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Forum Review Article

Metabolic, Metallic, and Mitotic Sources of Oxidative Stress in Alzheimer Disease

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ABSTRACT

Cell bodies of neurons at risk of death in Alzheimer disease (AD) have increased lipid peroxidation, nitration, free carbonyls, and nucleic acid oxidation. These oxidative changes are uniform among neurons and are seen whether or not the neurons display neurofibrillary tangles and, in fact, are actually reduced in the latter case. In consideration of this localization of damage, in this review, we provide a summary of recent work demonstrating some key abnormalities that may initiate and promote neuronal oxidative damage. First, mitochondrial abnormalities might be the source of reactive oxygen species yielding perikaryal oxidative damage. The common 5-kb deletion mitochondrial (mt)DNA subtype was greatly increased in the AD cases, but only in neurons at risk. The importance of such mitochondrial abnormalities to oxidative stress was indicated by a high correlation coefficient between the extent of the mtDNA increase and RNA oxidative damage (r^2 = 0.87). Nonetheless, because mitochondria in AD do not show striking oxidative damage, as one would expect if they were the direct producer of free radical species, we suspected that abnormal mitochondria supply a key reactant that, once in the cytoplasm, releases radicals. One such reactant, hydrogen peroxide, (H_2O_2), abundant in mitochondria, can react with iron via the Fenton reaction to produce $^{\cdot}OH$. To demonstrate this directly using a modified cytochemical technique that relies on the formation of mixed valence iron complexes, we found that redox-active iron is associated with vulnerable neurons. Interestingly, removal of iron was completely affected by using deferroxamine, after which iron could be rebound to re-establish lesion-dependent catalytic redox reactivity. Characterization of the iron-binding site suggests that binding is dependent on available histidine residues and on protein conformation. Taken together with our previous studies showing abnormalities in the iron homeostatic system including heme oxygenase, iron regulatory proteins 1 and 2, ceruloplasmin, and dimethylargininase, our results indicate that iron misregulation could play an important role in the pathogenesis of AD and therefore chelation therapy may be a useful therapeutic approach. Finally, we wanted to determine the proximal cause of mitochondrial abnormalities. One interesting mechanisms involves re-entry into the cell cycle, at which point organellokinesis and proliferation results in increased mitochondria. Supporting this, we have considerable *in vivo* and *in vitro* evidence for mitotic disturbances in AD and its relationship with the pathogenesis of AD. Antiox. Redox Signal. 2, 413–420.

NEURONAL VULNERABILITY in Alzheimer disease (AD) is marked by increases in oxidative damage to macromolecules such as sugars, lipids, proteins, and nucleic acids. The damage is not limited to the lesions of the disease, but instead involves strikingly the perikaryal cytoplasm with involvement of all vulnerable neurons with the onset of AD. The topic of oxidative damage in AD has recently been reviewed by us as well as others (Smith

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et al., 1995; Markesbery, 1997; Perry *et al.*, 1998a). Here, we instead focus on the significance of these findings to AD.

In vivo oxidative damage to macromolecules, until recently, was considered a relatively slow process that marked protein half-life as much as it did oxidative stress. Therefore, early descriptions of oxidative modifications of proteins in AD (Smith *et al.*, 1994; Vitek *et al.*, 1994) were greeted with skepticism (Mattson *et al.*, 1995) as to their significance because the pathological lesions have a strikingly long turnover (Cras *et al.*, 1995). However, a comprehensive study of oxidative damage in AD showed that neurofibrillary tangles (NFT) and senile plaques (SP), which may well accumulate modifications, are instead relatively spared while the greatest site of damage is localized to the cell bodies of vulnerable neurons. In fact, for hydroxyl radical-mediated damage, the vast majority occurs in apparently normal neurons among populations vulnerable to degeneration during the disease. Notably, the level of damage is at remarkably similar levels among neurons of the same population. The reactive oxygen responsible for most if not all of this damage, the $^{\cdot}OH$ radical, can only diffuse nanometer distances, implying that the source of reactive oxygen activity must be in close physical proximity to the damage, *i.e.*, within the neuronal cytoplasm. Therefore, whereas β-amyloid (Hensley *et al.*, 1994) in senile plaques is suggested as a source of reactive oxygen, oxidative damage to neuronal cell bodies distal to β-amyloid deposits indicates that any β-amyloid deposit-mediated damage is not sufficient to explain the pattern of damage. In fact, contrary to *in vitro* findings, correlations between cases with various extents of β-amyloid deposits or NFT show that oxidative damage is in fact reduced with increasing senile plaque and neurofibrillary tangle density (Nunomura *et al.*, 1999a). For β-amyloid there is a direct negative linear correlation with oxidative damage (Nunomura *et al.*, 1999b). These findings indicate that the formation of the β-amyloid plaques and NFT, long thought of as a deleterious process leading to neuronal death, may in fact be a cytoprotective response (Morsch *et al.*, 1999) to reduce oxidative damage. These findings of oxidative abnormalities clearly predate gross described neuronal cytopathology and support the primacy of oxidative damage as an early and dynamic change of AD.

