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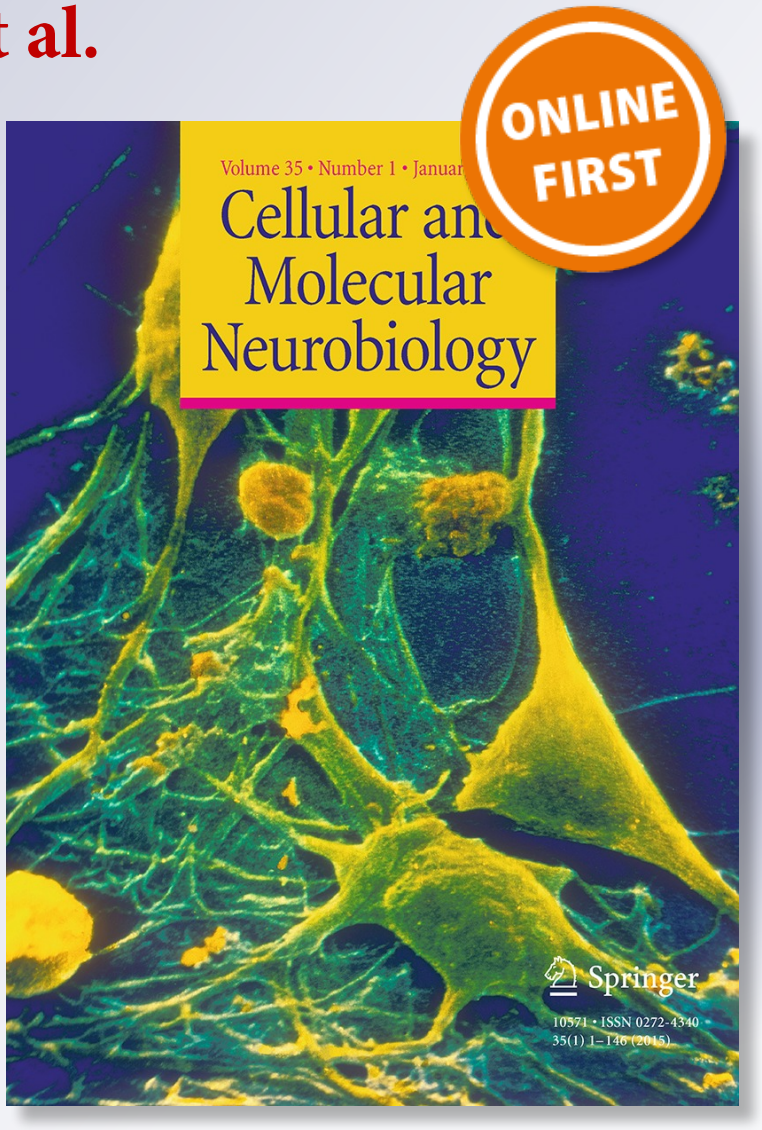

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REVIEW PAPER

Oxidative Stress in Alzheimer's Disease: Should We Keep Trying Antioxidant Therapies?

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Abstract The risk of chronic diseases such as Alzheimer's disease is growing as a result of the continuous increasing average life span of the world population, a syndrome characterized by the presence of intraneural neurofibrillary tangles and senile plaques composed mainly by beta-amyloid protein, changes that may cause a number of progressive disorders in the elderly, causing, in its most advanced stage, difficulty in performing normal daily activities, among other manifestations. Therefore, it is important to understand the underlying pathogenic mechanisms of this syndrome. Nevertheless, despite intensive effort to access the physiopathological pathways of the disease, it remains poorly understood. In that context, some hypotheses have arisen, including the recent oxidative stress hypothesis, theory supported by the involvement of oxidative stress in aging, and the vulnerability of neurons to oxidative attack. In the present revision, oxidative changes and redox mechanisms in Alzheimer's disease will be further stressed, as well as the grounds for antioxidant supplementation as adjuvant therapy for the disease will be addressed.

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Keywords Alzheimer's disease · Amyloid protein · Antioxidants · Free radicals · Oxidative stress

Abbreviations

AD	Alzheimer's disease
AGE	Advanced glycation end products
ApoE	Apolipoprotein E
ATPase	Adenylpyrophosphatase
βA	Beta-amyloid
BACE-1	Aspartate β-secretase 1
βAPP	Protein precursor of βA
CNS	Central nervous system
DHEAS	Reduced dehydroepiandrosterone sulfate
GSH-Px	Glutathione peroxidase
GSK-3β	Glycogen synthase kinase 3β
H_2O_2	Hydrogen peroxide
IL	Interleukin
iNOS	Inducible nitric oxide synthase
MDA	Malondialdehyde
NAC	*N*-Acetylcysteine
NFkB	Nuclear factor kappa B
NMDA	*N*-Methyl-D-aspartate
NO	Nitric oxide
$O_2^{\bullet -}$	Superoxide
$OH^{\bullet}$	Hydroxyl radical
$ONOO^-$	Peroxynitrite radical
PI3K	Phosphatidylinositol 3-kinase
PS	Presenilin
RAGE	AGE receptors
ROS	Reactive oxygen species
sAPPβ	Fragment of the amyloid precursor protein
SOD	Superoxide dismutase
TNF-α	Tumor necrosis factor alpha

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Introduction

Alzheimer's disease (AD) was first described in 1901 by the German psychiatrist Alois Alzheimer, who followed a 51-year-old patient until death and observed the patient's neuropsychological condition. After performing an autopsy, the doctor found a formation of plaques and tangles in the brain, which became the histopathological hallmark of the disease (Morris and Salmon 2007). Many years after the study by Alzheimer, the structures he studied have been well characterized and are known as neurofibrillary tangles and senile plaques consisting mainly of the beta-amyloid protein (βA protein; Kang et al. 1987; Glenner 1988; Braak and Braak 1991). AD is primarily a disorder of the cerebral cortex, and it appears that neurodegeneration spreads from there to other areas (Braak and Braak 1991).

This neuropathology is most commonly associated with aging and features certain particular characteristics that are observed at various clinical stages (Vas et al. 2001):

The first clinical feature noted in AD patients is short-term memory deficit. The most notable aspect is a pattern of intellectual function loss that follows the principle of "last to be learned, first to be lost". This feature is represented by the loss of cognitive and intellectual functions, which are largely dependent on the hippocampus and basal forebrain, and culminates in patient incapacitation.

More advanced stages of AD are characterized by spatial disorientation and planning disorders (executive functions) that culminate in the patient having difficulty performing daily activities such as bathing, oral care, and dressing. Moreover, the patient's behavior is impaired by the onset of frank psychosis, with agitation and disinhibition (Caramelli and Barbosa 2002).

Currently, the clinical stages of AD are divided into two groups according to the time of first symptom onset. Late-onset or senile AD, which emerges after the age of 65 years, affects nearly 90 % of patients. AD occurs more rarely before the age of 65 years (early-onset or pre-senile AD); early-onset AD is characterized by a rapid decline of cognitive functions and is subject to autosomal dominant genetic influence (Truzzi and Laks 2005).

Considering the trend toward an aging global population and a possible growth in cases of chronic diseases that typically affect individuals older than 60 years, there has been an increase in the number of studies attempting to elucidate the cellular and molecular events associated with neuronal cell death. Such studies indicate a strong involvement of free radicals and antioxidant defenses in the physiopathological phenomena observed in AD. As a result of such studies, new drugs may be developed to treat AD.

Disease Epidemiology

The aging of the global population reflects an increase in life expectancy, improvement of health services, and significant advances in the health sciences that have established novel prevention and treatment options for various illnesses. However, with aging, individuals are more likely to develop chronic degenerative diseases that particularly affect those older than 60 years of age (Alzheimer's Disease International 2009).

Within this context, it should be noted that chronic diseases are already the major cause of death in all regions of the world, except for Sub-Saharan Africa. This pattern increases the need for health policies that prioritize special care for the health of the elderly, guaranteeing equality in access to benefit elderly patients with disabilities such as senile dementia (Ferri et al. 2005).

Dementia can be considered a syndrome that may be caused by a series of progressive illnesses affecting memory, thought, behavior, and the ability to perform daily activities, especially in the elderly. However, the number of cases that begin before the age of 65 years is growing. After 65 years, the probability of developing dementia practically doubles every 5 years. AD is the most common type of dementia, followed by vascular dementia (Batsch and Mittelman 2012). It is estimated that 10 million adults suffer from AD worldwide (Cummings et al. 2006).

