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Oxidative Stress Signaling in Alzheimer's Disease

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Abstract

Multiple lines of evidence demonstrate that oxidative stress is an early event in Alzheimer's disease (AD), occurring prior to cytopathology, and therefore may play a key pathogenic role in AD. Oxidative stress not only temporally precedes the pathological lesions of the disease but also activates cell signaling pathways, which, in turn, contribute to lesion formation and, at the same time, provoke cellular responses such as compensatory upregulation of antioxidant enzymes found in vulnerable neurons in AD. In this review, we provide an overview of the evidence of oxidative stress and compensatory responses that occur in AD, particularly focused on potential sources of oxidative stress and the roles and mechanism of activation of stress-activated protein kinase pathways.

Keywords

Alzheimer disease; compensation; JNK pathway; oxidative stress; signal transduction

Introduction

Oxidative stress is defined as the imbalance between biochemical process leading to production of reactive oxygen species (ROS) and those responsible for the removal of ROS [1]. Under physiological conditions, ROS production is a normal consequence of cellular processes that is tightly controlled by antioxidants, including glutathione, α-tocopherol (vitamin E), carotenoids, and ascorbic acid, as well as by antioxidant enzymes such as catalase and glutathione peroxidases, which detoxify H_2O_2 by converting it to O_2 and H_2O [2]. However, when ROS levels exceed the antioxidant capacity of a cell under disease condition or by age or metabolic demand, a deleterious condition, oxidative stress, occurs causing molecular damage, promoting neuronal adaptation and leading to a critical failure of biological function [2].

The brain, as a relatively small organ mass, has a disproportionately high level of oxygen consumption due to its high ATP demand. In fact, the brain accounts for approximately 20% of the body's total basal oxygen consumption [3] and subsequently generates relatively high level of ROS. As such, the neurons in the brain are exposed to an environment with considerable ROS compared to other cellular systems of other organs. Since the aging process is associated

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with an increase in the adventitious production of ROS, together with a concurrent decrease in the ability to defend against such ROS, not surprisingly, studies on Alzheimer's disease (AD), an age-related neurodegenerative disease, over the past ten years have established that oxidative stress and damage are not only in the lesions of AD but also in the neurons at risk of death [4–11]. In fact, multiple lines of evidence have shown that oxidative stress is not only an early event in AD but also plays an important role in initiating the disease through provoking cell signaling pathways. Here, in this review, we will focus on the source of oxidative stress in AD and the signaling pathways that are induced by oxidative stress.

Sources of Oxidative Stress

In AD, in addition to a high metabolically-derived background level of ROS, there are a number of additional contributory sources that are thought to play an important role in the disease process. Among them, mitochondrial and metal abnormalities are the major sources of oxidative stress; however, amyloid-β (Aβ), astrocytes/microglia, advanced glycation end products (AGEs) have also been implicated.

