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# Role of oxidative stress in Alzheimer's disease (Review)

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**Abstract.** Alzheimer's disease (AD) is the most common cause of disability in individuals aged >65 years worldwide. AD is characterized by the abnormal deposition of amyloid β (Aβ) peptide, and intracellular accumulation of neurofibrillary tangles of hyperphosphorylated τ protein and dementia. The neurotoxic oligomer Aβ peptide, which is the neuropathological diagnostic criterion of the disease, together with τ protein, are mediators of the neurodegeneration that is among the main causative factors. However, these phenomena are mainly initiated and enhanced by oxidative stress, a process referring to an imbalance between antioxidants and oxidants in favour of oxidants. This imbalance can occur as a result of increased free radicals or a decrease in antioxidant defense, free radicals being a species that contains one or more unpaired electrons in its outer shell. The major source of potent free radicals is the reduction of molecular oxygen in water, that initially yields the superoxide radical, which produces hydrogen peroxide by the addition of an electron. The reduction of hydrogen peroxide produces highly reactive hydroxyl radicals, termed reactive oxygen species (ROS) that can react with lipids, proteins, nucleic acids, and other molecules and may also alter their structures and functions. Thus, tissues and organs, particularly the brain, a vulnerable organ, are affected by ROS due to its composition. The brain is largely composed of easily oxidizable lipids while featuring a high oxygen consumption rate. The current review examined the role of oxidative stress in AD.

**Contents**



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## 1. Introduction

Oxidative stress, a process increased in the brain with aging, is induced by an imbalance in the redox state, involving the generation of excess reactive oxygen species (ROS) or the dysfunction of the antioxidant system (1). The mitochondrial electron transport chain consumes almost 98% of molecular oxygen at the cytochrome oxidase complex and the remaining oxygen is reduced to hydrogen peroxide and superoxide radicals. During normal metabolism and various functions the oxygen radical superoxide ($O_2^{\bullet-}$) and the non-radical oxidant hydrogen peroxide ($H_2O_2$) and hypochlorous acid are produced (2). When the production of ($O_2^{\bullet-}$) and ($H_2O_2$) becomes excessive, they can result in tissue damage that often involves the generation of the highly reactive hydroxyl radical ($OH^{\bullet}$) and other oxidant molecules in the presence of catalytic iron or copper ions (3). Accordingly, since metal catalyzes redox reactions (3), one of the major forms of antioxidant defense consists of storing and transporting the iron in forms that do not catalyse the formation of reactive radicals (4), as is the case during tissue injury, in which there is an increase in iron availability that can accelerate free radical reactions (4).

Although it is rich in biometals and lipids, the brain has abundantly peroxidation-susceptible lipid cells and is an organ with a high demand for oxygen (5). Additionally, the cerebrospinal fluid cannot bind released iron ions (5). Consequently, oxidative stress on nervous tissue may seriously damage the brain via several interacting mechanisms, including an increase in intracellular free $Ca^{2+}$, release of excitatory amino acids, and neurotoxicity (5,6). Other important sources or modulators of oxidative stress, include reactive nitrogen species (RNS), including nitric oxide (NO) and peroxynitrite which can particularly be extremely reactive with proteins, lipids, nucleic acid and other molecules in further altering structure and/or functionalities leading to detrimental effects for the brain (7-9). Cells with an accumulation of oxidized products such as aldehydes and isoprostanes, protein carbonyls, and base adducts from DNA oxidation can be seriously altered (10). Consequently, the considerable ROS formation increased by the electron transport system within the mitochondria under stressful conditions and in aging constitutes a risk for developing Alzheimer's disease (AD), when no efficient antioxidant system is available. Thus, mitochondria function as both the source and target of toxic ROS since mitochondrial dysfunction and oxidative stress are important in aging and neurodegenerative diseases, particularly AD (11,12).

This late-onset and sporadic illness affects mostly individuals >65 years worldwide (13) and is characterized by the abnormal deposition of the amyloid β (Aβ) peptide, intracellular accumulation of neurofibrillary tangles of hyperphosphorylated τ protein, loss of synapses and dendritic spines, cholinergic denervation, hypoperfusion and hyperemia (14). The neurotoxic oligomer Aβ peptide (15), which is the neuropathological diagnostic criterion of the disease, together with τ protein, constitute mediators of neurodegeneration, which is among the main causative factors of impaired synaptic plasticity, neuroinflammation, part of vascular reactivity impairment, cholinergic denervation, neurotransmitter imbalance, neuronal loss, dendritic alterations and substantial synaptic loss (16) through oxidative stress (17). Mechanisms by which mitochondrial dysfunction leads to neuron degeneration in AD are believed to be associated with ROS generation, activation of mitochondrial permeability transition, excitotoxicity, impaired production of adenosine triphosphate and altered calcium homeostasis (18). They suggest a pivotal role for oxidative stress in the pathophysiology of AD, which is the focus of the current review.