Nitrini (1999) claims that AD has changed since the 1970s from a relatively rare condition to one of the most common dementias, causing substantial worry among the population. The author also claims that there are two causes for such a change: population aging and an extension of the concept of AD.

The World Alzheimer Report-2009 (Alzheimer's Disease International 2009) warned of the increase in dementia cases, estimating that 35.6 million persons worldwide lived with dementia in 2009. The report predicted that the number of persons affected would double every 20 years and reach 65.7 million in 2030 and 115.4 million in 2050. Most of the predicted cases (nearly 70 %) were in low- to middle-income countries. Such numbers are highly relevant for health systems around the world.

Due to the alarming picture of an emergency regarding dementia cases, the global cost of this disease was estimated at US$ 604 billion in 2010. The greatest preoccupation of global health agencies is to prepare health systems and financial systems for this future scenario and to ensure early diagnosis and treatment to slow degeneration (Wimo and Prince 2010).

Another important issue rose in the World Alzheimer Report-2011 (Prince et al. 2011) is that less than one in four persons worldwide with dementia receive a formal diagnosis; therefore, few patients receive appropriate care,

treatment, and support. The 2012 report follows up on this issue and reveals that nearly one in four persons with dementia (24 %) hides or conceals the diagnosis and reports social stigma as the main motive. In addition, 40 % of persons with dementia report that they are excluded from society, and nearly two out of three persons with dementia and their healers perceive a lack of understanding regarding dementia in their country (Batsch and Mittelman 2012).

Therefore, AD is one of the great challenges to be addressed in the Third Millennium by the elderly health-care sector. Fortunately, studies are steadily advancing to develop effective therapeutic strategies seeking to prevent neuronal cell death.

Disease Physiopathology

AD is an extremely complex illness that is histopathologically characterized by massive synaptic loss and neuronal cell death observed in the parts of the brain responsible for cognitive functions including the cerebral cortex, hippocampus, entorhinal cortex, and ventral striatum (Mann 1985; Hyman et al. 1990).

The main histopathological markers present in the brain parenchyma of patients with AD are as follows: the formation of extracellular senile plaques; the formation of intracellular neurofibrillary tangles from the accumulation of abnormal filaments of the tau protein (Fig. 1); glial activation; and inflammation (Alzheimer 1907; Terry 1985; Price 1986).

Based on these neuropathological markers, various hypotheses have been developed regarding disease pathogenesis: the cholinergic hypothesis (Whitehouse et al. 1982); the amyloid cascade hypothesis (Graeber et al. 1998; Golde 2006); the neuronal cytoskeleton hypothesis (Golde 2006); the tau and βA protein joint action hypothesis (Ittner and Gotz 2011); and the oxidative stress hypothesis (Christen 2000).

The Cholinergic Hypothesis

The cholinergic hypothesis was the first to be formulated in the description of physiological mechanisms of AD and suggests that the disease develops as a consequence of a cholinergic transmission deficiency in the patient (Whitehouse et al. 1982).

The cholinergic system originates in the forebrain and projects throughout the cerebral cortex. In AD, there is a marked loss of neurons in the basal forebrain nuclei; this loss generally exceeds 75 % of all cholinergic neurons at the moment of autopsy and leads to a reduction in the enzyme choline acetyltransferase in the hippocampus and cerebral cortex (Whitehouse et al. 1982; Lanctôt et al. 2003). This decrease in cholinergic activity in the central nervous system (CNS) correlates with dementia severity (Perry et al. 1978). A study supporting this hypothesis performed using an experimental model found that cholinergic system dysfunction is sufficient to produce a memory deficit similar to that described for AD (Bartus and Emerich 1999).

Another interesting finding from the brains of AD patients is the degeneration of cholinergic neurons, with reduced activity of the enzymes acetylcholinesterase and choline acetyltransferase in the cerebral cortex (Auld et al. 2002). The reduction in acetylcholinesterase in the frontal and parietal cortices correlates with the onset of dementia, the amount of senile plaques and intraneuronal neurofibrillary tangles, and early patient death (Gattaz et al. 2004). One of the early therapeutic strategies still in use seeks to improve the clinical condition of AD patients by restoring cholinergic transmission in the CNS using cholinesterase inhibitors, thereby increasing acetylcholine concentrations in the synaptic cleft (Uwano et al. 2012). Drugs such as tacrine, donepezil, and rivastigmine act by inhibiting the major isoforms of cholinesterase present in the CNS: acetyl and butyrylcholinesterase (Forlenza 2005).

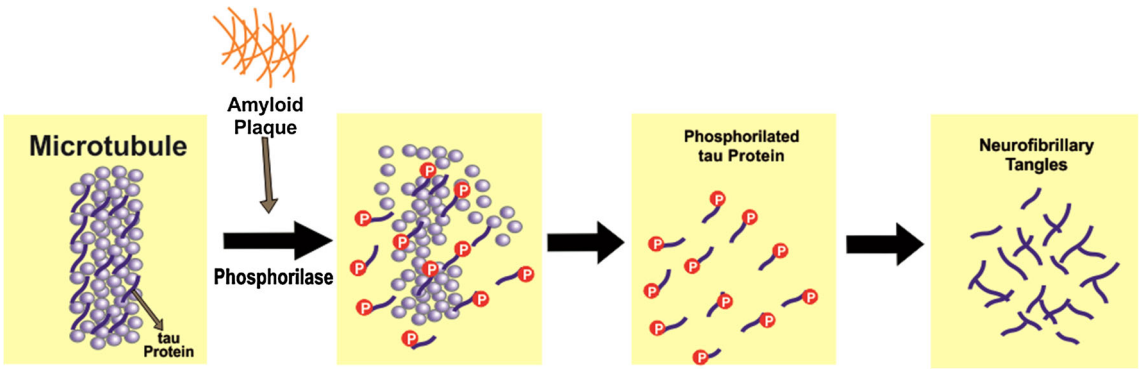

Fig. 1 Action of βA protein aggregates on tau protein. *βA* beta amyloid, *P* phosphorus

The Amyloid Cascade Hypothesis

This hypothesis was formulated due to studies indicating the involvement of a genetic disorder in the emergence of AD (Lowenberg and Waggoner 1934). This disorder is related to the expression of the protein precursor of βA (βAPP) or other genes that control amyloid processing. It is known that four genes are implicated in the pathogenesis of AD: the genes for βAPP (Cai et al. 1993; Lo et al. 1994; St George-Hyslop 1995; Tanzi et al. 1996); the presenilin 1 and 2 (PS1 and PS2) genes (Sherrington et al. 1995; Hutton et al. 1996; Hardy 1997); and the apolipoprotein E (ApoE) gene (Payami et al. 1993).

Notably, alteration of the processing of the βA protein, through its precursor βAPP, plays a critical role in AD pathogenesis. This finding increased interest in discovering the mechanism by which the βA protein is formed, describing the process by which it accumulates in the form of senile plaques, and elucidating how this protein can lead to neuronal damage (Golde 2006).

Various human diseases associated with amyloidosis such as type II diabetes mellitus and other brain amyloidosis such as transmissible spongiform encephalopathies share properties such as βA protein deposits associated with AD including the following: (I) a secondary structure (β-pleated sheet) that can easily polymerize and form aggregates; (II) low solubility; (III) filamentous microscopic aspect; (IV) ability to combine with other proteins such as proteoglycans and apolipoproteins; (V) emerald green color when stained with Congo Red and visualized under polarized light; and (VI) cytotoxicity under specific circumstances (Behl 1999).

The amyloid deposits present in AD consist of aggregates of βA proteins containing 40 or 42 amino acids. The βA40 protein is normally produced in low quantities, and mutations in the previously mentioned genes promote the overproduction of the βA42 protein (Hardy 1997). Both proteins are involved in the formation of senile plaques; however, the βA42 isoform has a greater tendency to participate than βA40 because it is less soluble and appears to be mainly responsible for aggregate formation (Behl 1999).

The isoforms are produced by proteolytic cleavage of βAPP—a transmembrane glycoprotein constitutively expressed in neurons with an unknown function—by the activity of enzymes that release its transmembrane domain, the βA portion (Zinser et al. 2007). The following three types of proteolytic enzymes participate in this process: α-, β-, and γ-secretases. After cleavage, βAPP can proceed to amyloidogenic processing, which leads to the release of a βA protein, or to non-amyloidogenic processing, which cleaves βAPP differently and prevents βA formation (Selkoe 1993).