Mitochondrial Abnormalities

Mitochondria have been shown to be the center of ROS production. In AD, damaged mitochondria have been observed [12,13], and the most consistent defect in mitochondria in AD are deficiencies in several key enzymes responsible for oxidative metabolism including α-ketoglutarate dehydrogenase complex (KGDHC) and pyruvate dehydrogenase complex (PDHC), two enzymes involved in the rate-limiting step of tricarboxylic acid cycle, and cytochrome oxidase (COX), the terminal enzyme in the mitochondrial respiratory chain that is responsible for reducing molecular oxygen [13–19]. These functional abnormalities in mitochondria favor the production of ROS. Additionally, we found damaged mitochondrial DNA (mtDNA) present in vulnerable neurons in AD [20], and formation of mitochondrial-derived lysosomes and lipofuscin were evident in almost all of AD neurons [21]. Quantitative morphometric measurements of the percentage of the different types of mitochondria (normal, partially damaged and completely damaged) confirmed that neurons in AD show a significantly lower percentage of normal mitochondria and a significantly higher percentage of the completely damaged mitochondria compared to an aged-matched control group [20]. Studies from cybrid cell lines with mitochondria DNA from AD patients also showed abnormal mitochondrial morphology, membrane potential and ROS production, confirming mutant mitochondrial DNA in AD contributing to the pathology [22–24]. The following is a ranking of factors, which likely contribute to mitochondrial dysfunction in AD: 1) Low vascular blood flow, which is a prominent feature of the brain during chronic hypoxia/hypoperfusion, has been implicated in the development of AD [25]; 2) Increased sporadic mutations in the mtDNA control region, with some being unique to AD, were found in AD patients compared to controls which is associated with deleterious functional consequences for mitochondrial homeostasis once they reach a critical mass in postmitotic cells in the brain [26]; and studies in 3) Aβ and the majority of amyloid-β protein precursor (AβPP) processing machinery are found in mitochondrial [27,28]. In fact, AβPP is present in the mitochondrial import channel and potentially impedes mitochondrial import [29] thus impairing mitochondrial function. Another study in Tg2567 mice model demonstrated that at mRNA level many genes expression related with mitochondrial metabolism and apoptosis were changed, suggesting mitochondrial energy metabolism is impaired by the expression of APP/Aβ [30]. A recent review by Reddy and Beal clearly reviewed the effect of Aβ on mitochondrial dysfunction [31]; 4) Hyperhomocysteinemia is a strong, independent risk factor for the development of AD [32] and homocysteine inhibits several genes encoding mitochondrial proteins and promotes ROS production [33]. 5) Apolipoprotein E4 (ApoE4) is another factor that could cause mitochondrial dysfunction. Previous data have shown that more ApoE4 fragment in AD brains than in age

matched controls [34], and it shows toxicity and impairs mitochondrial function and integrity [35].

Redox-Active Metals: Iron and Copper

Iron, as a transition metal, is involved in the formation of •OH by Fenton chemistry [9,36]. In AD, iron is an important cause of oxidative stress because of its over-accumulation in the brain, and it has been found the iron accumulates in the hippocampus, cerebral cortex and basal nucleus of Meynert, and colocalizes with AD lesions, senile plaques and neurofibrillary tangles (NFT) [9,37]. Recently, we also showed that RNA-bound iron plays a pivotal role in RNA oxidation in vulnerable neurons in AD [38]. Specifically, we found that rRNA provides a binding site for redox-active iron and serves as a redox center within the cytoplasm of vulnerable neurons in AD in advance of the appearance of morphological changes indicating neurodegeneration [38].

Copper is another metal ion that is important for many enzymes in brain metabolism and that has been implicated in disease pathogenesis. In AD patients, the homeostasis of copper is disturbed causing oxidative stress directly and indirectly. At least two pathways are associated with copper-related oxidative stress: (1) alterations in ceruloplasmin and (2) copper interaction with AβPP. The entry of copper to the brain is mainly mediated by ceruloplasmin, a copper binding protein that plays a role in protecting cells against oxidative stress. Specifically, ceruloplasmin is a key protein involved in the regulation of the redox state of iron by converting the ROS catalytic-Fe(II) to a less reactive Fe(III). While ceruloplasmin is increased in brain tissue and cerebrospinal fluid in AD [39], neuronal levels of ceruloplasmin remain unchanged [40]. Thus, while increased ceruloplasmin may indicate a compensatory response to increased oxidative stress in AD, its failure to do so in neurons may play an important role in metal-catalysed damage [40]. Copper has also been shown to play a role in generating ROS through its binding to Aβ. As with iron, copper concentrations are highly concentrated within Aβ plaques; Aβ binds copper in AD tissue, and Aβ:Cu complexes form a catalytic source of H_2O_2, reducing Cu(II) to Cu(I) involving an electron-transfer reaction that could enhance the production of •OH [41,42]. A recent study also reported that tau protein could bind to Cu, and inappropriately binding with tau protein may trigger oxidative stress [43].

