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Oxidative Stress and Neuronal Adaptation in Alzheimer Disease: The Role of SAPK Pathways

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ABSTRACT

Recent evidence indicates that oxidative stress occurs early in the progression of Alzheimer disease, significantly before the development of the hallmark pathologies, namely neurofibrillary tangles and senile plaques. The interaction of abnormal mitochondria, redox transition metals, and oxidative stress response elements contributes to the generation of reactive oxygen species in diseased neurons. Oxidative damage to major cellular molecules is seen in a number of disease states that are either acute or chronic and it is apparent that without eliciting compensations that restore redox balance, cells will rapidly succumb to death. Indeed, although oxidative stress is a prominent feature in Alzheimer disease, few vulnerable neurons show clear signs of apoptosis, suggesting that the level of oxidative stress does not significantly exceed neuronal oxidative defenses. In light of this observation, we propose that neurons in Alzheimer disease are exposed to low, but chronic, levels of oxidative stress that lead neurons to elicit adaptive responses such as the activation of stress-activated protein kinase pathways. *Antioxid. Redox Signal.* 5, 571–576.

INTRODUCTION

OXIDATIVE STRESS entails breaching oxidant defenses to an extent that is sufficient to lead to damage. However, given the dynamic nature of homeostatic systems in response to external insults, increases in oxidative damage do not necessarily suggest that the cell is succumbing to oxidative stress and its sequelae. This observation is especially true in neurodegenerative diseases. The neurons that experience increased oxidative damage, by their continued existence inherently testify that adaptations are reached as a consequence of exposure to reactive oxygen species (ROS). This is also the case for Alzheimer disease (AD), where those neurons that exhibit oxidative damage are also associated with induced antioxidant systems. Therefore, a prominent role must also be played in AD by the distinct biochemical changes that are associated with, and considered part of, the spectrum of disease, such as the activation of stress-activated protein kinase (SAPK) pathways and downstream events.

MITOCHONDRIAL ALTERATIONS

As the primary site of oxidative bioenergetics within the cell, the mitochondria contribute significantly to oxidative damage and related events. However, extensive evidence indicates that cerebral metabolism is reduced in AD (2). These conflicting observations confuse the role of mitochondria in AD (40, 41). It has been reported that activities of specific mitochondrial enzyme complexes are reduced in AD, including cytochrome oxidase (COX), the pyruvate dehydrogenase com-

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plex, and the α-ketoglutarate dehydrogenase complex (3, 16, 42, 44). Of particular interest is COX, which possesses a possible link to oxidative stress in AD (11). Because COX is the component of the mitochondrial electron transport chain that directly interacts with molecular oxygen, its abnormality in AD (3, 16, 44) could result in increased ROS production in mitochondria. Although side production of superoxide is a normal phenomenon in aerobic organisms, an increase in superoxide production is a possible phenomenon in AD due to a loss of COX activity, which could back up electrons at the complex III site, resulting in formation of ROS. Although it is hypothesized that mitochondria are significant producers of ROS, mitochondria themselves do not exhibit striking evidence of oxidative damage in AD. Using 8-hydroxyguanosine as a marker for nucleic acid oxidation, oxidative damage is limited primarily to the cytoplasm of susceptible neurons in AD, with no significant increase in mitochondria (19, 20). It is likely, therefore, that mitochondria in AD supply a key reactant that, once in the cytoplasm, produces free radicals (33). Although increased amounts of the superoxide radical (O_2^-) may be produced, it diffuses poorly past membranes. However, hydrogen peroxide (H_2O_2), produced by conversion of O_2^- via the mitochondrial specific enzyme manganese superoxide dismutase, can freely diffuse across the outer membrane of the mitochondria and into the cytoplasm. Once H_2O_2 is present in the cytoplasm, redox-active iron (see below) can interact with H_2O_2 to produce the highly damaging hydroxyl radical ($^{\bullet}OH$) via the Fenton reaction (33). Therefore, it is likely that mitochondrial abnormalities are involved as a source of ROS that culminates in perikaryal oxidative damage.

In AD, both mitochondrial DNA (mtDNA) and protein are increased, whereas mitochondrial number is decreased in vulnerable neurons (i.e., pyramidal neurons, but not granule cells or glia) (11). This dichotomy of mtDNA/protein increase and mitochondrial decrease indicates that vulnerable neurons in AD are accumulating mitochondrial degradation products (41). In fact, ultrastructural examination shows that the increased, mtDNA and protein are found in vacuoles associated with lipofuscin, a lysosome marker that, in previous studies, has been suggested as the site of mitochondrial degradation by autophagy (4). It is likely that the increase in degradation products is attributed to greater turnover of mitochondria either by autophagy or by reduction of proteolytic turnover leading to accumulation of mtDNA and protein. These data thereby support the notion of increased oxidative stress in AD due to an increase in dysfunctional mitochondria.

