

# Neurodegenerative Diseases and Oxidative Stress

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**Abstract:** *Oxidative stress has been implicated in the progression of Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis. Oxygen is vital for living organisms but is also potentially dangerous and a complex balanced system exists for utilizing it. Oxidative stress (OS) is the result of an imbalance in pro-oxidant/antioxidant homeostasis that leads to the generation of toxic reactive oxygen species. The systems in place to regulate the biochemistry of oxygen are complex and not very well known.*

**Keywords:** Oxidative stress, reactive oxygen species

## 1. Introduction

Absorption of oxygen by living organisms is carried out in two main directions: constructive – by enzymatic controlled processes of biological oxidation which give the necessary life energy and destructive – through free radical oxidation processes that violate the organism's normal biological functions. Under normal conditions there is a delicate balance between the production of reactive oxygen metabolites and their elimination by the defense systems of the human organism. There is enough evidence that demonstrate the involvement of ROS in a number of physiological and pathophysiological processes (Mills E et al. 1998, Abou-Seif M et al, 2000, Griendling K et al, 2000, Mileva M et al 2004, Gadjeva V et al., 2005). At low concentrations ROS play an important role as regulatory mediators in signaling processes in the course of cell differentiation, proliferation, apoptosis, cellular immunity, cellular defense against microorganisms, melanogenesis and aging (Shackelford R et al., 2000, Tatla S et al, 1999, Ghosh J et al. 1998, Lajarin F et al, 1999, Mates J et al, 2000). Conversely, at high concentrations free radicals and their derivative non-radical reactive compounds are dangerous to living organisms as they are detrimental to the major cellular components.

Violation of the balance between the ROS producing processes and the antioxidant defense system gives rise to oxidative stress, causing cellular damages and direct inhibition of enzyme proteins (Chopra S et al 1998, Hemnani T, Parihar M 1998). Oxidative stress is the imbalance between the biochemical ROS generating processes and the capacity of a certain biological system to neutralize them. As a result, ROS are formed faster than cellular defense systems can eliminate them (Gadzheva V, 2007). Development of oxidative stress and its consequences depend on the capabilities of the body, alone or with intervention from outside, to restore the physiological balance between pro-oxidants and antioxidants (Himmelfarb J, Hakim R, 2003, Patterson R, Leake D 1998).

The term “redox signaling” is used to describe a regulatory process in which the signal is given by oxidation reduction processes. Redox signaling is used by a large number of organisms, including bacteria, and serve to induce protective responses against oxidative damage and restore the normal state of “redox-homeostasis” after transient ROS attacks.

Neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis, are developed upon the progressive loss of specific neuronal cell populations and are associated with protein aggregate. A common feature of these diseases is oxidative stress, which might be responsible for the dysfunction or death of neuronal cells that contributes to disease pathogenesis. Oxidative stress is the result of unregulated production of reactive oxygen species (ROS), such as hydrogen peroxide, nitric oxide, superoxide and the highly reactive hydroxyl radicals. High oxygen consumption, relatively low antioxidant levels and low regenerative capacity result in brain tissue being susceptible to oxidative damage. Unsaturated lipids are particularly susceptible to oxidative modification and lipid peroxidation and are a sensitive marker of oxidative stress. Lipid peroxidation is the result of attack by radicals on the double bond of unsaturated fatty acids, such as linoleic acid and arachidonic acid, to generate highly reactive lipid peroxy radicals that initiate a chain reaction of further attacks on other unsaturated fatty acids. The chain reaction leads to the formation of breakdown products including 4-hydroxy-2,3-nonenal (HNE), acrolein, malondialdehyde and F2-isoprostanes. Elevated levels of this product have been observed in Parkinson's disease brain tissue (Dexter D et al 1989). Malondialdehyde is also increased.

All four bases of DNA are susceptible to oxidative damage involving hydroxylation (Gabbita S, Lovell M, Markesbery W, 1998). Increased levels of 8-hydroxyguanine and 8-hydroxy-2-deoxyguanosine are observed in Parkinson's disease. The selective attack on guanine bases is mediated by OH radicals as the oxidative species (Alam Z et al 1997). Cells have endogenous defence mechanisms against oxidative stress and changes in these are also used as markers

of this stress. In the brain of patients with Parkinson's disease and Alzheimer's disease the activity of the antioxidant proteins catalase, superoxide dismutase (SOD), glutathione peroxidase and glutathione reductase is increased.