The gene that encodes βAPP is located on human chromosome 21. Notably, patients with chromosome 21 trisomy, which occurs in Down's syndrome, develop neuropathological changes identical to those in AD patients, differing only by the young age at onset (Behl 1999).

The formation of βA begins when βAPP is subjected to the proteolytic action of enzymes with β-secretase activity such as the enzyme aspartate β-secretase 1 (BACE-1), which releases the soluble fragment of the amyloid precursor protein (sAPPβ) into the extracellular medium. The fragment that remains bound to the membrane is the target of an enzymatic complex with γ-secretase activity, which is responsible for the intramembrane cleavage of the remaining βAPP fragment and releases the βA protein into the extracellular medium (Selkoe 1993).

Non-amyloidogenic processing begins when βAPP becomes the target of enzymes with α-secretase activities, which are membrane-embedded metalloproteases that cleave βAPP within the amyloid domain and release the soluble fragment resulting from α-secretase activity, sAPPα, into the extracellular medium. This fragment plays a neuroprotective role by preventing βA formation (Zinser et al. 2007).

Various factors can influence the βAPP-processing pathway. Acetylcholine, activation of protein kinase C, and the female hormone estrogen can stimulate non-amyloidogenic processing of βAPP (Nitsch et al. 1994). It is known that sAPPα has an autocrine function, stimulates cell proliferation, and protects neurons against excitotoxic and oxidative damage (Saitoh et al. 1989; Schubert et al. 1989; Goodman and Mattson 1994; Goodman et al. 1994).

Mutations in βAPP genes and PS genes promote βA formation, especially βA42 (De Strooper et al. 1998; Behl 1999). Mutations in the ApoE gene, especially ApoE4, also predispose individuals to AD; this effect most likely occurs because ApoE4 promotes βA aggregation (Hardy 1997).

The finding that βA protein has neurotoxic properties was the first indication of a possible correlation between βA and neuropathological lesions specific to AD. Thus, it was proposed that the initial physiopathology of AD induced by βA involves changes to the structure and function of cellular membranes (Muller et al. 1995).

The neurotoxicity of βA aggregates may be related to the degree of oxidative stress induced by βA, given that such aggregates promote the formation of reactive oxygen species (ROS; Behl et al. 1994). In 1976, Harman et al. presented evidence that the action of antioxidants inhibits the formation of amyloid plaques in vivo. In addition, Behl et al. (1992) found that antioxidant molecules such as vitamin E protect neuronal cell cultures against toxicity from βA.

The Neuronal Cytoskeleton Hypothesis

This hypothesis argues that the reported changes in the tau protein, and in the consequent formation of intraneuronal neurofibrillary tangles, are responsible for inducing the AD mechanism; however, their role in AD requires further clarification (Reddy 2011).

The tau protein is a normal neuronal component and is associated with intracellular microtubules. Tau is involved in regulating the polymerization and depolymerization of microtubules, stabilizing them during axonal extension. Post-translational regulation of tau activity occurs through phosphorylation and dephosphorylation (Drechsel et al. 1992).

The tau protein can become hyperphosphorylated by the action of various kinases such as glycogen synthase kinase 3β (GSK-3β). Hyperphosphorylation impairs the binding of tau to tubulin, thereby leading to the destabilization of microtubules and fibrillation and the intracellular deposition of tau as paired helical filaments, which aggregate as neurofibrillary tangles after cell death (Hernandez and Avila 2007).

Microtubule dismantling, with the resulting disorganization of rapid axonal transport, combined with intracellular deposition of hyperphosphorylated tau protein promote biochemical and morphological changes in neurons that may result in loss of function and neuronal cell death (Hernandez and Avila 2007; Reddy 2011). In fact, the increase in tau phosphorylation has been associated with the release of βA and formation of senile plaques, which would result in greater formation of neurofibrillary tangles (Reddy 2011); however, the mechanism by which amyloid plaque formation of amyloid plaques and neurofibrillary tangles are connected is still not fully understood. Nevertheless, it is known that βA is involved in the activation of protein kinases, especially GSK-3β, which is the main enzyme involved in tau phosphorylation (Suh and Checler 2002).

GSK-3 β phosphorylates substrates involved in various intracellular signaling pathways and the regulation of transcription factors, controlling functions such as cell survival, cognitive processes, and mood-related functions. GSK-3β is deregulated in AD and contributes to tau phosphorylation in neurons (Grimes and Jope 2001). However, aberrant tau phosphorylation in AD does not result from variations in the tau gene or promoter (Russ et al. 2001).

Interactions between GSK-3β and PS and other proteins associated with AD require further study. PS1 binds to GSK-3β and may be an important modulator of that enzyme's activity. A mutant form of PS1 modifies GSK-3β activity and function, and all patients carrying PS gene mutations feature altered βAPP metabolism (Hardy 1997; Grimes and Jope 2001).

To promote cell survival, antiapoptotic signaling systems such as the phosphatidylinositol-3-kinase (PI3K) pathway exert inhibitory control over GSK-3β (Grimes and Jope 2001). Insulin and insulin-like growth factor 1 activate the PI3K enzyme. PI3K, which acts on phosphatidylinositol-3,4,5-triphosphate, promotes the activation of protein kinase B, which can regulate proteins involved in apoptosis such as caspase-9 (Cross et al. 1995).

Recently, Bonda et al. (2011) challenged the classical view of the tau protein (that phosphorylated tau is a central mediator of AD pathogenesis) and proposed that tau phosphorylation is a compensatory neuroprotective response expressed by neurons against oxidative stress. In these authors' opinions, this idea offers a better understanding of the pathophysiological mechanisms of AD and provides a window for therapeutic intervention.

The Tau and β-Amyloid Joint Action Hypothesis

It is known that both tau and βA have pathological effects in AD; however, their effects have not been fully clarified. Ittner and Gotz (2011) have suggested that one of the triggers for AD pathogenesis is the interaction between these two proteins, which could occur through three distinct mechanisms: (I) the amyloid protein induces tau phosphorylation; (II) tau mediates the toxic action of the β protein, which is a secondary effect following βA synthesis; and (III) the synergistic action of both proteins has a toxic effect most strongly observed in dendrites.

The Oxidative Stress Hypothesis

This recent hypothesis is supported by the theory of oxidative stress in aging, which suggests that oxidative damage plays a pivotal role in the cellular degeneration intrinsically related to aging (Behl et al. 1994). The harmful effects of oxidative damage have been implicated in numerous human illnesses including atherosclerosis and CNS illnesses. The vulnerability of neurons to such attack is an important characteristic for understanding neurodegenerative diseases related to aging. Therefore, the production of free radicals has taken the role of the main villain in AD pathogenesis and/or progression (Lohr 1991; Friedlich and Butcher 1994; Beal 1995; Behl 1999; Behl and Moosmann 2002).

Neurons appear particularly vulnerable to attack from free radicals for the following reasons: (I) neurons depend heavily on mitochondrial oxidative phosphorylation reactions to generate energy sources; (II) their membranes contain high levels of polyunsaturated fatty acids, which can serve as substrates for lipid peroxidation reactions; (III) high levels of iron in its ionic forms, that can catalyze free radical-generating reactions; (IV) lower levels of

glutathione, which is an endogenous antioxidant that is extremely important for metabolization of xenobiotics and elimination of free radicals and antioxidant enzymes compared with other tissues (Hazel and Williams 1990; Smith and Sayre 1995; Halliwell and Gutteridge 2007).

In addition to mitochondrial oxidative phosphorylation, other enzymatic and non-enzymatic methods can generate ROS: the enzymatic conversion of catecholamines and indolamines by monoamine oxidase; the non-enzymatic auto-oxidation of catecholamines; and the activities of lipoxygenases, cyclooxygenases, and other flavin oxidases (Behl 1999).

The following ROS are the main ones involved in AD: superoxide ($O_2^{\bullet -}$); hydrogen peroxide (H_2O_2); hydroxyl radical ($OH^{\bullet}$); and nitric oxide (NO). The latter acts as a secondary messenger in the signaling process and interacts with $O_2^{\bullet -}$ to generate the peroxynitrite radical ($ONOO^-$), which has a harmful action and directly alters the aromatic rings of amino acid residues. The peroxynitrite radical reacts with sulphydryls, lipids, proteins, and DNA and inactivates a series of mitochondrial enzymes involved in oxidative phosphorylation, which can lead to the release of calcium in this organelle (Packer and Murphy 1994; Packer et al. 1997).