Amyloid-β deposition

A number of studies have shown the Aβ exerts its toxicity by generating oxidative stress and induces the oxidation of different biomolecules, including peroxidation of membrane lipids [44] and lipoproteins [45], generates H_2O_2 [46] and hydroxynonenal (HNE) [47] in neurons, damages DNA [48] and inactivates transport enzymes [49]. However, three important conditions are required for Aβ to induce oxidation: fibrillation, the presence of transition metals and methionine 35, aggregation and fibrillation of Aβ occurs only if the peptide is “aged” and present in a relatively high concentration (micromolar range) [50,51]. Also, the presence of transition metals is a requisite for Aβ aggregation and its pro-oxidant activity [52–54]. The toxicity of Aβ is likely to be mediated by a direct interaction between this peptide and transition metals with subsequent generation of ROS [41,54]. Another factor essential for the pro-oxidative activity of Aβ seems to be the presence of methionine 35. It has been demonstrated that the substitution of this residue by another amino acid abrogates or diminishes significantly the pro-oxidant action of Aβ [44,55,56]. Methionine 35 can scavenge free radicals [57] and reduce transition metals to their high-active low-valency form [58], thereby exhibiting both anti- and pro-oxidative properties. Notably, the toxicity of Aβ appears to be only evident in *in vitro* culture experiments and, conversely, *in vivo* studies show a negative correlation between oxidative stress and Aβ deposition, indicating an antioxidant role for Aβ. 8OHG an oxidative marker markedly accumulates in the cytoplasm of cerebral neurons in AD. As Aβ increases in

the AD cortex, there is a decrease in neuronal levels of 8-hydroxyguanosine, i.e., decreased oxidative damage [59,60]. A similar negative correlation between Aβ deposition and oxidative damage is found in patients with Down syndrome [61]. Aβ deposits observed in both studies mainly consist of diffuse plaques suggesting that these diffuse amyloid plaques may be considered as a compensatory response that reduces oxidative stress [62–64].

Glycation, Glycoxydation and Advanced Glycation End Products

Advanced glycation end products (AGEs), a diverse class of posttranslational modifications, are generated by the non-enzymatic reaction of a sugar ketone or aldehyde group with the free amino groups of a protein or amino-acid specifically lysine, arginine and possibly histidine. [65]. Accumulation of AGEs in the brain is a feature of aging [66] are also implicated in the development of pathophysiology in age-related diseases such as diabetes mellitus, atherosclerosis, and AD [67–69]. AGEs, in the presence of transition metals can undergo redox cycling with consequent ROS production [70–72]. Additionally, AGEs and amyloid-β activate specific receptors such as the receptor for advanced glycation end products (RAGE) and the class A scavenger-receptor to increase ROS production and modulate gene transcription of various factors involved in inflammation through NFκB activation [73,74].

Activated Microglia/Astrocytes

Similar to situations in the periphery where damaged tissue and the chronic presence of inert abnormal materials cause inflammation, senile plaques, NFT and injured neurons may well provoke inflammation in the AD brain. Indeed, both activated microglia and astrocytes cluster at sites of Aβ deposition [75,76] and express a wide range of inflammatory mediators including cytokines and chemokines and cyclooxygenase [77]. Obviously, the secretion of ROS/reactive nitration species (RNS) by inflammatory cells is a major mechanism for attacking opsonized targets and activated microglia/astrocytes have the potential to produce large amounts of ROS/RNS by various mechanisms. Aβ peptide can also directly activate the NADPH oxidase of microglia which results in a burst of superoxide radicals and increased production of hydrogen peroxide [78,79]. Activated microglia and astrocytes can produce large amounts of nitric oxide (NO), which in turn can react with superoxide to form peroxynitrite, leaving nitrotyrosine as an identifiable marker. The footprint of excess NO production in AD is confirmed by the increased amounts of nitrotyrosine-modified proteins [10,80]. Increased expression of iNOS is also detected in astrocytes surrounding plaques in AD brain [81,82]. Another free radical generating mechanism in AD microglia involves the enzyme myeloperoxidase (MPO), and there is evidence that MPO immunoreactivity is present in selective highly activated microglia around amyloid plaques in the AD brain and that Aβ aggregates increase MPO mRNA expression in microglia-like cells *in vitro* [83]. MPO catalyzes a reaction between hydrogen peroxide and chloride to form hypochlorous acid which can further react with other molecules to generate other ROS including hydroxyl ions. MPO can also catalyze the formation of nitrotyrosine-modified proteins [84] as well as cause advanced glycation end product modifications [85], both of which are evident in AD [10,86].

