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Causes of oxidative stress in Alzheimer disease

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Abstract. Oxidative stress is one of the earliest events of Alzheimer disease (AD), with implications as an important mediator in the onset, progression and pathogenesis of the disease. The generation of reactive oxygen species (ROS) and its consequent cellular damage/response contributes to much of the hallmark AD pathology seen in susceptible neurons. The sources of ROS-mediated damage appear to be multi-faceted in AD, with interactions between abnormal mitochondria, redox transition metals, and other factors. In this review, we provide an overview of these potential causes of oxidative stress in AD.

Keywords. Alzheimer disease, amyloid-β, antioxidant, iron, metals, mitochondria, oxidative stress, pathogenesis, phosphorylation, reactive oxygen species, tau.

Mitochondria

A large number of studies implicate metabolic defects in Alzheimer disease (AD), such that a reduced rate of brain metabolism is one of the best-documented abnormalities in AD [1]. Substantial data from positron emission tomography (PET) consistently demonstrates reduced cerebral metabolism in temporoparietal cortices in AD [2]. An increased oxidative utilization in comparison with glucose utilization in AD patients is also well documented [3, 4]. Most importantly, such cerebral metabolic rate abnormalities precede, rather than follow, any evidence for functional impairment by neuropsychological testing and also precede brain atrophy [1]. Notably, metabolic derangements (e.g. hypoxia, hypoglycemia, vitamin deficiency) are sufficient by themselves, to induce mental and neurological deficits similar to those in AD [5]. These findings suggest that mitochondrial dysfunction may play very important roles early in AD.

Damaged mitochondria are less efficient producers of ATP and more efficient producers of reactive oxygen species (ROS), and it is likely not coincident that reduced energy production and increased oxidative stress, as well as damaged mitochondria, are characteristics of AD [6, 7]. The most consistent defect in mitochondria in AD are deficiencies in several key enzymes of 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 [7–13]. The function of mitochondria is dependent on their intact structure. Previously, we demonstrated that mitochondrial-derived lysosomes and lipofuscin deposits of various densities and sizes were prominent and unchanging features of neuronal abnormalities [14]. Different stages of mitochondrial abnormality, such as formation of mitochondrial-derived lysosomes and lipofuscin, were evident in almost all AD neurons [14]. Studies examining the presence of mitochondrial DNA in AD neurons have further shown that mitochondria are degraded in AD [15]. Quantitative morphometric measurements of the percentage of the different types of mitochondria (normal, partially damaged, and completely damaged) confirm that neurons in AD show a significantly lower percentage of normal mitochondria and a

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significantly higher percentage of the completely damaged mitochondria compared to an aged-matched control group. The following is a ranking of factors which likely contribute to mitochondrial dysfunction in AD: 1) Low vascular blood flow is a prominent feature of the brain during chronic hypoxia/hypoperfusion and has been implicated in the development of AD [16]; 2) Many more sporadic mutations in the mitochondrial DNA (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 post-mitotic cells in the brain [17]; 3) Amyloid-β (Aβ) and the majority of amyloid-β protein precursor (AβPP) processing machinery are found in mitochondria [18,19]. In fact, AβPP is present in the mitochondrial import channel and potentially impedes mitochondrial import [20] thus impairing mitochondrial function; 4) Hyperhomocysteinemia is a strong, independent risk factor for the development of AD [21], and it is demonstrated that homocysteine inhibits several genes encoding mitochondrial proteins and promotes ROS production [22].

Redox-active metals: iron and copper

Most types of oxidative damage noted in AD, including glycation, protein oxidation, lipid peroxidation, and nucleic acid oxidation, result directly or indirectly from metal-catalyzed hydroxyl radical formation. Therefore, it is not surprising that the loss of homeostasis of iron and copper in the brain is accompanied by severe neurological consequences characterized with increased oxidative damage.