As there are many sources of ROS in neurons, these cells maintain an antioxidant defense system to protect themselves against damage from free radicals. This system consists of enzymatic and non-enzymatic antioxidants that balance the physiological production of ROS with detoxification. The physiological antioxidant system consists of three basic elements (Halliwell and Gutteridge 2007):

1. The enzymatic antioxidant system: consisting basically of three types of enzymes. The first type is the superoxide dismutase (SOD) enzymes present in the mitochondria (the manganese-dependent form), the cytosol (zinc−copper dependent), and outside the cell (extracellular form, iron-dependent). SOD enzymes act by transforming $O_2^{\bullet -}$ into H_2O_2. Selenium-dependent glutathione peroxidase (GSH-Px) and catalase enzymes are also part of the enzymatic antioxidant system. These enzymes act by transforming H_2O_2 into H_2O.
2. The small molecule antioxidant system: molecules such as vitamins E and C that react directly with free radicals and reduce their activity.
3. The chelating protein antioxidant system: consisting basically of metallothioneins, low molecular weight proteins featuring thiol groups, such as glutathione, that are able to bind various metals and prevent them from catalyzing free radical-generating reactions.

The oxidative stress hypothesis of AD gained support with the demonstration that toxicity from βA aggregates found in senile plaques can be directly or indirectly mediated by oxidative stress in cells in vitro (Behl 1999).

Behl et al. (1994) showed that H_2O_2 is an intermediary of βA toxicity, and catalase serves a protective function for cells that are ROS targets. In addition, Sagara et al. (1996) selected clones of pheochromocytoma cells (PC12) resistant to βA toxicity and found that they contained high levels of catalase and GSH-Px. Other studies have also demonstrated a relationship between oxidative stress and βA toxicity using antioxidant substances such as vitamin E and suppressed toxic effects (Harman et al. 1976; Behl and Sagara 1997).

βA is itself a source of free radicals because it interacts with endothelial cells to produce excess $O_2^{\bullet -}$ radicals, which might be an important factor in degenerative processes by inducing oxidative and peroxidative events that lead to cell death (Thomas et al. 1996).

Regarding senile plaques, insoluble amyloid fibers form in the brain when βA occurs at high concentrations. Such fibers can combine with zinc and copper, thereby increasing neuronal toxicity, likely by catalyzing oxidative reactions (Huang et al. 1999).

There is also a correlation between metals, βAPP, and neurodegeneration in AD. Atwood et al. (1998) found that copper can promote βA aggregation to form a high affinity complex. The neurotoxicity of this compound is related to the production of hydrogen peroxide formed by the βA−copper complex in vitro. In addition, Lovell et al. (1998a) found metals such as copper, zinc, and iron in amyloid deposits from brains during necropsies of AD patients. Confirming these results, Cherny et al. (1999) demonstrated that zinc and copper chelators can solubilize βA fibers in *post mortem* tissue samples from AD patients. Moreover, inflammatory mediators released by immune response cells (microglia) attracted by βA aggregates can induce the formation of NO, which can react to form $ONOO^-$ and increase the oxidative load in brain regions (Beckman and Koppenol 1996).

Therefore, there is a body of evidence supporting an important role for oxidative stress in the genesis of AD, incorporating and complementing some points from other hypotheses related to AD. This article will discuss the state-of-the-art on the involvement of free radicals and antioxidant defenses in the physiopathogenesis of AD.

Oxidative Stress in Alzheimer's Disease

Oxidative Changes in Antioxidant Defenses in Alzheimer's Patients

In addition to the markers typically found in histopathological studies, which include an accumulation of senile

plaques and intraneuronal neurofibrillary tangles, the brains of AD patients show signs of damage from ROS (Pratico and Sung 2004). Summarizing the results of various studies, it may be said that βA aggregates can promote H_2O_2 accumulation in neurons, most likely caused by the induction of enzymatic systems that generate the superoxide radical, which is one of the main pathways of ROS formation and can lead to oxidative attack with consequent cell death (Behl et al. 1992). Subbarao et al. (1990) suggested that the cause of neuronal cell death is peroxidation of lipid membranes through βA action.

Lipid peroxidation begins by the reaction of an unsaturated fatty acid with ROS capable of hydrogen abstraction, such as the hydroxyl radicals, through a process that rearranges lipid chains and forms new free radicals. Consequently, damage spreads and may become severe if the reaction occurs in membrane lipids, which may impair the structure and function of the plasma membrane (Halliwell and Gutteridge 2007). Various studies have demonstrated an increase in lipid peroxidation in the brains and sera of AD patients compared with those of healthy individuals (Subbarao et al. 1990; Zafrilla et al. 2006; Padurariu et al. 2010).

The plasma membrane of neurons is rich in polyunsaturated fatty acids, especially arachidonic acid and docosahexaenoic acid, which are susceptible to lipid peroxidation (Pratico and Sung 2004). Oxidation of these fatty acids produces aldehydes including malondialdehyde (MDA), 4-hydroxynonenal, and 2-propen-1-al (acrolein). Various researchers have found evidence of thiobarbituric acid reactive substances in different brain areas, especially the frontal and occipital lobes, the hippocampus, and the cortex. Such studies suggest that lipid peroxidation resulting from neurotoxic reactions produced by ROS may be important for the neurodegeneration observed in the brain under oxidative stress (Subbarao et al. 1990; Butterfield and Kanski 2002; Pratico and Sung 2004; Zafrilla et al. 2006; Padurariu et al. 2010). Pratico et al. (2002) analyzed isoprostanes in plasma, urine, and LCR samples and found relatively high levels of these substances in AD patients with slight cognitive impairment. This finding confirms that lipid peroxidation is elevated in AD and suggests the possible use of quantifying isoprostane concentrations in cerebrospinal fluid as a biomarker for AD.

Recently, some studies have shown high levels of lipid peroxidation products (MDA and isoprostanes) in brain samples from patients with slight cognitive impairment and AD; thus, there may be similarities in their pathogeneses (Keller et al. 2005; Markesbery et al. 2005; Padurariu et al. 2010).

ROS can mediate attacks on proteins, oxidizing them on both the central and lateral chains. The latter type produces metabolites with a carbonyl function that are more easily identified in protein oxidation studies. Levels of these protein oxidation byproducts are greater in the parietal lobe and hippocampus of AD patients compared with age-matched controls (Smith et al. 1991; Hensley et al. 1995).

Sultana et al. (2011) measured the rates of protein oxidation and lipid peroxidation in mitochondria isolated from lymphocytes from healthy subjects and AD patients. Those authors found evidence of greater rates for both processes in AD patients, suggesting that mitochondrial oxidative stress in peripheral lymphocytes from AD patients may be a viable diagnostic biomarker.

Butterfield and Kanski (2002) reported the molecular mechanisms by which oxidative stress associated with βA causes neurotoxicity and proposed that methionine residue 35, the only one on the βA molecule, exhibits this property.

Mecocci et al. (1994) described an increase in the base 8-hydroxy-2-deoxyguanosine, a molecule produced by oxidative attack on DNA, when observing nuclear and mitochondrial DNA from AD patients compared with those of healthy age-matched controls. This finding suggests that AD patients have impaired DNA repair mechanisms.

Munch et al. (1997) reported the formation of cross oxidation associated with aging, involving proteins and sugars and leading to the formation of advanced glycation end products (AGE). These products are present in the brains of individuals with such pathology and appear to be intimately associated with senile plaques. AGE can modify intracellular structures involved in various processes including gene transcription.

A common finding in AD is an early diagnosis of hypometabolism in the parietal, temporal, and posterior cingulate lobes. Such changes are easily detected by positron emission tomography. One factor observed is reduced cytochrome oxidase activity, which is an intracellular measure of energetic metabolic capacity, in cells of the cingulate cortex layers in samples from AD patients. This pattern possibly contributes to the emergence of certain behavioral symptoms of AD. Interestingly, the decrease in metabolic activity was greater in samples from female patients (Valla et al. 2001).

Regarding the activities of antioxidant defense system enzymes in AD patients, there are some differences between SOD and catalase in the cerebral cortex. Chen et al. (1994) described a significant reduction in SOD activity and a non-significant increase in catalase activity. In contrast, Gsell et al. (1995) found an increase in SOD activity with age in the basal nucleus region, which is an important area in neuropsychiatry; however, there was no difference between AD patients and healthy controls. Those authors also reported a significant decrease in catalase activity in the parietotemporal cortex, basal ganglia, and amygdala of AD patients.

