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·Review·

Oxidative stress in Alzheimer's disease

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Oxidative stress plays a significant role in the pathogenesis of Alzheimer's disease (AD), a devastating disease of the elderly. The brain is more vulnerable than other organs to oxidative stress, and most of the components of neurons (lipids, proteins, and nucleic acids) can be oxidized in AD due to mitochondrial dysfunction, increased metal levels, inflammation, and β-amyloid (Aβ) peptides. Oxidative stress participates in the development of AD by promoting Aβ deposition, tau hyperphosphorylation, and the subsequent loss of synapses and neurons. The relationship between oxidative stress and AD suggests that oxidative stress is an essential part of the pathological process, and antioxidants may be useful for AD treatment.

Keywords: Alzheimer's disease; oxidative stress; β-amyloid; tau; metals; antioxidants

Introduction

The human brain, although it constitutes only 2% of the body weight, consumes ~20% of the oxygen supplied by the respiratory system[1]. The high energy-consumption of the brain means that it is more susceptible to oxidative stress than any other organ. As the basic functional unit of the brain, the neuron is particularly vulnerable to oxidative damage because it has a higher metabolic rate than other cells[2]. The oxidation of lipids, proteins, and nucleic acids in neurons is a common pathological feature of Alzheimer's disease (AD)[3]. Neurons contain a large amount of polyunsaturated fatty acids (PUFAs) that can interact with reactive oxygen species (ROS), leading to a self-propagating cascade of lipid peroxidation and molecular destruction[4]. Furthermore, neurons contain low levels of glutathione, an essential antioxidant for eliminating free radicals[5]. Therefore, neurons are highly susceptible to oxidative stress.

An increased oxidative burden has been reported in the brains of non-demented elderly and/or sporadic AD patients[6, 7]. Increased levels of oxidative stress biomarkers in the blood reflect such stress in the brain[8, 9]. Currently, many blood markers of oxidative stress have been identified in AD patients or related animal models, including protein carbonyls and 3-nitrotyrosine[10, 11], 8-hydroxydeoxyguanosine (8-OHdG), 8-hydroxyguanosine (8-OHG), malondialdehyde (MDA)[12], 4-hydroxynonenal (4-HNE), and F2-isoprostanes (F2-IsoPs)[13-16]. Apart from the intracellular accumulation of free radicals, changes in the activities or expressions of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase, have also been described in both the central nervous system and peripheral tissues of AD patients[14, 17]. Thus, oxidative stress is an important pathological feature in AD.

However, how and where the oxidative stress originates in AD are open questions. Research has suggested that mitochondrial dysfunction[12, 18, 19], metal accumulation[12, 20, 21], hyperphosphorylated tau[22, 23], inflammation[24, 25], and β-amyloid (Aβ) accumulation[12, 19] are the basic mechanisms underlying the induction of oxidative stress. Deficiency or destruction of components of the antioxidant system such as SOD in the mitochondria (Mn-SOD or SOD2) and cytosol (Cu-Zn-SOD or SOD1),

glutathione peroxidases, and catalase, is also involved in the induction of oxidative stress[14, 17, 26]. Inactivation and deficiency of these enzymes reduce the clearance of free radicals. On the other hand, oxidative stress is an important contributor to Aβ accumulation and tau hyperphosphorylation, suggesting that it plays an essential role in the pathogenesis of AD[12, 19, 27], and may be a biomarker and treatment target for AD[27-29].