Using 8-hydroxyguanosine (8OHG) as a marker of nucleic acid oxidation, oxidative damage in AD seems to occur throughout the neuronal cell body, and immunoelectron microscopy shows that the change is most pronounced in the cytosol. This distribution is surprising not only because the damage is mostly at RNase-sensitive sites, but because 8OHG is the product of $^{\cdot}OH$ attack, which cannot pass cell membranes, and therefore, must be generated in the cytosol in intimate proximity to RNA. Although the cytosolic site of damage seemingly excludes mitochondria, since they show little 8OHG, we suspect that mitochondria play a key role that involves a complex relationship with O_2^- and hydrogen peroxide (H_2O_2) generated from mitochondria that interact with cytosolic redox-active metals that themselves result from mitochondrial abnormalities (Fig. 1). Although by no means proven, this mechanism places mitochondrial abnormalities at the center of AD pathogenesis.

An analysis of mitochondrial DNA deletions, enzyme levels, and ultrastructure is consistent with mitochondrial abnormalities in AD (Hirai *et al.*, 1998) that leave many in lysosomal structures but with the mitochondrial number relatively unchanged. These findings are intriguing but are quite distinct from genetic mitochondrial disease where mitochondrial number is increased. To understand how mitochondria might be involved, we must consider that they produce O_2^- as part of normal

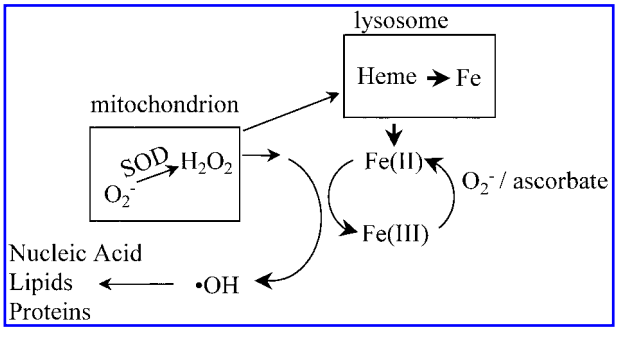

FIG. 1. Mitochondrial–lysosomal abnormalities may promote oxidative damage through release of redox-active iron into the cytosol to catalyze $^{\cdot}OH$ production through Fenton or Haber-Weiss reactions.