Results from other studies have shown that not just enzymatic activity but all other parts of the antioxidant defense system can be affected in AD patients.

Padurariu et al. (2010) assessed the serum levels of antioxidant enzymes SOD and GSH-Px and MDA in elderly patients with AD, elderly patients with slight cognitive impairment, and healthy controls. Those authors found a significant reduction in the levels of the antioxidant enzymes and a significant increase in MDA levels for both groups with cognitive impairment relative to the control group.

Bourdel-Marchasson et al. (2001) compared AD and healthy elderly patients and found a significant reduction in α-tocopheryl and retinol combined with a significant increase in plasma MDA in AD patients. Moreover, AD patients exhibited an inverse correlation between levels of MDA and antioxidant vitamins, which are believed to have been depleted due to excess free radical production.

A simultaneous increase in the activities of the enzymes glutathione reductase and GSH-Px in AD patients has been reported (Lovell et al. 1995). However, Marcus et al. (1998) found normal GSH-Px activity in various brain regions in the same individuals. Rinaldi et al. (2003) showed that AD patients exhibited depleted levels of vitamins A, C, and E combined with a lower activity of SOD and glutathione peroxidase (Lovell et al. 1995).

The activity of glutathione-*S*-transferase is reduced in the amygdala, hippocampus and parahippocampus, inferior parietal lobe, and the basal nucleus of Meynert in AD patients (Lovell et al. 1998b). Glutathione was, however, a highly significant and independent predictor of cognitive scores in patients; lower plasma levels were associated with more severe cognitive impairment (McCaddon et al. 2003).

Sinclair et al. (1998) assessed the levels of blood oxidative markers (circulating lipid peroxides) and antioxidants (total antioxidant capacity, vitamins C and E, and beta-carotene) in patients diagnosed with symptoms of AD or vascular dementia and healthy controls. The concentration of vitamin E was the only significant different parameter; it was lower in AD patients, possibly because of a compensatory antioxidant defense mechanism involving mobilization of other molecules with a similar function.

Other studies have correlated the levels of vitamin E circulating in the body with cognitive performance, showing that this antioxidant molecule plays an important role in defending the CNS against oxidative damage (Perkins et al. 1999; Masaki et al. 2000; Morris et al. 2002; Grodstein et al. 2003).

Oxidative Mechanisms in Alzheimer's Disease

AD is recognized as a chronic neurodegenerative condition with a long asymptomatic period preceding the recognition of symptoms of clinical dementia. Many lines of research have shown the key role of oxidative stress in the pathogenesis of neurodegenerative diseases such as AD through various mechanisms, especially the formation of AGE (Srikanth et al. 2011), tau protein metabolism (Wataya et al. 2002), nuclear factor kappa B (NFkB; Akama et al. 1998), transition metals (Huang et al. 1999), and βA protein (Behl et al. 1994; Behl 1999).

Advanced Glycation End Products

The pathological effects of AGE are related to their ability to modify the chemical and functional properties of many biological structures through the formation of free radicals, protein cross linkages, or interactions with cell receptors promoting oxidative stress, morphofunctional changes, and greater expression of inflammatory mediators, factors that appear to be involved in AD pathogenesis (Brownlee 2001; Bigl et al. 2008).

AGE represent much of the variety of substances formed from non-enzymatic amino carbonyl interactions between reducing sugars or oxidized lipids and proteins, aminophospholipids, or nucleic acids (Monnier 2003). In addition to the classical pathway of AGE formation, which are glycation reactions (Maillard reaction), there are alternative mechanisms for forming these compounds that include the so-called "carbonylic stress" pathway, by which oxidation of lipids or sugars generates highly reactive intermediate dicarbonylic compounds (Huebschmann et al. 2006). Glycolysis and autoxidation of glucose, for example, produce methylglyoxal and glyoxal, which interact with amino acids to form AGE. These dicarbonylic compounds become 20 thousand times more reactive than glucose and are the main intermediates of AGE formation (Meade et al. 2003). It should be noted that ROS are generated during some reactions resulting in AGE formation, and they occur in parallel with structural and functional damages to macromolecules (Hidalgo and Zamora 2005).

AGE formation in vivo can involve neutrophils, monocytes, and macrophages, which produce myeloperoxidase and the enzyme NADPH oxidase following inflammatory stimulation; such products induce AGE formation by amino acid oxidation (Huebschmann et al. 2006).

The endogenous AGE pool basically reflects the kinetic balance between two opposing processes: the endogenous formation and absorption of exogenous AGE and the degradation and elimination of AGE by specialized systems (Jakus and Rietbrock 2004).

AGE formation occurs slowly under physiological conditions and primarily affects molecules with a long half-life (Forbes et al. 2005). Under hyperglycemic conditions or oxidative stress, AGE formation increases dramatically (Lapolla et al. 2005). AGE formation is predominantly endogenous; however, AGE can be

introduced into the body from exogenous sources such as smoking and diet (Peppa et al. 2003; Leslie et al. 2003). Nevertheless, the body possesses defense mechanisms against the degenerative accumulation of AGE. Detoxifying enzymatic systems and scavenger cells such as macrophages are part of this defense (Thornalley 2003). Scavenger cells engulf AGE via receptors and release low molecular weight soluble AGE peptides into the bloodstream following intracellular degradation; these AGE peptides are excreted in the urine (Bierhaus et al. 1998).

Together with formation/absorption and degradation/elimination processes, genetic factors can affect AGE metabolism in individuals and, consequently, their predisposition for development of pathologies associated with AGE, such as AD (Takeuchi and Yamagishi 2004). Supporting this claim, various studies since the 1990s have shown an accumulation of AGE in senile plaques that might be involved in the development of brain plaques in AD patients (Kimura et al. 1995; Münch et al. 1998, 2002; Kuhla et al. 2004; Richter et al. 2005).

One mechanism proposed for the damage induced by AGE is derived from the production of ROS released by AGE, especially superoxide and hydrogen peroxide (Carubelli et al. 1995; Ortwerth et al. 1998; Muscat et al. 2007). The formation of oxygen free radicals is associated with the oxidation of sugars and other compounds. For example, protein glycation has been viewed as a factor increasing the production of free radicals approximately 50-fold at physiological pH compared with non-glycated proteins (Mullarkey et al. 1990).

Moreover, because the initial studies on AGE in vivo, there has been speculation regarding the possible existence of an AGE-receptor system that is responsible for their removal from tissues to limit their damaging effects. Originally, it was shown that proteins modified by AGE were recognized by specific receptors that were associated with scavenger receptor systems (Vlassara and Palace 2002).

Lue et al. (2001) claimed that AGE receptors (RAGE) are strongly expressed in the microglia and neurons and play a key role in brain oxidative stress with pathological consequences.

Among the variety of receptors for AGE or proteins that bind AGE described in the literature, RAGE is most likely the best-characterized molecule (Yonekura et al. 2005; Lin 2006; Xue et al. 2011; Srikanth et al. 2011). RAGE belongs to the cell surface immunoglobulin superfamily, and its gene is located on chromosome 6 in the major histocompatibility complex between the genes for classes II and III. The regions for nuclear factor-κB and interleukin-6 (IL-6) are located on the RAGE gene promoter. These regions control receptor expression and link RAGE to inflammatory responses (Lin 2006).

Chen et al. (2007b) suggested that RAGE interactions increase neuronal stress by causing neuroinflammation and lead to learning and memory impairments.

The results of Cruz-Sánchez et al. (2010) show clear expression of AGE and RAGE in the brains of AD patients, and those results agree with prior observations by Sato et al. (2006) and Takeuchi and Yamagishi (2004). Cruz-Sánchez et al. (2010) further suggest that there is an organized distribution pathway for oxidative stress related to the high expression of AGE and RAGE that begins in region CA3 and proceeds to other hippocampal regions and the cerebral cortex.

In addition, Valente et al. (2010) attribute the severity of AD to interactions between RAGE and specific AGE, such as *N*ε-carboxy-methyl-lysine and *N*ε-carboxy-ethyl-lysine.

Byun et al. (2012a) describe another compound derived from AGE, AGE-albumin (glycated albumin), that is synthesized in microglia and secreted in the human brain. Metabolism of this compound is related to RAGE-mediated neuronal cell death, which eventually leads to neurodegenerative diseases. Another study along the same line of research by Byun et al. (2012b) found that the concentrations of both intracellular and secreted AGE-albumin are positively correlated with the degree of oxidative stress in experiments with hydrogen peroxide on human microglia. In conjunction, AGE-albumin stimulates an increase in RAGE production that appears to be a strong indicator of neuronal apoptosis in AD (Takeuchi et al. 2007).