## 2. Oxidative stress

Oxidative stress encompasses a variety of molecules and free radicals deriving from molecular oxygen. These free radicals are chemical species carrying one unpaired electron in the outer shell (1). Molecular oxygen in the ground state is a bi-radical with two single electrons in the outer shell, sharing the same spin. Accordingly, since the oxygen molecule is able to react with one electron at a time, oxygen is not extremely reactive with the electrons in a chemical bond (1). Therefore, when one of the two electrons is excited it spins. The two electrons exhibit opposing spins and are able to quickly react with other pairs of electrons, particularly double bonds. The resulting singlet oxygen becomes a powerful oxidant (19). The reduction of oxygen by one electron produces fairly stable intermediates leading to the formation of a superoxide anion ($O2^{\bullet -}$), the precursor of most ROS and mediator in oxidative stress chain reactions. Additionally, $O2^{\bullet -}$ is partially reduced by antioxidants to a hydroxyl radical ($OH^{\bullet}$), one of the strongest oxidants in nature. This reaction is catalysed by reduced transition metals, which in turn may be reduced again by $O2^{\bullet -}$ thereby propagating the process (19). Furthermore, $O2^{\bullet -}$ also reacts with other radicals such as $NO^{\bullet}$ under the control of the rate of diffusion of the two radicals and results in the formation of peroxynitrite (20), which is an extremely powerful oxidant driving oxidants termed RNS (21,22). Accordingly, ROS and/or RNS constitute the main players, which in the presence of limited antioxidant defences induce oxidative stress. ROS and/or RNS have a dual role in intracellular signalling, cell proliferation and survival (23,24). However, when a slight fluctuation in the steady-state concentration becomes uncontrolled it may lead to increases in the steady-state concentration, resulting in free radical-mediated chain reactions that indiscriminately target lipids (25), proteins (26), polysaccharides (27) and even DNA (28,29).

However, as mentioned above, *in vivo* $O2^{\bullet -}$ is produced by mitochondria, under the control of enzymatic and non-enzymatic processes (30). The mitochondria electron transport chain contains a number of redox centres that leak electrons to oxygen, and contains the main sources of $O2^{\bullet -}$ in the majority of tissues (30,31). Thus, the major enzymatic sources of $O2^{\bullet -}$ are NADPH oxidases located in various cell membranes, including polymorphonuclear, macrophages and endothelial cells (32-34), as well as cytochrome $P450^{\bullet -}$ and $H_2O_2$-dependent oxygenases (35,36). Another enzymatic source of $O2^{\bullet -}$ as a source of $OH^{\bullet}$ is the proteolytic conversion of xanthine dehydrogenase to xanthine oxidase (37). The non-enzymatic production of $O2^{\bullet -}$ occurs via the direct transfer of oxygen by reduced coenzymes or prosthetic groups, such as flavin, iron sulfur clusters, or by xenobiotics after a previous reduction by enzymes, including anticancer agents or herbicides (38).

However, mitochondria also prevent ROS and regulate the steady-state concentration of $O2^{\bullet -}$ in the intermembrane space by three different mechanisms. The first mechanism involves the enzyme superoxide dismutase (SOD) (39), acting through the dismutation of $O_2$ and producing hydrogen peroxide (H2) in fully reduced water product. There are two types of SOD including the specific mitochondrial matrix containing the manganese active site (40) (MnSOD or SOD2), which eliminates $O2^{\bullet -}$ formed in the matrix or on the inner side of the inner membrane, and SOD containing copper and zinc (41) instead of manganese SOD (copper-zinc SOD or SOD1) located in the cytoplasm of eukaryotic cells. The second mechanism is associated with cytochrome *c* in the intermembrane space that can reduce $O2^{\bullet -}$ (42) to regenerate oxygen in the process (43), glutathione peroxidase which mostly decomposes $O2^{\bullet -}$ and $OH^{\bullet}$ (44), and catalase, the major detoxifying enzyme identified in peroxisomes (45). Ubiquinol (QH2) is another carrier appearing to have a detoxifying role against ROS, acting as a reducing agent in the elimination of various peroxides in the presence of succinate (46). The mitochondrion also has a variety of DNA-repairing enzymes that correct errors resulting from $O_2$ damage, since the mitochondrial chromosome contains 5% (vs. 95% encoded by nuclear DNA) of genes from several important proteins such as the subunits of nicotinamide adenine dinucleotide dehydrogenase and cytochrome oxidase and cytochrome *b* (9).