Oxidative Stress Is a Common Pathological Feature in AD

Lipid Oxidation

The brain is rich in phospholipids, which are critical to the processes of neurotransmission, and the basis of neuronal interactions and cognition. Brain phospholipids contain a high proportion of PUFAs, especially docosahexaenoic acid and arachidonic acid. It has been found that as free radical production increases, the PUFAs contents in the brain gradually decline[30, 31]. In addition, the lipid hydroperoxides are particularly unstable and can automatically decompose into various products, including MDA, 4-HNE, ketones, epoxides, and hydrocarbons in the presence of iron[30]. Several studies have confirmed an increase of MDA and 4-HNE levels in the brains of patients with AD and mild cognitive impairment (MCI)[13, 32, 33]. Isoprostane production is another outcome of lipid peroxidation. F2-IsoPs are produced from arachidonic acid *via* esterification. In AD, increased levels of F2-IsoPs and F4-IsoPs have been detected in the cerebrospinal fluid (CSF)[15, 34]. Interestingly, the level of F2-IsoPs in the ventricular fluid is negatively correlated with brain weight[35]. Another study also found that the amount of F2-IsoPs is increased in MCI patients[36].

Protein Oxidation

Increased level of protein carbonyl, a marker of oxidative damage to proteins, has been demonstrated in the AD brain[33]. Reactions of various reactive oxygen and nitrogen species with tyrosine result in the production of 3-nitrotyrosine and dityrosine. In particular, the 3-nitrotyrosine residue concentration in the CSF is negatively correlated with the Mini-Mental State Examination score[37]. Furthermore, protein nitration is an early event in the pathogenesis of AD. For example, the levels of total protein nitration in the inferior parietal lobule and in the hippocampus from patients with MCI are much higher than those in healthy control subjects[38].

Nucleic Acid Oxidation

DNA oxidation can lead to the formation of 8-OHdG. The 8-OHdG level in mitochondrial DNA isolated from the parietal cortex of AD patients is significantly increased (three times) as compared to control subjects[39]. Oxidative modification to RNA is also increased in the AD brain[40]. Interestingly, 8-OHG appears to precede all the typical hallmarks of AD, such as neurofibrillary tangles (NFTs) and Aβ plaques, and specifically occurs decades before Aβ aggregation in AD patients. Another way to measure DNA oxidation is to determine DNA strand breakage. It has been reported that the level of DNA breakage in the cerebral cortex of AD patients is twice that in controls[41].

All of these products of the oxidation of lipids, proteins, and nucleic acids have been considered as blood biomarkers for early AD diagnosis[30]. Their efficacy as early biomarkers of AD needs further study.

Oxidative Stress Is Induced by Multiple Mechanisms

Mitochondrial Dysfunction

The mitochondria are much more susceptible to oxidative stress as the site of the electron transport chain for adenosine triphosphate (ATP) production and the main source of ROS[42, 43]. Mitochondrial dysfunction and subsequent metabolic abnormality have been found in hippocampal neurons of AD patients[44, 45]. Deficiency of cytochrome oxidase, a key electron transport enzyme, is responsible for the increase of ROS production and the reduction in energy stores in AD[46]. Mn-SOD, an antioxidant enzyme that protects mitochondria from oxidative stress, is inactivated in APP/PS1 transgenic mice, and Mn-SOD inactivation further promotes mitochondrial dysfunction, oxidative stress, and apoptosis[47]. All these findings indicate that ROS production is intimately associated with mitochondrial dysfunction, especially abnormality of the electron transport chain.

Aβ is the most important culprit for mitochondrial dysfunction, and thus contributes to the ROS production in AD (Fig.1). Accumulating evidence shows that Aβ disturbs the electron transport chain by reducing the activities of key enzymes[48] and disrupting mitochondrial dynamics[19, 49]. These pathological changes are involved in oxidative