respiration and in greater quantities when respiration is compromised. While O_2^- diffuses poorly past membranes, its dismutation product H_2O_2 can diffuse freely. More importantly, in the presence of redox active metals, *e.g.*, iron or copper, H_2O_2 is the biological substrate for $^{\cdot}OH$ generation. Notably, both redox active iron (Smith *et al.,* 1997a) and copper (Sayre *et al.,* 2000) are prominent in the lesions as well as within cytoplasmic granules and in the cytosol of all vulnerable neurons closely paralleling the distribution of 8OHG. Taken together with the alterations in mitochondra, these findings suggest that the source of reactive oxygen responsible for neuronal oxidative damage is consequent to the complex interplay between mitochondrial and metal abnormalities (Fig. 1). Although we cannot know the exact nature of the mitochondrial abnormality, our observations of mitochondrial ultrastructural abnormalities in AD are consistent with mitochondrial turnover and consequent heme release, a feature that is also consistent with the induction of heme oxygenase-1. Heme oxygenase leads to free, redox-active iron that must be sequestered in a "redox-inactive" form. Binding to tau, a microtubule-associated protein found in NFT, may serve this function intraneuronally since binding to either iron or copper serves to reduce redox activity (Sayre *et al.,* 2000). Consistent with this interpretation, the distribution of heme oxygenase-1 and a tau epitope specified by the monoclonal antibody, Alz-50, are identical, suggesting that heme oxygenase-1 and tau are coordinate responses to increased heme and redox-active iron (Takeda *et al.,* 2000). Rather than increasing oxidative damage, the induction of heme oxygenase, instead is associated with a 50–60% reduction in 8OHG levels (Nunomura *et al.,* 1999b). β-Amyloid deposition is also associated with a reduction in oxidative damage, perhaps analogous to tau, by modifying metal-catalyzed redox activity, and by acting as a superoxide dismutase (Atwood, Bush, and Tanzi, personal communication) or as a peroxidase (Smith *et al.,* 1997b). Such mechanisms would certainly explain why increased β-amyloid and tau deposits are associated with reduced oxidative stress. The hypothesis that β-amyloid and tau are responses that reduce oxidative damage by acting as reactive oxygen scavengers is certainly consistent with the localization of the progenitor of β-amyloid, β-protein precursor (Smith and Perry, 1996), as well as apolipoprotein E (Han *et al.,* 1994) to the outer mitochondrial membrane. Additionally, mitochondria lie in close proximity to tau-containing microtubules, the "tracks" used to move mitochondria within neurons. Furthermore, the recent finding that nitrotyrosine, a prominent oxidative product in AD, can also lead to microtubule disassembly (Eiserich *et al.,* 1999) further buttresses the idea of coordinated responses to oxidative stress. Therefore, the fundamental abnormalities in AD may serve to regulate and preserve mitochondrial metabolism and, thereby, limit oxidative damage. If this system "functioned" perfectly, it would limit oxidative damage to near-physiological levels, and this is indeed the case, since, surprisingly, cases with extensive β-amyloid deposits have 8OHG levels comparable to controls.

The scenario we have outlined suggests neuronal metabolic abnormalities lie at the heart of oxidative damage and the pathological changes of the disease. Alone, the mitochondrial abnormalities can not explain the exquisite specificity of AD to involve selected pyramidal and subcortical neurons. Furthermore, whatever factor(s) is responsible for the neuronal metabolic abnormalities must require aging for full expression, and that affects every member of a vulnerable neuronal population. This clearly suggests that although genetic factors may contribute to the time course of AD, other factors play a central role in AD expression.

One of the most striking features of the human brain is its respiratory requirements, 20–25% of total body basal respiration occurs in less than 2% of the body's mass occupied by the brain and most of that in the even smaller mass occupied by neurons. The total dependence of the brain on oxygen is shown by the failure of neurons post-ischemia. More intriguing is that short periods of ischemia result in delayed death following reperfusion for the pyramidal neurons of the hippocampus—neurons that are highly vulnerable in AD. Numerous reports have implicated vascular abnormalities in AD, including smooth muscle atrophy (Perry *et al.,* 1998b) as well as lowered

perfusion (Perry and Smith, 1998). Further, studies show middle-aged individuals with myocardial infarction, the sequela of chronic ischemia, have high levels of β-amyloid deposition (Sparks, 1997). These findings suggest oxygen may be the diffusible factor that forces neurons into compensatory metabolic changes.

The apolipoprotein E (apoE) genotype is the major genetic risk factor for AD, with only two amino acid substitutions being responsible. The rare, but AD-protective, $apoE_2$ contains two cysteines, the common $apoE_3$ contains one cysteine, whereas $apoE_4$, the risk factor for AD, contains no cysteine. Those patients with $apoE_4$ develop AD earlier than other patients and are among the cases with the greatest extent of β-amyloid deposition. Vulnerable neurons contain and express abundant apoE, some of which is localized to the outer mitochondrial membrane.