Therefore, under normal conditions, there is a balance between ROS formation and antioxidant. This equilibrium is disrupted during several pathological scenarios in which the antioxidant defences become insufficient, resulting in oxidative stress often leading to apoptosis, a mechanism used by organisms to eliminate redundant or damaged cells (47), and/or cell death.

## 3. Role of oxidative stress in Alzheimer's disease

The brain of patients suffering AD present a significant extent of oxidative damage associated with the abnormal marked accumulation of Aβ and the deposition of neurofibrillary tangles (48). Mounting evidence suggests an important role played by biometals including iron, zinc and copper in Aβ and neurodegeneration (49). In concordance with those findings, there are high affinity binding sites for copper and zinc on the N-terminal metal-binding domains of Aβ and its precursor APP (50,51) while copper is a potent mediator of the highly reactive hydroxyl radical ($OH^{\bullet}$), and consequently contributes to the increase of oxidative stress characteristic of AD

brain (52) according to the high concentration of copper found in amyloid plaques (53). This seems to be associated with the length of Aβ fragments, with Aβ (1-42) being more toxic than Aβ (1-40) and the most likely candidate to generate hydrogen peroxide and other ROS (54). In addition, high concentrations of zinc were associated with memory and cognitive regions of the brain, including the neocortex and amygdala, and hippocampus, which are mostly affected in AD pathology (55,56). This binding of zinc has a highly ordered conformational state of Aβ (1-40), leading to the production of toxic, fibrillary, Aβ aggregates. Consequently, the immunological/inflammatory response to non-soluble Aβ plaques involves the disruption of zinc homeostasis followed by uncontrolled cerebral zinc release, which is typical for oxidative stress. Thus, the uncontrolled accumulation of zinc or Aβ leads to zinc-induced and Aβ-mediated oxidative stress and cytotoxicity (57).

Therefore, whereas the brain membrane phospholipids are composed of polyunsaturated fatty acids, this organ is particularly vulnerable to free radical attacks. Their double binds allow the removal of hydrogen ions (58) and increased lipid peroxidation, which is the most prominent feature in which degenerative change is most pronounced in the AD brain (59). In addition, the oxidation of proteins by free radicals may be significant in AD as the oxidation of brain proteins can affect enzymes critical to neuron and glial functions. This is the case for two enzymes especially sensitive to oxidative modification, that of glutamine synthetase and creatine kinase, which are markedly reduced in AD brains (60), reflecting the alteration of glutamate concentrations and enhancement of excitotoxicity, whereas oxidative impairment of creatine kinase may cause decreased energy metabolism in AD (61). The pathologic aggregation of protein leads to fibril formation and insolubility (62). Thus, neurofibrillary tangles are characterized by the aggregation and hyperphosphorylation of the τ protein into paired helical filaments. Phosphorylation is linked to oxidation through the microtubule-associated protein kinase pathway and through activation of the transcription factor nuclear factor-κB, thus potentially linking oxidation to the hyperphosphorylation of τ proteins (63). Protein oxidation is also capable of inducing advanced glycation end products as a post-translational modification of proteins that are formed when amino group of proteins react non-enzymatically with monosaccharides (64). Furthermore, oxidation of the brain can affect DNA, producing strand breaks, sister chromatid exchange, DNA-protein crosslinking, and base modification (65).

Thus, the overproduction of ROS resulting in oxidative stress may have a deleterious effect and can be an important mediator of damage to cell structures and consequently various disease states and aging. However, antioxidant treatments have demonstrated that AD is associated with oxidative stress, being a more complex disease.

## 4. Conclusion

Although AD is probably associated with multiple etiologies and pathophysiologic mechanisms, oxidative stress appears as a major part of the pathophysiologic process. Accordingly, the mitochondrial respiratory chain constitutes the main intracellular source of ROS in most tissues. The resulting oxidants are maintained at a non-toxic steady-state concentration by a variety of antioxidant defences and repair enzymes. The delicate balance of oxidants/antioxidants defences and ROS production may be disrupted by deficient antioxidant defences, inhibition of electron flow or exposure to xenobiotics, becoming the common denominator in pathological processes associated with oxidative insult leading to tissue damage and/or death. Therefore, changes in the balance of redox transition metal, particularly of iron and copper are crucial. This is a significant role for oxidative brain in AD since the brain is vulnerable to oxidative stress. However, multicenter trials support the capacity of antioxidant treatment effects in the retardation of the progression of AD, suggesting the complexity of AD. Additional studies are required to gain a better understanding of the disease.

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