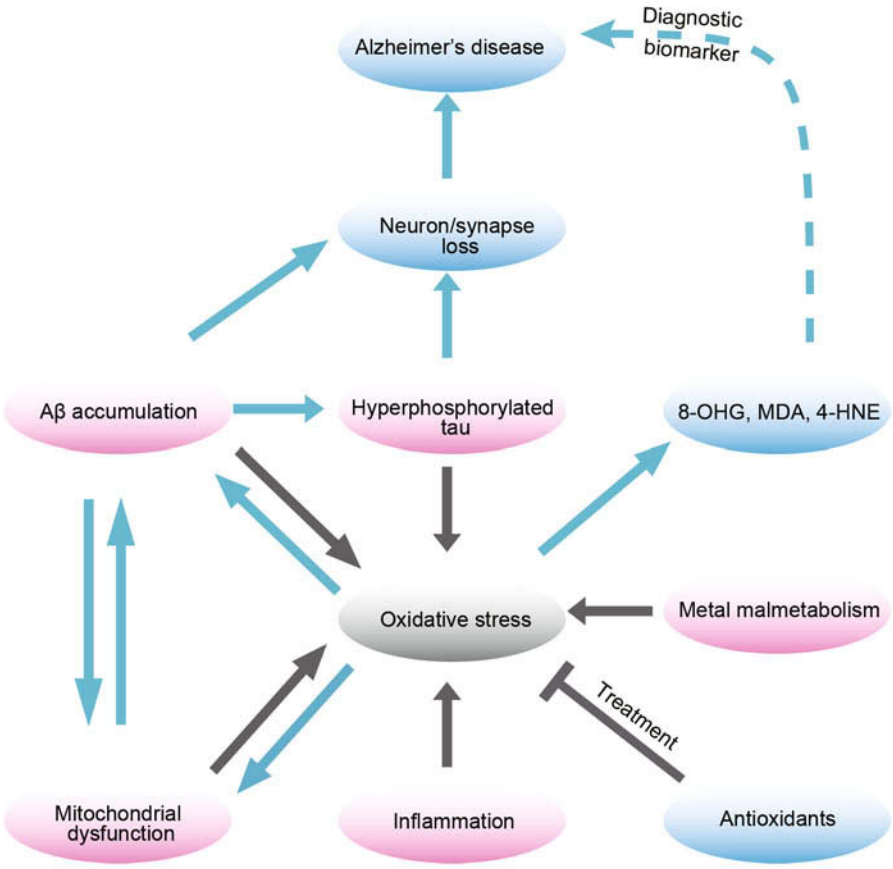

Fig. 1. Oxidative stress in Alzheimer's disease. The schematic shows how oxidative stress can be induced by mitochondrial dysfunction, metal malmetabolism, inflammation, hyperphosphorylated tau and Aβ accumulation in AD. Besides, the products of oxidative stress in the brain, such as 8-OHG, MDA, and 4-HNE may be used for AD diagnosis. Finally, considering the essential role of oxidative stress in AD, antioxidants may be used for treatment.

stress[12], dysfunction of mitochondrial axonal transport[50], and mitochondrial DNA (mtDNA) mutation[19]. Soluble Aβ is correlated with increased hydrogen peroxide levels and decreased activity of cytochrome *c* oxidase in Tg2576 mice, prior to the appearance of Aβ plaques[51]. In isolated mitochondria, Aβ treatment causes oxidative injury to the mitochondrial membrane, impairs lipid polarity and protein mobility, and inhibits key enzymes of the respiratory chain. Consequently, mitochondrial membrane permeability and cytochrome *c* release are increased, and apoptosis is evoked[48, 52]. Hirai *et al.* (2001) also reported that intracellular Aβ interferes with oxidative phosphorylation and ROS production within mitochondria, and this is related to the decreases in mitochondrial membrane potential, complex IV (cytochrome *c* oxidase) activity, and ATP production[44]. Consistently, various AD transgenic mouse models carrying mutants of amyloid precursor protein (APP) and presellien-1 (PS-1) exhibit increased hydrogen peroxide and nitric oxide production as well as elevated oxidative modification of proteins and lipids correlated with age-associated Aβ accumulation, indicating that Aβ promotes oxidative stress[53-55]. Aβ also binds to Aβ-binding alcohol dehydrogenase (ABAD), a member of the short-chain dehydrogenase reductase family in mitochondria, to induce apoptosis and ROS production in neurons, which can be prevented by ABAD inhibitors[56]. Besides, mitochondria are dynamic organelles that constantly undergo fission (splitting) and fusion (combining). Abnormal mitochondrial dynamics is associated with the production of free radicals. Particularly, excessive mitochondrial fragmentation results