Previously, Smith and Perry (1994) claimed that the combination of high concentrations of RAGE ligands and an increase in autocrine regulation of RAGE can lead to a vicious cycle of inflammation mediated by RAGE that leads to degeneration in AD. In addition, Yan et al. (1997) found that the increase in neuronal RAGE expression is strongly correlated with neuronal cell death and AD development and progression.

Srikanth et al. (2011) claimed that AGE accumulation in cells and tissues is a normal feature of aging that is accelerated in AD and that AGE and RAGE can play an important role in the pathogenesis of AD because they are found in pathological deposits such as amyloid plaques and neurofibrillary tangles. Moreover, AGE could explain many pathological and biochemical characteristics of AD such as glial oxidative stress and neuronal cell death. Oxidative stress and AGE could initiate, through normal changes related to aging, a positive feedback cycle leading to the development of a physiopathological cascade.

Despite the normal aging-related changes that occur in the body, the physiological formation of molecules such as AGE and their derivatives can lead to an increase in oxidative stress and inflammation with subsequent dysfunction and even neuronal cell death characteristic of AD.

Tau Protein

Castellani et al. (2006) suggested that the formation of senile plaques and neurofibrillary tangles occurs as a result of oxidative stress. This process can be triggered by the tau protein, which is attacked on the serine domain when phosphorylated and becomes spongy with oxidative activity despite having a composition rich in lysine, serine, and proline that confers an antioxidant property (Wataya et al. 2002). The oxidative stress induction capability of truncated tau protein was later demonstrated by Cente et al. (2006), who suggested that oxidative stress is a secondary mechanism in Alzheimer's pathogenesis induced by prior modifications on tau protein, such as truncation.

Studies conducted in 1994 demonstrated the oxidative action of tau by analysis of brain tissue from AD patients. Those studies claimed that tau from neurofibrillary tangles might be an ideal target for non-enzymatic action such as glycation and found glycated tau and high levels of MDA and heme oxygenase along with neuronal dysfunction (Yan et al. 1994).

The mechanism of glycation was identified as a process triggered by stimulation from the βA protein, which promotes the production of reactive oxygen and nitrogen species that act mainly on triphosphate isomers leading to changes in the conformation of tau and precipitation of tangles of helical filaments (Guix et al. 2009).

Another oxidative mechanism associated with tau protein was described by Kovac et al. (2011), who after a series of elegant experiments demonstrated that administration of human truncated tau protein to glial cell cultures promoted a six-fold increase in nitric oxide synthesis on a MAPK-dependent pathway, along with the production of several inflammatory cytokines, such as IL-1β, IL-6, and TNF-α.

Tau can also impair the transport of peroxisomes, which are organelles rich in antioxidant molecules within neurons. In addition, the formation of neurofilaments, organelles, and sAPPβ may be inhibited, thus making the neuron more vulnerable to oxidative stress (Stamer et al. 2002).

In contrast, recent studies have shown that tau plays a protective role for neuronal genomic DNA against stress from mild heat. Such results highlight a novel role for nuclear tau as a key protein in protection against acute oxidative stress (Sultan et al. 2011).

Nuclear Factor Kappa B

Studies performed in 1996 demonstrated the contribution of oxidative stress to the cholinergic deficit and neuronal dysfunction in AD. To that end, human neuroblastomas were exposed to carbachol, a cholinergic agonist, and H_2O_2. The authors found that the peroxide inhibited stimulation by carbachol and promoted an increase in the concentrations of transcription factor NFkB. In addition, H_2O_2 impaired inositol phosphate signaling, suggesting that oxidative stress can influence cholinergic signaling (Li et al. 1996).

NFkB is a transcription factor (TF) that regulates many genes and is activated in response to infection, stress, inflammation, and apoptosis. NFkB is latent and inactive in the cytoplasm, and expression has been found in mature B lymphocytes, plasmocytes, macrophages, neurons, lung, liver, cartilage, and coronary arteries in both humans and animals (Bartosz 2009; Kriete and Mayo 2009; Kim et al. 2010).

In addition to participating in cholinergic stimulation (Li et al. 1996), this TF is involved in the production of enzymes that generate reactive nitrogen species as shown in astrocytes, which are normally found in βA plaques. In mice stimulated with βA protein, inducible nitric oxide synthase (iNOS), the enzyme that produces NO, is expressed via NFkB (Akama et al. 1998). Moreover, Kovac et al. (2011) found a remarkable increase in NFkB1 (seven-fold) and NFkB2 (16-fold) production after stimulation of glial cell cultures with truncated tau protein.

A study using cultured astrocytes stimulated with βA by Akama and Van Eldik (2000) found that βA initially promotes the production of interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-α), followed by the production of iNOS. That study also found that inhibiting the IL-1 receptor associated with TNF-α inhibits iNOS activity, which appears to be mediated by both cytokines via nuclear factor kappa B-inducing kinase.

Another study by Combs et al. (2001) reported the presence of NFkB in AD. Those authors administered fibrillar βA peptides to human monocytes and mouse microglia and found that TNF-α expression depends on spleen tyrosine kinase and NFkB; following production of that cytokine, a stimulation of iNOS expression, nitric oxide production, and formation of peroxynitrite occurs, which results in apoptosis.

In addition to participating in cholinergic stimulation (Li et al. 1996) and NO production (Akama et al. 1998; Akama and Van Eldik 2000), a study demonstrated that the nuclear factor NFkB is involved in the production of βA protein (Buggia-Prevot et al. 2008). A study on the mechanism of action for β-secretase and aspartate BACE-1 in mouse brain tissue demonstrated that BACE-1 can be regulated by NFkB (Buggia-Prevot et al. 2008). Inhibiting NFkB is one possible route for blocking the pathological action of βA protein, as caused by the production of nitrogen-derived free radicals.

Transition Metals

Transition metals such as iron, zinc, copper, and aluminum exhibit the capacity to interact directly with βA peptide,

thus increasing its neuronal toxicity by catalyzing oxidative reactions (Huang et al. 1999).

Huang et al. (1999, 2004) demonstrated that the Cu^{2+} ion is reduced in the presence of βA with simultaneous production of ROS such as H_2O_2 and $OH^{\bullet}$, which can cause damage in primary neuron cultures. Supporting those results, Barnham et al. (2004) showed that the tyrosine 10 residue of βA is important for catalyzing the oxidative reactions that generate H_2O_2. Dai et al. (2006) proposed that βA aggregation induced by Cu^{2+} may be responsible for the local injury observed in AD and that interaction between both provides possible mechanisms for metal ion enrichment in amyloid plaques. This element can also affect antioxidant enzyme metabolism as demonstrated by Curtain et al. (2001), who found that Cu^{2+} strongly binds βA to form a structure similar to the Zn/Cu-dependent SOD enzyme.

Ali et al. (2005) showed that Cu^{2+} exposed to H_2O_2 can catalyze βA oxygenation, most likely on the sulfur atom of methionine, and other products of the redox reaction catalyzed by Cu^{2+} such as endogenous aldehydes (Chen et al. 2007a). This pathway for generating free radicals is related to the capacity of the tyrosine residue to contribute to βA neurotoxicity. This residue has been viewed as an important factor in the formation of βA aggregates and amyloid. It is possible that the formation of the tyrosyl radical in βA leads to greater aggregation by formation of dityrosine, which would be the first step of this undesired mechanism (Ali et al. 2006).

Iron is another transition metal involved in redox reactions. This metal concentrates near amyloid plaques in the human brain and can amplify the pattern of oxidative damage and increase neuronal vulnerability (Zecca et al. 2004). In addition, iron is involved in modulating the expression of various proteins including βAPP (Rogers et al. 2002).

It should be noted that there is evidence that Fe^{2+} levels are elevated in tissues affected by both AD and Parkinson's disease, while copper levels are lower (Rogers et al. 2002; Religa et al. 2006). In this context, in AD, there is an abnormal distribution of iron and proteins in the brain that are responsible for its regulation including hemosiderin and ferritin; the latter is a component of senile plaques (Grundke-Iqbal et al. 1990; Rogers et al. 2002; Quintana et al. 2006).