Oxidative Stress Induced Cell Signaling Pathways

It is clear that alterations in the expression and enzyme activity induced by cellular stress such as oxidative stress are mediated through the interplay of multiple signaling pathways. Among these, stress-activated protein kinase (SAPK) pathways are the central mediators that amplify stress signals to the nucleus. c-Jun N-terminal kinases (JNK)/SAPK and p38/SAPK2 are the two major SAPKs.

In an effort to delineate the oxidative stress signaling events in AD, we found that the entire JNK/SAPK pathway was altered in AD. JNK2 and JNK3 were related to neurofibrillary

pathology and JNK1 was related to Hirano bodies in cases of AD but were only weakly diffuse in the cytoplasm of all neurons in control cases and in non-involved neurons of diseased brains [87]. More importantly, JNK is not only activated but also redistributed, from nuclei to the cytoplasm, in a manner that correlates with the progression of the disease such that phospho-JNK is exclusively localized in association with neurofibrillar alterations in severe AD cases [87,88]. Notably, its immediate upstream activator, JKK1, and its downstream effector, c-Jun, are also activated in AD [89,90], further indicating the activation of the entire JNK/SAPK pathway in AD. JNK/SAPK activation apparently precedes amyloid deposition [87,91,92], and it is also interesting to note that the nuclear localization of active JNK/SAPK is almost uniformly detected in most susceptible neurons in early AD stages, a pattern that is similar to the oxidative marker 8OHG, suggesting that oxidative stress is a likely activator of the JNK/SAPK pathway in AD and that the same molecule may initiate both events.

Given that Aβ appears to play a key role in the pathogenesis of AD and that oxidative events mediate Aβ toxicity, it is plausible that SAPKs may be activated by Aβ. In support of this, studies from several groups consistently show that Aβ induces a two- to three-fold activation of JNK/SAPK in different neuronal cell types and that this activation directly contributes to Aβ-induced cell death [93–96]. This is further supported by an *in vivo* study showing JNK/SAPK and p38 are age-dependently activated in Tg2576/PS1P264L mice and that JNK/SAPK activation is localized to abnormal neurites within amyloid deposits [97]. Since oxidative stress is also a prominent feature of some transgenic mice, and lipid peroxidation, a marker of oxidative stress, precedes Aβ deposition in Tg2576 mice [98], it is tempting to suggest that oxidative stress, as an earlier event, may activate JNK/SAPK and that elevated levels of Aβ, as a later event, contribute to the continued and chronic activation of JNK/SAPK. A systematic examination of the temporal relationship between oxidative stress, JNK/SAPK activation and Aβ deposition in these mice is definitely needed and will certainly help to delineate this issue. Moreover, how Aβ leads to JNK/SAPK activation is also an issue of debate, although it is likely that an oxidative stress-type mechanism may be responsible. Indeed, given that some transgenic mice (such as PS1P264L mice) with elevated Aβ levels do not show JNK/SAPK activation and that not all Aβ-containing neurons show JNK/SAPK activation [88], additional factors, other than Aβ, are clearly involved. Interestingly, we found that JNK/SAPK is strongly activated in AβPP transgenic mice with extensive iron accumulation and oxidative damage but not in AβPP transgenic mice with little iron accumulation and oxidative damage [9]. Since Aβ deposits in both mice, this finding suggests that iron and some ROS may play an important role in mediating Aβ induced JNK/SAPK activation. In this regard, it is important to note that some *in vitro* studies suggest that ROS, like hydrogen peroxide, mediate JNK/SAPK activation induced by Aβ [99,100]. Of note, recent studies demonstrate that oxidative stress *in vitro* induces increased expression of BACE1 and PS1, thereby enhancing Aβ production which involves JNK/c-jun pathways [101–103]. Given Aβ also as one of the oxidative stress sources, oxidative stress production and Aβ generation may set up a vicious cycle, in which oxidative stress contributes to Aβ accumulation; and Aβ in turn induces oxidative stress, resulting in JNK/c-jun activation and increased level of BACE1 and γ-secretase, which further enhances Aβ production.