in increased ROS production. For example, mitochondrial fragmentation accounts for increased high-glucose-induced respiration and ROS overproduction, which can be prevented by inhibition of mitochondrial fission[57]. Fission of mitochondria in AD seems to be more prevalent than fusion[19, 58]. The level of dynamin-related protein 1 (Drp1), a regulator of mitochondrial fission, is reduced in sporadic AD fibroblasts, and it may be correlated with exposure to Aβ[59]. Uncoupling proteins (UCPs) are a family of mitochondrial anion carrier proteins that are anchored to the inner membrane and have diverse physiological functions[60]. UCP2 and UCP3 are activated in response to oxidative stress to protect mitochondria[61]. However, this protective effect is disrupted in cells overexpressing APP or mutant APP[62], which further leads to progressive mitochondrial dysfunction and ROS production.

Mutations in mtDNA play a significant role in mitochondrial dysfunction in AD. Studies have revealed a causal relationship between mtDNA mutations and ROS production in the affected tissues of patients with mitochondrial diseases, when the mutation load of mtDNA reaches a threshold[63, 64]. For example, skin fibroblasts isolated from patients with myoclonic epilepsy with red ragged fibers (MERRF) show enhancement of intracellular hydrogen peroxide levels and oxidative damage, and an imbalance of gene expression of antioxidant enzymes[65]. Similar phenomena have also been found in patients with mitochondrial encephalomyopathy and lactic acidosis with stroke-like episodes (MELAS)[66] and Leber's hereditary optic neuropathy (LHON)[67].

Metal Accumulation

In the hippocampus, amygdala, and other brain regions with severe histopathological changes in AD patients, abnormal levels of copper, zinc, and iron have been reported[68]. Metals can interact with Aβ to induce oxidative stress (Fig.1). By binding to copper or iron, Aβ produces ROS by redox activity, and metal chelators reduce Aβ levels and prevent its aggregation by attenuating the metal overload[21, 69, 70]. Aβ binds Cu^{2+} with high affinity, forming a cuproenzyme-like complex[71]. During this process, the electron is transferred from Aβ to Cu^{2+}, converting Cu^{2+} to Cu^{+} and forming the Aβ radical ($A\beta^{+\bullet}$)[72]. In addition, Cu^{+} can donate two electrons to oxygen, generating H_2O_2[72, 73], and further producing hydroxyl radicals (Fenton-type reaction)[74]. Iron accumulation is also present in cells associated with neuritic plaques in AD[75], which results in the increase of oxidative stress. However, it has been shown that hemochromatosis mutations are associated with increased oxidative stress and progression of disease pathology[76]. Similar to the copper-Aβ interaction, the binding of iron to Aβ results in a reduction of Fe^{3+} to Fe^{2+} and the generation of H_2O_2[77]. In SH-SY5Y cells overexpressing the Swedish mutant form of human APP, the intracellular iron is significantly elevated along with increased oxidative stress[78]. These findings show that ROS are produced by the interactions between Aβ and metals. In addition, aluminum is associated with AD neurodegeneration by oxidative stress and inflammation[3]. As one of the key components in amyloid plaques and cerebrovascular amyloidosis, zinc is also considered to be correlated with AD. Evidence from triple-transgenic mice demonstrated that APP, PS1, and PS2 mutations produce ROS to mobilize zinc from extracellular metallothionein[79], which may be involved in Aβ accumulation[80].