REDOX-ACTIVE METALS

The generation of oxygen free radicals and the consequent cellular oxidative stress are thought to be mediated by redox reactions that are associated with transition metals. Changes in metal homeostasis (primarily iron and copper) result in a number of cellular disturbances characterized by free radical production. Recent data have shown that redox-active iron and copper have been associated with, and are concentrated within, the major pathological markers of AD, including senile plaques, neurofibrillary tangles (NFT), and neuropil threads (15, 33, 37).

Oxidative stress, *in vivo,* is thought to be mediated by redox transitions associated with "free" iron, more than any other transition metal. The association of, and interaction between, iron and amyloid-β (Aβ) have shed much light around the debate concerning Aβ toxicity and its subsequent relation to oxidative stress. Although it is clear that Aβ causes oxidative stress, the precise mechanism by which Aβ leads to increased oxidative stress still remains elusive. Recently, it has been shown that the pro-oxidant and cytotoxic effects of Aβ are likely mediated by its interaction with redox-active iron (32). Pretreatment with the iron chelator deferoxamine significantly decreases *in vitro* neurotoxicity of preaggregated Aβ, whereas subsequent incubation of Aβ with excess redox-active iron restores Aβ neurotoxicity (32). Although senile plaques accumulate iron in both Fe(II) and Fe(III) redox states, Fe(II) can be oxidized by H_2O_2 increasing Fe(III) levels at the expense of Fe(II) (33). Importantly, the reaction of Fe(II) and H_2O_2 is the primary source of highly damaging $^{\bullet}OH$. Thus, redox-active iron is needed for Aβ-induced oxidative stress. Furthermore, dysregulation of cellular iron metabolism supports the notion that impaired iron homeostasis plays an important role in this disease. For example, iron regulatory protein-2 (IRP-2) is increased in AD and selectively associated with the pathologic hallmarks of AD (38). Also, an increase in iron concentration with a concurrent decrease in ferritin is seen in AD brain (6, 13). IRPs are involved in the regulation of intracellular iron homeostasis by regulating the expression of iron storage protein, ferritin, by interacting with a conserved RNA structure termed the iron-responsive element (IRE). A wealth of data supports the idea that alterations in the IRP/IRE interaction are the cause of the observed disruption in iron homeostasis (24, 38). Such an increase in iron, without an appropriate increase in ferritin to detoxify the iron, would leave the neuron vulnerable to ROS.

Copper has a functional role in many enzymes that require oxidation–reduction reactions. For example, this metal is found in the catalytic site of COX in the mitochondrial electron transport chain and copper-zinc superoxide dismutase. In AD, copper interactions have the potential to yield oxidative damage by at least two pathways: alterations in ceruloplasmin and through copper interaction with amyloid-β protein precursor (AβPP). The entry of copper into the brain is mediated mainly by ceruloplasmin, a copper binding protein that plays a role in protecting cells from 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). Whereas ceruloplasmin is increased in brain tissue and cerebrospinal fluid in AD (14), neuronal levels of ceruloplasmin remain unchanged (5). Thus, although 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-catalyzed damage (5). In fact, studies directed at clarifying the relationship between oxidative stress and tissue metal ion levels indicate that the ratio of copper to zinc and the level of ceruloplasmin are significantly higher in cases with neurodegeneration (17). Copper has also been shown to play a role in generating ROS through its binding to AβPP. AβPP can reduce Cu(II) to Cu(I) involving an electron-transfer reaction that could enhance the

production of •OH through formation of an AβPP-Cu(II)-hydroxyl radical intermediate (37). As with iron, copper concentrations are also focally increased within Aβ plaques, setting up conditions for Fenton-type chemistry through the reduction of Cu(II) by Aβ-H_2O_2 reactions.