Similarly, zinc is being increasingly established as a novel class of second messenger by participating in reactions similar to calcium (Frederickson et al. 2005). One of the most important discoveries related to this metal was the elucidation of its participation in glutamatergic transmission in the cortex and hippocampus, which are incidentally the areas where senile plaque deposition begins and most likely causes the memory dysfunctions of AD. Zinc is released in the glutamatergic synapse by pre-synaptic fibers in both the free ionic form and the permutable ionic form. This metal is only stored by glutamatergic vesicles through the action of membrane transporters called ZnT_3. Zinc is released with glutamate during neurotransmission and modulates the response of glutamatergic *N*-methyl-D-aspartate (NMDA) receptors involved in long-term potentiation (Danscher and Stoltenberg 2005; Frederickson et al. 2006).

Similar to Zn, Cu^{2+} is released into the synaptic cleft during glutamatergic neurotransmission by post-synaptic neurons activated by NMDA receptors. Copper is stored in the vesicles of post-synaptic glutamatergic neurons by the action of the Cu7a adenylpyrophosphatase (ATPase) enzyme. When released into the synaptic cleft, its role is similar to that of zinc toward NMDA receptors (Schlief et al. 2005, 2006). As βA peptide can bind metals released during glutamatergic transmission and consequently precipitate, many studies are seeking a relationship between levels of these metals in the brain and the development of AD or senile dementia (Adlard and Bush 2006; Cappai and Barnham 2007).

Lee et al. (2002) and Friedlich et al. (2004) found that excising the ZnT3 gene inhibits βA deposition, thus demonstrating that zinc released in the glutamatergic synapse plays an important role in the formation of extracellular amyloid plaques.

It has been shown that aluminum accumulation in the brains of AD patients accelerates βA production due to defective proteolysis of βAPP and that using metal chelators can reduce βA plaque formation by solubilizing aluminum (Clauberg and Joshi 1993; Cherny et al. 2001).

Assessments of progressive metal accumulation in the brains of AD patients revealed that Cu, Fe, and Zn levels are elevated in early stages of the disease, while Al accumulates in late stages and are progressively deposited in the diseased brain (Rao et al. 1999).

Al appears to be present in questions related to oxidative stress linked with AD. Al can stabilize the ferrous ion by reducing its oxidation rate. The ferrous ion is a strong inducer of reactions that generate oxidative stress because it catalyzes Fenton reactions. Al can also activate SOD and inhibit catalase to induce H_2O_2 formation and maintenance. Excessive Al accumulation leads to the production of $OH^{\bullet}$ radicals that then damage various proteins, DNA, and membrane lipids (Clauberg and Joshi 1993; Ritchie et al. 2003).

The importance of metal ions in AD pathogenesis is highlighted by the promising results obtained using an oral metal chelator (clioquinol) capable of crossing the blood–brain barrier. Clioquinol reduced βA deposition in a transgenic mouse model expressing human βA, thus restoring the health and body weight of treated animals (Sano et al. 1997; Sung et al. 2004).

In addition, studies have shown that βA solubilization from *post mortem* brain tissue of AD patients increases in the presence of metal chelators such as clioquinol (Dai et al. 2006).

βA Protein

The βA protein is involved in diverse oxidative processes affecting AD. βA plays an important role in increasing the production of glycated proteins. As shown in studies performed with brain tissue from humans and rats exposed to the protein, this increase is closely linked to oxidative stress (Byun et al. 2012b). βA is also related to nitro-oxidative action on tau (Guix et al. 2009). In addition, βA has been shown to promote the production of reactive nitrogen species via NFkB (Yan et al. 1994). Lastly, βA has a great capacity to interact with metals such as copper, and such interaction promotes the amplification of neuronal damage and catalyzes oxidation (Huang et al. 1999). Thus, we reiterate the importance of oxidative stress in AD progression.

Use of Antioxidant Supplements in Alzheimer's Patients or Experimental Studies

In recent years, there has been discussion on the inclusion in adjuvant therapy for AD of antioxidant supplements such as vitamins E or α-tocopherol (Stocker 1994; Sano et al. 1997) and C (Bowman 2012), lipoic acid (Siedlak et al. 2009), curcumins (Lim et al. 2001), *N*-acetylcysteine (NAC; Moreira et al. 2007), and others. Such supplements could provide protection against oxidative stress by reducing the production of free radicals or neutralizing them with a consequent decrease in neuronal damage.

Sano et al. (1997) used α-tocopherol in clinical trials and found a slowing of disease progression and reduced levels of free radicals in patients with moderate AD. Such results suggest the significance of oxidative stress as an intermediate risk factor for the progression of the neurodegeneration characteristic of AD and its clinical significance against functional deterioration in AD patients.

Studies in vitro revealed that vitamin E protects neurons against damage from neurotoxins such as glutamate and 6-hydroxydopamine (Schubert et al. 1992; Perumal et al. 1992), and it inhibits β-amyloid aggregation (Yang et al. 2010). In addition, it was found that administering vitamin E to Tg2576 rats in the initial stages of disease inhibits lipid peroxidation in the brain and significantly reduces βA levels and amyloid deposition. Later administration, when plaques have already been deposited, results in reduced brain oxidative stress (Helson 1984).

Alpha tocopherol crosses the blood−brain barrier and can stimulate coagulation when given at high doses over a long period (Helson 1984). Moreover, the use of a single antioxidant for long periods can be harmful because the molecule may be oxidized and become a pro-oxidative substance. Therefore, it is recommended to use multiple antioxidants at appropriate doses for the treatment of AD patients, thereby avoiding the toxicity associated with using a single antioxidant (Prasad et al. 2002). Thus, the efficacy of α-tocopherol can be considerably increased by co-supplementation with ascorbic acid (Vitamin C; Bowman 2012).

Vitamin C is a water-soluble antioxidant, a strong inhibitor of lipid peroxidation by promoting the recycling of vitamin E in this process, and acts as an important defense against free radicals in plasma (Valko et al. 2004; El-Agamey et al. 2004). In addition, Bagi et al. (2003) showed that chronic treatment with vitamin C reduces elevated isoprostane levels and oxidative stress in vivo, increases the bioavailability of NO, restores the regulation of shear stress in arterioles, and normalizes induced high systemic arterial blood pressure in rats.

Other studies supplemented AD patients with a combination of vitamins E and C, such as the work of Arlt et al. (2012), in which twelve AD patients were supplemented with this mixture daily for a period of 1 year and, despite no differences in clinical outcomes, a significant increase in antioxidant in the cerebrospinal fluid was observed. Likewise, Galasko et al. (2012) found a decrease in lipid peroxidation, as measured by cerebrospinal fluid F2-isoprostane levels in 66 mild-to-moderate AD patients supplemented with vitamin E associated to vitamin C and α-lipoic acid.

In addition to vitamins E and C, vitamin B12 can play an important role in AD treatment. Regland et al. (1991) reported that serum levels of vitamin B12 were significantly lower in AD patients than in a control group. Such differences could partly contribute to neuronal degeneration. In addition, Ikeda et al. (1992) claimed that administering vitamin B12 improves cognitive function in AD patients. Nevertheless, there is disagreement in the literature regarding the actual benefit of vitamin B12 supplementation for AD patients. Aisen et al. (2008) and McMahon et al. (2006) reported that treatment with vitamin B12 reduces serum levels of homocysteine on AD patients; however, there is no effect on progressive cognitive decline in patients with mild/moderate AD or on preservation of cognitive function in healthy adults. Thus, there is continuing uncertainty regarding how vitamin B12 deficiency could be linked to dementia and what the potential benefits of vitamin B12 supplementation might be. Chai et al. (2013) recently concluded that administration of betaine attenuates the observed pathological

changes and memory deficits caused by hyper-homocysteinemia in AD patients, similar to results obtained by joint administration of folate and vitamin B12.

Antioxidant therapy, whether by dietary guidelines (Smith et al. 1999) or supplementation, is considered a low-risk therapeutic strategy for AD patients (Ancelin et al. 2007).

According to Siedlak et al. (2009), long-term use of antioxidants against the effects of human aging is healthy. That claim is supported by positive results obtained using lipoic acid in combination with other antioxidants. However, the effect of such therapy on cognitive decline or amyloid was not significant.

Studies on the action of lipoic acid and other antioxidants both in neuronal cell culture and animal models have demonstrated significant and specific beneficial effects such as the reduction of the lipid peroxidation mediated by AGE (Gasic-Milenkovic et al. 2003). Studies by Hager et al. (2007) found that the progression of dementia reported for AD develops significantly slower in patients treated with α-lipoic acid than in untreated patients.