Hyperphosphorylated Tau

Hyperphosphorylated tau protein, the major component of NFTs and a hallmark of AD, is significantly correlated with the neurodegeneration and cognitive decline[81]. Interestingly, neurons with NFTs have significantly lower 8-OHG levels despite obvious oxidative damage. This implies that tau phosphorylation and NFT formation may play a role in protecting neurons from oxidative insult[82] (Fig.1). However, most studies indicate that tau is involved in the neurodegeneration associated with oxidative stress in AD. In a *Drosophila* model of human tauopathy (tau R406W), a reduction in the gene dosage of thioredoxin reductase or mitochondrial SOD2 promotes tau-induced neurodegenerative histological abnormalities and neuronal apoptosis[23]. On the contrary, overexpression of these antioxidant enzymes or treatment with vitamin E decreases the tau-induced neuronal death[22]. In addition, cortical neurons expressing truncated tau show increased levels of ROS, and antioxidants such as vitamin C eliminate this alteration[83]. A relationship between oxidative stress and tau pathology has also been demonstrated in P301S and P301L transgenic mice. The functional analysis of proteomics finds mitochondrial dysfunction together with reduced NADH-ubiquinone oxidoreductase activity impairs mitochondrial oxidative phosphorylation and ATP synthesis[84-86]. Accordingly, coenzyme Q10 (CoQ10), an antioxidant and key component of the electron transport

chain, significantly enhances complex I activity and reduces lipid peroxidation, and consequently, significantly improves survival and the behavioral deficits in P301S mice[87].

Inflammation

Inflammation also participates in the production of ROS (Fig.1). Both microglia and astrocytes release pro-inflammatory mediators such as cytokines, chemokines, ROS, and complement proteins[88]. Aβ attracts and activates microglia, leading to their clustering around Aβ deposits in the brain. Microglia also express scavenger receptors to interact with Aβ, and cause ROS secretion and cell immobilization[89]. Astrocytes are also activated by Aβ, and hence produce chemokines, cytokines, and ROS that may result in neuronal damage[90, 91].

Oxidative Stress Is an Important Contributor to the Pathology of Alzheimer's Disease

Studies have found that Aβ at physiological levels plays a self-protective role in the neuronal response to oxidative stress. Picomolar or low nanomolar levels of Aβ are neurotrophic or neuroprotective[92], efficiently suppress the auto-oxidation of lipoproteins in the CSF and plasma[93], and dramatically increase hippocampal long-term potentiation[94], whereas high nanomolar concentrations induce the well-established neurotoxicity. Low concentrations of Aβ are not detrimental until their accumulation reaches a threshold level. However, neuronal oxidative damage is more pronounced in AD patients with less Aβ deposition or with a shorter disease duration[95]. There is an inverse relationship between the degree of oxidative damage of nucleic acids in neurons and the amounts of intraneuronal $A\beta_{42}$ in the hippocampus of the AD brain[96]. How can this contradiction be interpreted? As discussed above, ROS can be produced by disruption of oxidative phosphorylation in mitochondria or through other reactions. For example, respiratory chain dysfunction can lead to the release of free radicals, including ROS[12, 19]. To eliminate these free radicals, neurons may initiate mechanisms for the prevention of oxidative damage. Interestingly, some studies suggest that Aβ is initially a compensation for overwhelming concentrations of ROS[97, 98]. Aβ has antioxidant activity and protects lipoproteins from oxidation in the CSF and plasma; and patients with Down syndrome with the most severe Aβ deposition show the lowest levels of 8-OHG, while neurons lacking Aβ pathology have significantly higher levels of 8-OHG[99]. Thus Aβ may be characterized as an environmental stress on neurons that is induced by oxidative stress, or other pathological factors.