The reactive oxygen species (ROS) are very reactive and will react with a multitude of different molecules to initiate neuronal cell death and hence neurodegeneration through an array of different pathways. Oxidative stress (that is, oxidation of lipids, proteins and DNA) results in impaired cellular functions and the formation of toxic species, such as peroxides, alcohols, aldehydes, ketones and cholesterol oxide. The latter is toxic to lymphocytes and blood vessel macrophages (Ferrari C, 2000).

The oxidatively modified lipids acrolein and HNE induce toxicity by crosslinking to cysteine, lysine and histidine residues. Acrolein down-regulates the uptake of glutamate and glucose from cell culture (Lovell M, Xie C, Markesbery W, 2000), whereas HNE modifies proteins resulting in a multitude of effects, including inhibition of the neuronal glucose transporter type-3, the glutamate transporter GLT-1, as well as the Na, K ATPases (Mark R, Hensley K, Butterfield D et al, 1995). HNE activates c-Jun aminoterminal kinases and mitogen-activated protein kinase-1, thereby stimulating an apoptotic cascade (Tamagno E et al, 2003). Modifications to proteins result in the impairment of enzymes, for example, glutamine synthase, superoxide dismutase, etc., whereas ROS interactions with DNA lead to mutations.

The excessive generation of ROS leads to dysregulation of intracellular calcium signalling, and such dysregulation has been widely spread in neurodegenerative diseases in which aberrant calcium levels stimulate multiple pathways that ultimately induce an apoptotic cascade.

One of the downstream events that occurs in response to an ROS-induced calcium influx is an excitotoxic response (Mattson M, Chan S, 2003, Yamamoto K et al 1998).

The generation of ROS requires the activation of molecular oxygen. As its utilization is a prerequisite for most life forms, its side effects must be overcome. Organisms have evolved a range of metalloenzymes to take advantage of the interactions between oxygen and metal ions to activate molecular oxygen as ROS. The subsequently formed free radicals are a part of normal metabolism. As ROS are also toxic, cells have developed highly elaborate mechanisms of regulating both metal ion interactions and the generation of ROS. The same properties that cells harness for beneficial means become destructive when the regulatory processes breakdown. ROS are produced by a number of different pathways, including direct interactions between redox-active metals and oxygen species via reactions such as the Fenton and Haber-Weiss reactions, or via indirect pathways involving the calcium activation of metallo-enzymes such as phospholipases, nitric oxide synthase and xanthine dehydrogenase. Calcium is crucial to signal transduction and as such is sensitive to a number of different stimuli and able to elicit a variety of different cellular responses. There is a large body of evidence documenting disruption of calcium homeostasis in

neurodegenerative diseases, leading to a breakdown in a large number of cellular processes. Increases in intracellular calcium have been reported to induce the production of ROS (Lewen A, Matz P, Chan P, 2000) and, furthermore, ROS have been shown to be important cell signalers that induce an increase in cytosolic calcium. As a general principle, the chemical origin of the majority of ROS is the reaction of molecular oxygen with the redox-active metals copper and iron (Hallwell B, Gutteridge J, 1999). One of the consequences of normal aging is that the levels of the redox-active metals copper and iron in the brain increase. This increase could lead to hypermetallation of proteins that normally bind redox-active metals at shielded sites. Adventitious binding - for example; at a loading site - will increase the likelihood that ROS are generated inappropriately, leading to the oxidative stress that is observed in neurodegenerative diseases.

Several clinical studies in mice have shown that one of the consequences of normal aging is a rise in the levels of copper and iron in brain tissue (Maynard C et al, 2002). The brain is an organ that concentrates metal ions and recent evidence suggests that a breakdown in metal homeostasis is a key factor in the development of a variety of age-related neurodegenerative diseases (Bush A, 2003).

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