In AD, overaccumulation of iron in the hippocampus, cerebral cortex, and basal nucleus of Meynert colocalizes with AD lesions, senile plaques, and neurofibrillary tangles [23, 24]. Iron is an important cause of oxidative stress in AD because it accumulates in the brain [25] and, as a transition metal, is involved in the formation of $^{\bullet}OH$ via the Fenton reaction [24, 26]. Recently, we showed that RNA-bound iron plays a pivotal role for RNA oxidation in vulnerable neurons in AD [27]. We observed that the cytoplasm of hippocampal neurons showed significantly higher redox activity and iron staining than age-matched controls. Notably, both were susceptible to RNase, suggesting a physical association of iron with RNA, and both ribosomal RNA (rRNA) and messenger RNA (mRNA) showed twice the iron binding as transfer RNA (tRNA). rRNA, extremely abundant in neurons, was considered to provide the greatest number of iron binding sites among cytoplasmic RNA species. Reflecting these differences in iron binding capacity, oxidation of rRNA by the Fenton reaction formed 13 times more 8-hydroxyguanosine (8OHG) than tRNA, and consistent with such *in situ* findings, ribosomes purified from hippocampus of cases of AD contained significantly higher levels of RNase-sensitive iron and redox activity than controls. Furthermore, only rRNA from cases of AD contains 8OHG in an immunoprecipitation reverse transcriptase-PCR. Addressing the biological significance of ribosome oxidation by redox-active iron, *in vitro* translation with oxidized ribosomes from rabbit reticulocyte showed a significant reduction of protein synthesis. These results suggest 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 [27].

Copper has a functional role in many enzymes that require oxidation-reduction reactions. For example, copper is found in the catalytic site of COX, of the mitochondrial electron transport chain, and Cu-Zn superoxide dismutase (SOD). In AD, copper interactions have the potential to yield oxidative damage by at least two pathways: (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 [28], neuronal levels of ceruloplasmin remain unchanged [29]. 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-catalyzed damage [29]. 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 levels of ceruloplasmin are significantly higher in cases with neurodegeneration [30]. 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 $^{\bullet}OH$ through formation of an AβPP-Cu(II)-hydroxyl radical intermediate. As with iron, copper concentrations are also highly concentrated within Aβ plaques, setting up conditions for Fenton-type chemistry through the reduction of Cu(II) by Aβ-H_2O_2 reactions.

Lesions

While oxidative damage was first established in AD, the source of ROS was initially suspected to be the lesions. However, this is now far more controversial, and in fact, it appears more likely that oxidative damage associated to AD elicits compensatory mechanisms, such as Aβ deposition and hyperphosphorylated tau, that restore redox balance in an attempt to avoid neuronal death [31]. However, during the progression of the disease the antioxidant activity of both agents evolves into pro-oxidant representing a typical gain-of-function transformation, which can result from an increase in reactive species and a decrease in clearance mechanisms.

Aβ peptide is formed upon proteolytic processing of AβPP by β- and γ-secretases. Aβ was commonly considered a dangerous byproduct of AβPP processing, despite the fact that this peptide is present in the cerebrospinal fluid and plasma of healthy individuals throughout life [32]. Recently, Kamenetz et al. [33] reported that Aβ is secreted from healthy neurons in response to activity and that Aβ, in turn, downregulates excitatory synaptic transmission. This negative feedback loop provides a physiological homeostatic mechanism aimed to maintain normal levels of neuronal activity. Previous studies also suggest that Aβ might act as a regulator of ion channel function in neurons [34, 35].

An antioxidant role for Aβ *in vivo* is in agreement with recent data on the distribution of oxidative damage to AD neurons. As said above, 8OHG markedly accumulates in the cytoplasm of cerebral neurons in AD. However, as Aβ increases in the AD cortex, there is a decrease in neuronal levels of 8OHG, i.e., decreased oxidative damage [36, 37]. Similar negative correlation between Aβ deposition and oxidative damage is found in patients with Down's syndrome [38]. 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 [39–41].

The strong chelating properties of Aβ for zinc, iron and copper explain the reported enrichment of these metals in amyloid plaques in AD [25] and suggest that one function of Aβ is to sequester these metal ions [42]. Chelation of transition metals in a redox-inactive form may theoretically serve to inhibit metal-catalyzed oxidation of biomolecules. Methionine at residue 35 in the Aβ sequence can both scavenge free radicals [43] and reduce metals to their high-active low-valency form [44], possessing thereby both anti- and pro-oxidative properties. As discussed above, reduced metal ions are highly active oxidants and can catalyze further oxidation of biomolecules. These data indicate that Aβ is a lipophilic metal chelator with metal-reducing activity. However, an intricate combination of metal chelation, metal reduction and radical scavenging can thus be expected to govern the overall activity of Aβ towards oxidation, which may basically embrace the full spectrum of anti- and pro-oxidative effects. Indeed, it has been shown that Aβ efficiently initiates oxidation of different biomolecules. It induces peroxidation of membrane lipids [45] and lipoproteins [46], generates H_2O_2 [47] and hydroxynonenal (HNE) [48] in neurons, damages DNA [49] and inactivates transport enzymes [50].