More recently, the role of lipoic acid as a strong therapeutic antioxidant was confirmed. Lipoic acid functions as a co-enzyme of mitochondrial pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. In addition, it participates in the recycling of other antioxidants such as vitamins C and E and glutathione, increases acetylcholine production, and acts as a metals chelator with redox activity to combat the accumulation of lipid peroxidation products (Siedlak et al. 2009). Thus, lipoic acid is used in combination with acetylcarnitine to protect neurons through cell signaling mechanisms including extracellular kinase signaling pathways, which are deregulated in AD (Zhu et al. 2004). In addition, long-term administration of lipoic acid as an antioxidant has been reported to reduce expression of lipid peroxidation markers, but not βA levels in the brains of both control animals and those with AD (Quinn et al. 2007).

Moreira et al. (2007) assessed the effect of lipoic acid and NAC on fibroblasts from AD patients. Both lipoic acid and NAC exert a protective effect demonstrated by a reduction in markers of oxidative stress and apoptosis. In addition, the protective effect of both antioxidants was greater when administered simultaneously, which leads us to believe that antioxidant therapies based on lipoic acid and NAC can be very promising.

Similarly, Suchy et al. (2009) believe that an antioxidant-deficient diet is a factor that accelerates aging-related cognitive decline. Those authors demonstrated that dietary supplementation with α-lipoic acid, acetyl-L-carnitine, glycerophosphocholine, docosahexaenoic acid, and phosphatidylserine could reduce ROS production by up to 57 % in the brains of rats fed a vitamin-deficient, iron-enriched diet and improved their cognitive performance.

Additional example of the benefits of combining antioxidants comes from a study by Sinha et al. (2010), who showed that the brains of elderly rats exhibited elevated homocysteine levels (42 %) and reduced dehydroepiandrosterone sulfate (DHEAS; 32 %) relative to the brains of young rats aged 4–6 months. Such changes in brain levels of homocysteine and DHEAS in elderly rats are avoided when the daily diet of rats is supplemented with a combination of the antioxidants *N*-acetylcysteine, α-lipoic, and α-tocopherol.

Another antioxidant being investigated is curcumin, a strong polyphenol antioxidant. A study by Lim et al. (2001) showed that curcumin reduces oxidative stress and the formation and deposition of amyloid plaques in transgenic mice. In addition, Ishrat et al. (2009) examined the effect of administering curcumin to rats with a significant cognitive deficit and possible oxidative damage. Their results showed that the cognitive deficit was reduced following 3 weeks of curcumin treatment, suggesting that this antioxidant can be an effective adjuvant for the prevention of dementia in AD. Nevertheless, in a 6-month placebo-controlled clinical trial in patients with AD, curcumin failed to promote clinical benefits, although an increase in vitamin E plasma levels was noticed (Baum et al. 2008). Similar results were found by Ringman et al. (2012).

Other antioxidants tested in AD patients included ginkgo biloba (Vellas et al. 2012) and estrogen (Mulnard et al. 2000), yet no differences upon clinical progression of AD were seen.

Recently, novel diagnostic markers for AD have been investigated. Ahmed (2012) found that acetylcholinesterase activity and homocysteine levels were elevated in rats with AD, while levels of folic acid, vitamin B12, and Na/K-dependent ATPase were low in the brains of those animals. In addition, low plasma levels of insulin and high plasma concentrations of TNF-α and IL-1β were found. However, treatment with the antioxidants vitamin E, acetylcarnitine, and lipoic acid restored the previously mentioned parameters to nearly normal levels. These findings suggest that insulin, total homocysteine, IL-1β, and TNF-α may be used as biomarkers for AD and show the potential effects of antioxidants in slowing disease progression.

Final Considerations

Despite various studies demonstrating the strong effects of oxidative stress in the pathogenesis of neurodegenerative diseases and the use of antioxidants as aids for the prevention or reduction of damage caused by free radicals, the efficacy of antioxidants in clinical patients is still debated. Most antioxidant supplements yield optimal results in animal models and have yet to be shown in human studies.

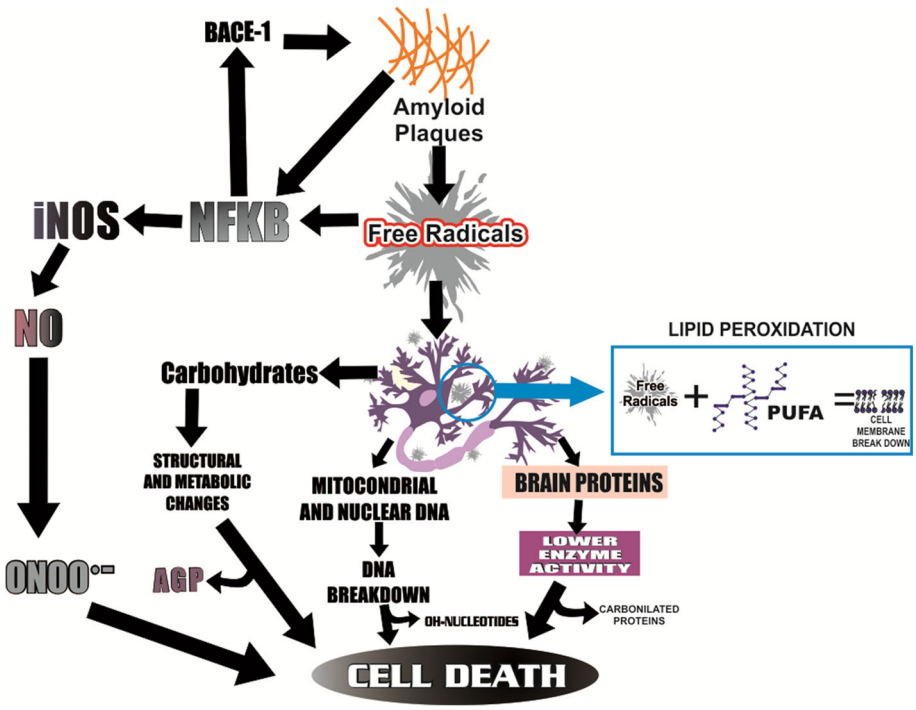

Fig. 2 Oxidative stress pathways in Alzheimer's disease. *NFkB* nuclear factor kappa B, *iNOS* inducible nitric oxide synthase, *NO* nitric oxide, *BACE-1* beta-secretase 1, *NO* nitric oxide, $ONOO^{\bullet-}$ peroxynitrite, *AGP* advanced glycation end products, *βA* beta amyloid, *PUFA* polyunsaturated fatty acids

Clinical trials for the prevention and treatment of AD with antioxidants are just beginning, and results so far have been rather disappointing and most studies have failed due to several reasons (Persson et al. 2014).

The probable reasons for the lack of evident beneficial effects of antioxidants tested on clinical trial are due to (a) small number of subjects enrolled on trials, yielding great dispersion of values among individuals and, therefore, masking statistical differences; (b) short-term antioxidant supplementation, which would not allow enough time for the desired outcomes to appear; (c) doses of antioxidants used, as low doses may not be enough to reach clinical beneficial levels, whereas high doses may lead to adverse effects, including pro-oxidation; (d) specific effects of the antioxidants tested, considering that an ideal antioxidant supplementation must rely on several antioxidant molecules instead of the use of a single one; (e) Clinical conditions of AD patients enrolled on trials, since the establishment of the disease involves multiple signaling pathways that can generate oxidative stress in an auto sustained manner. Thus, more studies are needed to determine whether using antioxidants can reduce the risk or slow disease progression in AD patients (Feng and Wang 2012; Persson et al. 2014).

In regard to this last possibility, some studies have addressed antioxidant supplementation to non-demented middle-aged individuals and found positive evidence that preventive antioxidant supplementation might become an effective approach to AD. Chan et al. (2010) supplemented adults without dementia of both genders a nutraceutical formulation (consisting of Vitamins E and B12, *S*-Adenosylmethionine, NAC, folic acid, and acetyl-L-carnitine) achieving statistical improvement of cognitive performance when compared to matched controls. Likewise, Disilvestro et al. (2012) demonstrated that a low-dose curcumin supplementation can produce a variety of health promoting effects, including increased antioxidant levels and lowering plasma βA concentration, in healthy middle-aged people.

Nevertheless, considering that participation of oxidative stress in AD is well studied and involves multiple physiopathological mechanisms (Fig. 2), supplementation with antioxidants may become a promising preventing strategy for disease development if started early or, preferentially, before symptom onset and it may contribute to the maintenance of cognitive function.

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