SAPK PATHWAYS IN AD

Alterations in gene expression and enzyme activity induced by cellular stresses are mediated through the interplay of multiple signaling pathways. Among these are the SAPK pathways, which are the central mediators that propagate signals from the membrane to the nucleus. In neuronal cells, potentially deleterious stimuli, such as deprivation of trophic factors, UV irradiation, free radicals, hypoxia, ischemia, heat shock, and cytokines, provoke an intracellular stress response that either leads to apoptosis or defensive-protective adaptations. SAPK and its downstream effectors are the major cellular factors involved in this bipartite response, which can lead to neurodegeneration or neuroprotection depending on the cellular and environmental conditions, as well as the influence of other signaling pathways (18). c-Jun N-terminal kinase (JNK) and p38 are the two major SAPKs. As SAPK pathways play an important role in these cellular processes, from gene expression and inflammation to cell death, that are likely involved in a chronic disease, the importance of the SAPK pathway as a pathological modulator is being increasingly recognized.

We found that JNK2 and JNK3 were associated with neurofibrillary pathology and JNK1 with Hirano bodies in cases of AD, but were only weak and diffuse in the cytoplasm in all neurons in control cases or in uninvolved neurons in diseased brain (48). More importantly, JNK is not only activated, but also redistributed (35, 48), from the 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 neurofibrillary alterations in severe AD cases (48). Notably, the immediate upstream activator, JKK1, is also activated in AD (50). As the role of oxidative stress in AD and AβPP transgenic mice is well documented as one of the earliest events in disease pathogenesis (12, 25, 41), we suspect that the activation of the JNK pathway is a response to oxidative stress. This notion is supported by our recent finding that JNK is strongly activated in AβPP transgenic mice with extensive oxidative damage, but not in AβPP transgenic mice with little oxidative damage (39, 46). The observation that JNK is able to phosphorylate 10 proline-directed sites on tau *in vitro* (9, 29–31), as well as the upregulation of tau-associated active JNK, indicates that active JNK may be involved in the phosphorylation of tau *in vivo*. In fact, several groups reported that JNK can phosphorylate tau in neuronal and nonneuronal cells and in two different animal models (for review, see 49). Notably, we have demonstrated that oxidative damage is reduced by the formation of neurofibrillary lesions. Given the fact that NFT can survive for decades, it is tempting to suggest that the formation of neurofibrillary pathology is a further neuronal adaptation to chronic activation of the JNK pathway.

An increase in p38 level and activity in AD brain tissues has also been described (1, 8, 10, 45, 47). Immunocytochemical studies show that p38 is associated with neurofibrillary pathology including NFT and senile plaque neurites in the AD brain (1, 8, 10, 45, 47). Further, the increase in and activation of MKK6, the immediate upstream activator of p38, provides compelling evidence that the p38 pathway is abnormally activated in AD (45, 47). Notably, the activation of MKK6-p38 appears to be specific because it is more prominent in susceptible neurons than in microglia, suggesting that this pathway may directly contribute to the degeneration of neurons in AD (47). The essentially identical staining pattern for phospho-JNK and phospho-p38 in severe AD cases suggests that JNK and p38 are activated by the same signal (47), a signal that, as described above, likely relates to oxidative stress. The activation of the p38 pathway has been shown to mediate expression of downstream antioxidant proteins, including heme oxygenase-1 (26, 34, 36), as well as heat shock proteins (21, 28), which are likely a part of the adaptation of neurons to increased oxidative stress. The possibility that p38 phosphorylates tau and thus causes the formation of NFT *in vivo* suggests that it is likely to play an important role in further adaptations in cases of chronic oxidative stress.

A comparison of JNK and p38 immunocytochemical staining showed a nearly identical immunoreactivity for both activated JNK and p38 kinases in severe AD cases. This finding suggests that these two SAPKs might be activated by the same signal, a signal that likely relates to oxidative stress. Although high levels of acute oxidative stress would inflict neuronal death, this type of oxidative damage is not the case in AD. Such high and acute levels of oxidative stress are seen in cases of trauma and ischemia in which the consequent neuronal pathology is significantly different from that in AD. Rather, oxidative challenges in AD must not exceed oxidative defenses because rapid apoptotic death would result. This is exactly the case because few vulnerable neurons in AD show clear signs that they are undergoing apoptosis (22, 23). Indeed, although the extent of neuronal loss in AD can be great (7) and upstream caspases associated with apoptosis are activated, the concurrent activation of downstream caspases required to complete apoptosis are virtually absent (27) or very rare (43). With no significant signs of neuronal apoptosis brought on exclusively by oxidative stress, it is likely that neurons in AD are being subjected to chronically low levels of oxidative stress in which SAPKs may serve as part of an adaptive response by mobilizing downstream neuroprotective mechanisms such as the induction of heme oxygenase-1 and/or pathologic alterations such as the phosphorylation of tau protein (Fig. 1). Given that neurons bearing neurofibrillary pathology actually have decreased oxidative stress and can survive for decades, SAPK-induced tau phosphorylation may also be considered a neuroprotective mechanism.