However, three important conditions are required for Aβ to induce oxidation: fibrillation, the presence of transition metals, and methionine 35. Indeed, aggregation and fibrillation of Aβ occurs only if the peptide is 'aged' and present in a relatively high concentration (micromolar range) [51, 52]. The presence of transition metals is a requisite for Aβ aggregation and its pro-oxidant activity [42, 53, 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 [42, 55]. 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 [45, 56, 57]. Methionine 35 can scavenge free radicals [58] and reduce transition metals to their high-active low-valency form [59], thereby exhibiting both anti- and pro-oxidative properties.

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. In the first step of protein glycation, a labile Schiff base is formed, which subsequently rearranges into a stable Amadori product. Finally, through a complex cascade of dehydration, fragmentation, oxidation and cyclization reactions, AGEs are formed as a mixture of protein-bound nitrogen- and oxygen-containing heterocyclic compounds [60]. Monosaccharides, in equilibrium with their enediol, undergo autooxidation in the presence of transition metals to form an enediol radical which can reduce molecular oxygen to generate the superoxide radical. The Amadori products are converted to protein dicarbonyl compounds in the presence of transition

metals and molecular oxygen via protein enediol, generating the superoxide radical. AGEs in the presence of transition metals can also undergo redox cycling with consequent ROS production. Accumulation of AGEs in the brain is a feature of aging [61], and the Maillard reaction is implicated in the development of pathophysiology in age-related diseases such as diabetes mellitus, atherosclerosis and AD [62–64]. Since advanced glycation endproducts are accelerated by, and result in formation of, oxygen-derived free radicals, they represent an important source of the oxidative stress in AD [65].

The possible role of AGEs in AD pathogenesis was initially proposed because of a drastic three times increase of their content in AD brains when compared to age-matched controls [66–68]. Shuvaev et al. [69] reported an increased accumulation of Amadori products in all major proteins of cerebrospinal fluid (CSF) of AD patients. In addition, *in vitro* studies demonstrated that AGE-modified Aβ promotes rapid aggregation [67]. AGEs were detected in neurofibrillary tangles, and the glycation of tau has been proposed to play a role in stabilizing paired helical filament aggregation leading to neurofibrillary tangle formation [67, 70–72]. We and others have identified increased levels of several specific and non-specific products of Maillard chemistry, including pyrraline, pentosidine, carboxymethyl lysine and hexitol lysine, in association with neurofibrillary pathology in AD [64, 73]. Importantly, the detection of hexitol-lysine following borohydride reduction indicates the presence of the metastable Amadori intermediates generated upon early lysine glycation [73], which clearly demonstrate that active glycation is still occurring in these lesions throughout their existence. That AGEs play an active role in the disease process is also demonstrated both by the neurotoxicity and their ability to increase levels of Aβ [74, 75]. Furthermore, AGEs and Aβ activate specific receptors such as the receptor for advanced glycation end products (RAGE) and the class A scavenger-receptor to increase intracellular ROS production and modulate gene transcription of various factors involved in inflammation through NFκB activation [76, 77].

Activated microglia/astrocytes

Similar to situations in the periphery where damaged tissue and the chronic presence of inert abnormal materials cause inflammation, senile plaques, neurofibrillary tangles and injured neurons may well provoke inflammation in the AD brain. Indeed, both microglia and astrocytes cluster at sites of Aβ deposition [78, 79]. The altered morphology and increased expression of MHCII and various cytokines, chemokines and complement components indicate that these microgla are activated [80]. Astrocytes, and to a lesser extent, neurons, are also capable of expressing a wide range of inflammatory mediators, including complement, cytokines and cyclooxygenase [80]. Obviously, the secretion of ROS/reactive nitrogen 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 [81,82]. Not surprisingly, microglial expression of NADPH oxidase subunit p22-phox is enhanced in AD brain [80], implicating increased microglial respiratory burst activity. Following induction of the iNOS gene, 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 [83, 84]. Increased expression of iNOS is also detected in astrocytes surrounding plaques in AD brain [85, 86]. 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 [87]. 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 [88] as well as cause advanced glycation end product modifications [89], both of which are evident in AD [70, 84].