When we consider that glutathione, a storage form of cysteine, and the glutathione, redox cycle play a crucial role in maintaining mitochondrial integrity (Cooper and Kristal, 1997), it is interesting to note that allele-specific antioxidant activity of ApoE ($E_2 > E_3 > E_4$) (Miyata and Smith, 1996) is parallel to the number of cysteines contained. One possibility of apoE involvement in mitochondrial abnormalities is for the cysteine containing apoEs to transport reducing equivalents from damaged mitochondria to other cellular compartments, allowing them to maintain metabolic function. Because $apoE_4$ cannot participate in transport, it would prevent this compensation for altered metabolism. The cysteine-containing apoEs could interact with sulfhydryls of tau- and β-protein precursor, residues that may also play in important role in oxidant defenses (Multhaup *et al.,* 1998; Raina *et al.,* 1999; Russell *et al.,* 1999).

Rather than oxidative damage inflicting neuronal death, the oxidative stress of AD cannot exceed oxidative defenses or rapid apoptotic death will result. This is the case because few vulnerable neurons in AD show established signs of apoptosis, even though the mitochondria are abnormal (Perry *et al.,* 1998c,d). Instead, although the extent of neuronal loss in AD can be great in some cases, it is often not greater than seen in other aged individuals not suffering from AD (Cras *et al.,* 1995). In AD, the neurons that die with NFT leave the remnants of the NFT in the extracellular space (E-NFT), which in some cases can equal the density of neurons for normal individuals. In other cases with extensive neuronal loss, few E-NFT are seen, suggesting that NFT formation is not always a part of the pathway of neuronal death. It would be interesting to study whether neurons that form NFT are protected as a result of heme oxygenase-1 induction, preventing neuronal death from cytochrome-*c*-mediated apoptosis. An important aspect of our scenario is that loss of function (appropriate synaptic connections) is proximal to NFT, β-amyloid, and even neuronal loss. This is in part because the mitochondrial abnormalities we have observed are likely to destabilize microtubules and free tau to play a role in metal regulation, as well as obliterating the kinesin-dynein-based microtubule "track" of axons. Neurons live but do not function. How such a nonproductive response to AD could occur must be viewed in the context of the alternatives. The chronic nature of AD provides no respite to the alternatives of apoptosis or existence, but given the adaptive significance of neuroprotective mechanisms, the changes we see may be of value in trauma, ischemia, or other conditions that do not result in sustained reactive oxygen production and require a sustained increase in oxidant protection that forms the majority of AD pathology. This hopeful interpretation opens the door for recovery of function if the underlying oxidant stress is removed through metal chelation, antioxidant therapy, or metabolic enhancement therapy and bodes poorly for any strategy based for stopping the downstream effects of AD pathophysiology without removing its underlying cause.

The stage now is set: mitochondrial abnormalities lie at the heart of AD pathogenesis, whereas the fundamental pathological changes of the disease are coordinated responses to limit oxidative damage. But what factor(s) is responsible for the mitochondrial abnormalities? One interesting and emerging mechanism involves attempted re-entry into the cell cycle; at a certain point, organellokinesis and proliferation results in increased mitochondria. Therefore, it is not coincident that all of the major ge-

