterized by the deposition of abnormal forms of specific proteins in the brain. AD is characterized by the presence of extracellular amyloid plaques and intraneuronal neurofibrillary tangles in the brain. Biochemical analysis of amyloid plaques revealed that the main constituent is fibrillar aggregates of a 39-42 residue peptide referred to as the amyloid-β protein (Aβ). PD is associated with the degeneration of dopaminergic neurons in the substantia nigra pars compacta. One of the pathological hallmarks of PD is the presence of intracellular inclusions called Lewy bodies that consist of aggregates of the presynaptic soluble protein called α-synuclein. There are various factors influencing the pathological depositions, and in general, the cause of neuronal death in neurological disorders appears to be multifactorial.

However, it is clear, that the underlying factor in the neurological disorders is increased oxidative stress substantiated by the findings that the protein side-chains are modified either directly by reactive oxygen species (ROS) or reactive nitrogen species (RNS), or indirectly, by the products of lipid peroxidation. The increased level of oxidative stress in AD brain is reflected by the increased brain content of iron (Fe) and copper (Cu) both capable of stimulating free radical formation (e.g. hydroxyl radicals via Fenton reaction), increased protein and DNA oxidation in the AD brain, enhanced lipid peroxidation, decreased level of cytochrome c oxidase and advanced glycation end products (AGEs), carbonyls, malondialdehyde (MDA), peroxynitrite, and heme oxygenase-1 (HO-1). AGEs, mainly through their interaction with receptors for advanced glycation end products (RAGEs), further activate signaling pathways, inducing formation of proinflammatory cytokines such as interleukin-6 (IL-6). The conjugated aromatic ring of tyrosine residues is a target for free-radical attack, and accumulation of dityrosine and 3-nitrotyrosine has also been reported in AD brain. The oxidative stress linked with PD is supported by both postmortem studies and by studies showing the increased level of oxidative stress in the substantia nigra pars compacta, demonstrating thus the capacity of oxidative stress to induce nigral cell degeneration. Markers of lipid peroxidation include 4-hydroxy-trans-2-nonenal (HNE), 4-oxo-trans-2-nonenal (4-ONE), acrolein, and 4-oxo-trans-2-hexenal, all of which are well recognized neurotoxic agents. In addition, other important factors, involving inflammation, toxic action of nitric oxide (NO·), defects in protein clearance, and mitochondrial dysfunction all contribute to the etiology of PD.

It has been suggested that several individual antioxidants or their combinations can be neuroprotective and decrease the risk of AD or slow its progression. The aim of this review is to discuss the role of redox metals Fe and Cu and non-redox metal zinc (Zn) in oxidative stress-related etiology of AD and PD. Attention is focused on the metal-induced formation of free radicals and the protective role of antioxidants [glutathione (GSH), vitamin C (ascorbic acid)], vitamin E (α-Tocopherol), lipoic acid, flavonoids [catechins, epigallocatechin gallate (EGCG)], and curcumin. An alternate hypothesis topic in AD is also discussed.