On the other hand, when Aβ accumulates to certain extent it exhibits a detrimental effect on neurons and elicits further oxidative stress[82]. Oxidative stress reduces the activity of α-secretase and promotes the expression and activation of β- and γ-secretases[100-102]. The oxidative stress-induced β-site APP-cleaving enzyme 1, PS1 expression, and γ-secretase activation are mediated by activation of the c-Jun N-terminal kinase pathway[103]. Furthermore, antioxidants such as EGb 761, curcumin, and green tea catechins reduce brain Aβ level and the Aβ plaque burden[12, 104-106]. Modification of the antioxidative system by overexpressing Mn-SOD in Tg19959 APP-mutated transgenic mice decreases protein oxidation and increases antioxidant defense in the brain, resulting in a reduced Aβ plaque burden and restoration of memory[107]. Aβ oligomerization is also increased in the Tg2576 APP-overexpressing AD mouse model by deleting cytoplasmic SOD1[108]. In sum, oxidative stress plays an important role in Aβ pathology (Fig.1).

Accumulating evidence suggests that oxidative stress also contributes to tau pathology in AD. Oxidation of fatty acids accelerates the polymerization of tau, and thus serves as a possible link between oxidative stress and the development of fibrillar pathology in AD[109]. This polymerization is hypothesized to occur *via* a cysteine-dependent mechanism[110]. In Tg2576 AD transgenic mice, a deficiency in mitochondrial SOD2 or a reduction of cytoplasmic SOD1 induces tau phosphorylation[111]. In addition, p38 mitogen-activated protein kinase, a kinase responsible for tau phosphorylation, is activated by oxidative stress *in vitro*[112]. The hyperphosphorylation of tau makes it susceptible to conformational changes by the production of paired helical filaments and subsequent NFTs. However, further studies are needed to fully clarify the role of oxidative stress in tau pathology.

Antioxidants as a Treatment for Alzheimer's Disease

The antioxidants are potential therapeutics by eliminating ROS and exerting neuroprotective effects on neurons in AD

(Fig.1). For example, CoQ10, also known as ubiquinone, reduces oxidative stress and has neuroprotective properties both *in vitro* and *in vivo*[113]; its administration to transgenic AD mice also dramatically reduces the amyloid plaque burden[114, 115]. Although CoQ10 has not been tested in clinic trials, its analog, idebenone, has been assessed in AD patients, and has beneficial effects on memory and attention[116, 117]. However, it failed to prevent disease progression in a later large-scale study[118]. Another CoQ10 derivative, mitoquinone mesylate or mitoQ, has also been applied to prevent oxidative damage in AD[119]. Latrepirdine (Dimebon), a nonselective antihistamine, has shown promise *in vitro* for preventing ROS-mediated damage in neurodegenerative diseases[120]. In a phase-2 trial, Dimebon was found to be well-tolerated and improved cognition, activities of daily living, and overall function in MCI and AD patients as compared to placebo[121]. However, more recently, the phase 3 CONNECTION trial in AD patients did not reveal any beneficial effects[122]. Curcumin has also been tested in AD patients in a pilot trial with a duration of 6 months, but had no effects on cognition and levels of isoprostanes and Aβ[123]. Acetyl-L-carnitine (ALCAR) and R-alpha lipoic acid are also potential antioxidants for AD therapy. Particularly, ALCAR has been tested in many clinical trials[124-126]. Other drugs, including vitamin E[93, 127], pramipexole[128], and Szeto-Schiller peptides[129] have also been investigated widely, but none has received convincing confirmation of efficacy. The reason for the low efficacy or failure of the clinical trials may be that the basic pathological changes, including Aβ accumulation and tau hyperphosphorylation, are not efficiently changed, even when the elimination of oxidative stress seems to be realized. Besides, as AD is a multi-factorial degenerative disease, combined treatment to target multiple pathological mechanisms should be explored in order to develop effective disease-modifying therapies[130].

Conclusion

Oxidative stress is an important pathophysiological change in AD. It is closely correlated with amyloid pathology and tau pathology by forming vicious pathophysiological cycles, inducing mitochondrial dysfunction and promoting metal toxicity. Oxidative stress is an essential pathological marker of AD, but also serves as a potential treatment target.

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