CONCLUSIONS

Oxidative stress, as a proximal event in AD pathogenesis, plays an important role in the formation of AD pathology. Oxidative damage may be due, in part, to mitochondrial abnormalities that are present in the vulnerable neurons in AD. By acting as a source of H_2O_2, dysfunctional mitochondria propagate a series of interactions between redox metals and

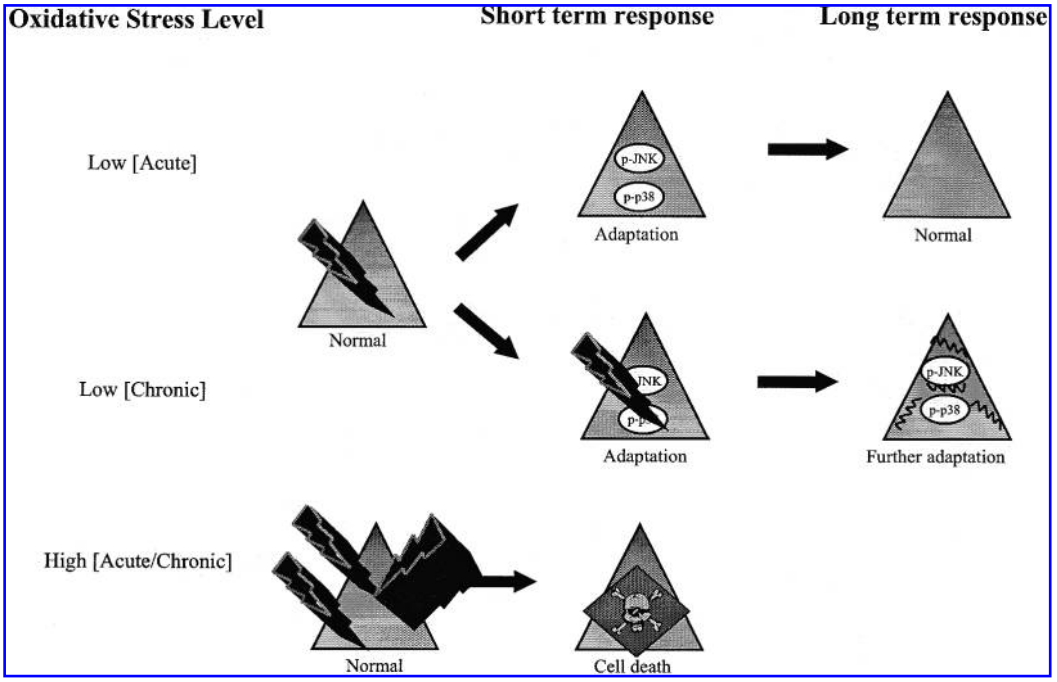

FIG. 1. Neuronal responses to varying degrees and periodicities of oxidative stress. Following high levels of oxidative stress (⚡⚡⚡), which exceed cellular defenses, neurons rapidly die. On the other hand, faced with low-level stress (⚡), neurons adapt through the induction of antioxidant systems via the activation of SAPK pathways (p-JNK and p-p38). If the stress (⚡) is chronic and persists, further cellular adaptations such as large-scale structural alterations will occur. In AD, where chronic low levels of oxidative stress are evident, primary adaptations involving the activation of stress response pathways (JNK and p38) are followed by secondary adaptations involving cytoskeletal alterations such as phosphorylation of tau protein (〰).

oxidative stress response elements contributing to a pro-oxidant environment, with concomitant AD pathology marked by Aβ and NFT. Although oxidative stress is a pervasive feature of AD, what is striking is that few neurons exhibit the characteristic signs of apoptosis (27). The chronic presence of oxidative stress induces adaptive changes in these neurons that promote survival. The relentless nature of oxidative stress in AD and the genesis of such stress preceding AD pathology suggest that therapies involving the prevention of oxidative stress and effective removal of ROS would be beneficial in the initial stages of this disease.

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ABBREVIATIONS

Aβ, amyloid-β; AD, Alzheimer disease; AβPP, amyloid-β protein precursor; COX, cyclooxygenase; H_2O_2, hydrogen peroxide; IRE, iron-response element; IRP, iron regulatory protein; JNK, c-Jun N-terminal kinase; mtDNA, mitochondrial DNA; NFT, neurofibrillary tangles; O_2^-, superoxide radical; $^{\bullet}OH$, hydroxyl radical; ROS, reactive oxygen species; SAPK, stress-activated protein kinase.

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