netic and protein elements, including β-protein precursor (βPP), presenilins, tau, and, possibly, ApoE, which are dysregulated in AD and/or confer increased susceptibility to AD, are altered during the cell cycle. In AD, hyperphosphorylation of tau renders it unable to stabilize microtubular dynamics and results in neuronal dysfunction (Lindwall and Cole, 1984; Alonso *et al.,* 1996). However, hyperphosphorylation of tau also occurs when cells are mitotically active, in which case, phosphorylation is driven by cyclin-dependent kinases (CDKs) (Brion *et al.,* 1985, 1994; Kanemaru *et al.,* 1992; Goedert *et al.,* 1993; Pope *et al.,* 1994). Notably, CDKs have been localized *in vivo* to lesions in AD and phosphorylate tau in *in vitro* assays in a manner similar to that found in AD *in vivo* (Arendt *et al.,* 1995, 1996; Vincent *et al.,* 1996; Nagy *et al.,* 1997a,b). Mutations in the βPP gene are linked to the inevitable onset of familial AD. Given the role of mitotic re-entry in AD, it is notable that βPP is upregulated secondary to mitogenic stimulation (Ledoux *et al.,* 1993) and that βPP metabolism is regulated by cell cycle-dependent changes (Suzuki *et al.,* 1994). β-Amyloid is mitogenic *in vitro* (McDonald *et al.,* 1998; Pyo *et al.,* 1998) and therefore may play a direct role in the induction and/or propagation of cell cycle-mediated events in AD. The ApoE4 alleles that confer increased susceptibility both to AD and prostate cancer suggest an association between the E4 allele and a propensity toward developing a dysregulated cell cycle (Slooter *et al.,* 1997). In support of such a notion, ApoE is itself associated with the amyloid deposits found in pituitary adenomas (Steusloff *et al.,* 1998). Mutation in the human presenilin genes 1 and 2 found on chromosomes 14 and 1, respectively, are also linked to early-onset AD (Smith, 1998) and are implicated in development and the regulation of cell death. The association of presenilins with centrosomes and centromeres suggests that they play a role in cell division and segregation of chromosomes (Li *et al.,* 1997). Additionally, overexpression of presenilins leads to arrest in the G_1 phase of the cell cycle, which is potentiated by expression of the PS2(N141I) mutation (Janicki and Monteiro, 1999). Therefore, we propose that neurons in AD are attempting to re-enter the cell cycle but are blocked from progression at the G_1/S phase boundary by presenilin (and possibly βPP) mutations. The block at G_1 would result in accumulation of cell cycle control proteins as is seen in AD.

In fact, a number of recent findings have highlighted the similarities between neurogenesis during development as well as tumorigenesis and neurodegeneration during AD. Indeed, neuronal populations that are known to degenerate in AD exhibit phenotypic changes characteristic of cells re-entering the cell division cycle. The parallels between the cell cycle and AD include the activation of signal transduction pathways, cell phase-dependent kinases, and transcriptional activation that lead to cytoskeletal alterations and increases in mitochondrial metabolic activity and DNA replication. For example, the induction of Ras and Cdc42/Rac signal transduction pathway and MAPK pathway are involved in the abnormality of cell cycle events in AD. Most notably, the re-expression of Cdc2, CDk4, cyclin B, cyclin D, and/or Ki67 in AD clearly suggest that the susceptible neurons, which are supposed to be postmitotic, are no longer quiescent.

However, as yet, there is no evidence suggesting a successful nuclear division nor chromosomal condensation in AD, implying that the neurons do not complete mitosis (M phase) and that the proteins associated with exit from the cell cycle, such as p16, are apparently upregulated (McShea *et al.,* 1997). In fact, terminally differentiated neurons may lack the ability to complete the cell cycle such that they proceed variously (Zhu *et al.,* 1999) through to a point prior to the actual event of cellular division, to a characteristic "molecular phenotype" representing a neuron arrested in a transitional phase of the cycling process. Because there is both division of organelle nucleoids and organellokinesis before mitosis, such that during late S, G_2, and mitotic phases mitochondrial proliferation is most evident (Barni *et al.,* 1996). These events are crucial for the high energy demands required for cell division, but in cells where the cell cycle is interrupted, mitochondrial dysregulation poses them as sources of reactive oxygen and calcium imbalance (Sousa *et al.,* 1997). These neuronal populations are the same as those that also have cell cycle-related abnormalities, subsequent oxida-

tive damage, and cell death in AD. Thus, cell cycle arrest, when and where mitochondrial mass should be at its highest, poses an elevated, significant, and possibly a chronic oxidative insult to the cell, far beyond the blunting capacity of endogenous antioxidants. Indeed, this redox imbalance may herald a permanent change in the "state" of energy in the cell. However, the environmental or genetic cues that trigger the cells to enter the cell cycle remain to be determined. Nonetheless, because cell cycle abnormalities seem to be proximal events in AD, they may represent an effective target for therapeutic intervention in the future.

ABBREVIATIONS

AD, Alzheimer disease; apoE, apolipoprotein E; βPP, β-protein precursor; CDK, cyclin-dependent kinase; E-NFT, extracellular neurofibrillary tangle; 80HG, 8-hydroxyguanosine; mt, mitochondrial; H_2O_2, hydrogen peroxide; NFT, neurobibrillary tangle; SP, senile plaque.

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