Although the activation of JNK/c-Jun is implicated in Aβ-induced apoptosis *in vitro* [93,94, 96], actual cell death by apoptosis in AD is rare at any given time despite large populations of neuronal cells demonstrating activated JNK/c-Jun [104]. Our study on c-Jun found that the level and distribution of c-Jun phosphorylated at Ser73 site are considerably altered in susceptible neurons in all AD brains examined compared with that in age-matched controls, associating with all of the major pathologies including NFT, dystrophic neurites around senile plaques, and GVD, in addition to extensive nuclear staining [90]. Furthermore, all the neurons with phospho-c-Jun (Ser73) positive pathologies were devoid of TUNEL staining [90], suggesting that c-Jun activation in the nucleus is not necessarily causally linked with neuronal

death in AD. Extensive phospho-c-Jun (Ser73) nuclear staining was also seen in neurons in Tg2576 mice brains, where no substantial neuronal death was noted. Therefore, the nuclear localization of active JNK/SAPK-c-Jun [87,90] further suggests that it may affect gene expression associated with cell survival and, as such, represents an adaptation effort in the face of various stimuli such as oxidative stress that activate the JNK pathway, rather than initiation of apoptotic machinery in response to oxidative stress. In this regard, it is worth noting that the activation of JNK/SAPK pathway can modulate the induction of several antioxidant enzymes that are induced in AD such as HO-1 and SOD1 [4,105,106].

The observation that JNK is able to phosphorylate 10 proline-directed sites on tau *in vitro* [107–110], as well as the upregulation of tau-associated active JNK and its co-localization with NFT in AD, indicates that active JNK may be involved in the phosphorylation of tau *in vivo*. In fact, several groups have now reported that JNK can phosphorylate tau in cells and in animal models [111]. Like JNK, an increase in p38 levels and activity in AD brain tissues has also been described [112–116]. Immunocytochemical studies show that p38 is also associated with neurofibrillary pathology including NFT and senile plaque neurites in the AD brain [112–116]. The essentially identical localization pattern for phospho-JNK and phospho-p38 in severe AD cases observed in our study suggests that JNK and p38 are activated by the same signal that likely relates to oxidative stress [117], and in late stage AD they play a role in phosphorylation of tau protein and likely in the formation of NFTs as well. This notion is confirmed by our chronic oxidative stress cell model, in which activated JNK was observed along with increased phosphorylated tau at PHF-1 sites [118], which are hyperphosphorylated in AD patients. Notably, we have demonstrated that oxidative damage is reduced by the formation of neurofibrillary lesions [119]. Given the fact that neurons with NFT can survive for decades, which is consistent with data in mouse model that NFTs are not involved in neuronal death [120,121], it is tempting to suggest that the formation of neurofibrillary pathology is a further neuronal adaptation to chronic oxidative stress [122]. In this regard it is interesting to note that a recent study demonstrated that phosphorylation of tau antagonizes apoptosis by stabilizing beta-catenin [123]. Therefore in a chronic oxidative stress situation when induction of anti-oxidant enzymes is insufficient, which is likely the case in chronic neurodegenerative diseases such as AD, neuronal cells may mobilize further structural adaptations such as the phosphorylation of tau protein via JNK/SAPK activation and formation of NFTs to serve an anti-oxidant function [119].

Conclusion

Oxidative stress, as one of the earliest events in AD pathogenesis, plays a significant role in the formation of AD pathology. Each source of oxidative stress appears to interact with each other, acting like a web and most sources have positive feedback. However which particular source first come into play to ultimately induce most of others is still not clear. Nonetheless, the overall result is damage including AGEs [124], nitration [10,80,125,126], lipid peroxidation adduction products [127–133] as well as carbonyl-modified neurofilament protein and free carbonyls [7,8,124,133–135] with the involvement extending beyond the lesions to neurons not displaying obvious degenerative changes. Accompanying damage, compensatory responses, provoked by oxidative stress via the activation of SAPK pathway and downstream adaptations such as induction of anti-oxidant enzymes, tau phosphorylation and NFT formation may provide some protective mechanisms to ensure neuronal cells do not succumb to such oxidative insults. This shift in homeostasis, achieved via the dynamic balance between oxidative damage and compensatory responses, likely results in the panoply of changes in AD.

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