Proteolysis dysfunction

Cells possess a remarkable and complex intracellular organization, which guarantees, among other things, that the potentially harmful and irreversible processes of proteolysis remain restricted to certain compartments such as the proteasome and lysosome. The degradation of non-functional, oxidized proteins is an essential part of the antioxidant defenses of cells. The proteasome is a large intracellular protease (26S) with more than 60 subunits that is principally responsible for the turnover of most short-lived, misfolded, oxidized and truncated proteins, which involves

ubiquitination of target proteins through sequential steps [90]. The 26S proteasome contains a core catalytic complex (i.e., 20S) with multiple active sites and two distally positioned regulatory complexes (i.e., 19 S). All of these components are affected by oxidative stress to various degrees, with the 26S proteasome being most sensitive to oxidative stress [91]. Proteasomal activity declines with age [92], and dysfunction of the proteasome is implicated in AD pathogenesis by the fact that PHF-τ is extensively ubiquitinated [93]. Further studies demonstrate disease-specific alterations in the level and distribution of proteasomal subunits and deubiquitinating enzyme ubiquitin carboxyl-terminal esterase L1 (UCH-L1) [94] and decreased proteasome activity in the AD brain [95]. In fact, inhibition of proteasomal activity, in many regards, recapitulates neuropathology and neuronal death both *in vitro* and *in vivo* similar to that observed in AD [96,97]. Interestingly, chronic low-level proteasome inhibition, in addition to increased protein insolubility, induces elevated levels of protein oxidation and dramatically inhibits the activity of mitochondrial complexes I and II and alters specific aspects of mitochondrial homeostasis and turnover in neuronal cells [98–100], which could potentially proceed in a feed-forward fashion and greatly add to the oxidative burden observed in AD brain.

The lysosome, by a process called autophagy, is involved in the normal turnover of organelles as well as most long-lived proteins. Autophagic degradation of iron-containing proteins such as ferritin and mitochondrial electron-transport complexes results in the intralysosomal occurrence of redox-active low molecular weight iron [101], which can result in lysosomal oxidative stress with consequent membrane labilization and rupture [102]. Therefore, the release of lysosomal contents, including redox-active iron, not only directly adds to the oxidative stress but also induces mitochondrial damage with secondarily enhanced production of ROS [103]. In fact, studies using antibodies to lysosomal hydrolases reveal striking intracellular and extracellular manisfestations of altered lysosomal function, including elevated acid hydrolase-containing compartments in atrophic and degenerating neurons or their processes [104–108]. In a recent study, Nixon and colleagues [109], using immunogold labeling with compartmental markers and electron microscopy on neocortical biopsies from AD brain, identified autophagosomes and other prelysosomal autophagic vacuoles in AD brains, particularly within neuritic processes, including synaptic terminals. Lysosomes also gradually accumulate non-degradable, polymeric lipofuscin, which is believed to be a result of not only continuous oxidative stress, causing oxidation of mitochondrial constituents and autophagocytosed material, but also of the inherent inability of cells to completely remove oxidatively damaged structures [110, 111]. Although lipofuscin-loaded lysosomes continue to receive newly synthesized lysosomal enzymes, the pigment is non-degradable. Therefore, advanced lipofuscin accumulation may greatly diminish lysosomal degradative capacity by preventing lysosomal enzymes from targeting functional autophagosomes, further limiting mitochondrial recycling and thus increasing oxidative burden [111]. In this regard, it is likely not coincident that neurons showing increased oxidative damage in AD also have a striking and significant increase in mtDNA in neuronal cytoplasm and in vacuoles associated with lipofuscin [15], the proposed site of mitochondrial degradation by autophagy [112]. Electron microscopic analysis also shows that COX-1, a mitochondrial protein, is increased in the cytosol and is associated with mitochondria undergoing phagocytosis. These observations highlight the interrelated nature of lysosomal and mitochondrial damage which may irreversibly lead to functional decay of neuronal cells (for review see [111]).

Concluding remarks

An exact determination of the contribution of each source of oxidative stress is complicated, if for no other reason than that these sources of oxidative stress interact with each other, acting like a web, and most sources have positive feedback. In fact, for this same reason, it is possible, even likely, for whichever particular source that first comes into play to ultimately induce most of the others. However, what may be the initiating factor and how this whole process is set off is still unclear. Nonetheless, the overall result is damage, including advanced glycation end products [113], nitration [83, 84, 114, 115], lipid peroxidation adduction products [116–122] as well as carbonyl-modified neurofilament protein and free carbonyls [68, 113, 122–125], with the involvement extending beyond the lesions to neurons not displaying obvious degenerative change.

1 Blass, J. P. (2000) The mitochondrial spiral: an adequate cause of dementia in the Alzheimer's syndrome. Ann. N.Y. Acad. Sci. 924, 170 – 183.
2 Minoshima, S., Giordani, B., Berent, S., Frey, K. A., Foster, N. L. and Kuhl, D. E. (1997) Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. Ann. Neurol. 42, 85 – 94.
3 Fukuyama, H., Ogawa, M., Yamauchi, H., Yamaguchi, S., Kimura, J., Yonekura, Y. and Konishi, J. (1994) Altered cerebral energy metabolism in Alzheimer's disease: a PET study. J. Nucl. Med. 35, 1 – 6.
4 Hoyer, S. (1993) Intermediary metabolism disturbance in AD/SDAT and its relation to molecular events. Prog. Neuropsychopharmacol. Biol. Psychiatry 17, 199 – 228.

5 Blass, J. P. and Gibson, G. E. (1999) Cerebrometabolic aspects of delirium in relationship to dementia. Dement. Geriatr. Cogn. Disord. 10, 335 – 338.
6 Castellani, R., Hirai, K., Aliev, G., Drew, K. L., Nunomura, A., Takeda, A., Cash, A. D., Obrenovich, M. E., Perry, G. and Smith, M. A. (2002) Role of mitochondrial dysfunction in Alzheimer's disease. J. Neurosci. Res. 70, 357 – 360.
7 Gibson, G. E., Sheu, K. F. and Blass, J. P. (1998) Abnormalities of mitochondrial enzymes in Alzheimer disease. J. Neural. Transm. 105, 855 – 870.
8 Chandrasekaran, K., Giordano, T., Brady, D. R., Stoll, J., Martin, L. J. and Rapoport, S. I. (1994) Impairment in mitochondrial cytochrome oxidase gene expression in Alzheimer disease. Brain Res. Mol. Brain Res. 24, 336 – 340.
9 Cottrell, D. A., Blakely, E. L., Johnson, M. A., Ince, P. G. and Turnbull, D. M. (2001) Mitochondrial enzyme-deficient hippocampal neurons and choroidal cells in AD. Neurology 57, 260 – 264.
10 Maurer, I., Zierz, S. and Moller, H. J. (2000) A selective defect of cytochrome c oxidase is present in brain of Alzheimer disease patients. Neurobiol. Aging 21, 455 – 462.
11 Nagy, Z., Esiri, M. M., LeGris, M. and Matthews, P. M. (1999) Mitochondrial enzyme expression in the hippocampus in relation to Alzheimer-type pathology. Acta Neuropathol. 97, 346 – 354.
12 Parker, W. D., Jr., Mahr, N. J., Filley, C. M., Parks, J. K., Hughes, D., Young, D. A. and Cullum, C. M. (1994) Reduced platelet cytochrome c oxidase activity in Alzheimer's disease. Neurology 44, 1086 – 1090.
13 Parker, W. D., Jr., Parks, J., Filley, C. M. and Kleinschmidt-DeMasters, B. K. (1994) Electron transport chain defects in Alzheimer's disease brain. Neurology 44, 1090 – 1096.
14 Zhu, X., Smith, M. A., Perry, G. and Aliev, G. (2004) Mitochondrial failures in Alzheimer's disease. Am. J. Alzheimers Dis. Other Demen. 19, 345 – 352.
15 Hirai, K., Aliev, G., Nunomura, A., Fujioka, H., Russell, R. L., Atwood, C. S., Johnson, A. B., Kress, Y., Vinters, H. V., Tabaton, M. et al. (2001) Mitochondrial abnormalities in Alzheimer's disease. J. Neurosci. 21, 3017 – 3023.
16 de la Torre, J. C. (1997) Cerebromicrovascular pathology in Alzheimer's disease compared to normal aging. Gerontology 43, 26 – 43.
17 Coskun, P. E., Beal, M. F. and Wallace, D. C. (2004) Alzheimer's brains harbor somatic mtDNA control-region mutations that suppress mitochondrial transcription and replication. Proc. Natl. Acad. Sci. USA 101, 10726 – 10731.
18 Lustbader, J. W., Cirilli, M., Lin, C., Xu, H. W., Takuma, K., Wang, N., Caspersen, C., Chen, X., Pollak, S., Chaney, M. et al. (2004) ABAD directly links Abeta to mitochondrial toxicity in Alzheimer's disease. Science 304, 448 – 452.
19 Manczak, M., Anekonda, T. S., Henson, E., Park, B. S., Quinn, J. and Reddy, P. H. (2006) Mitochondria are a direct site of A beta accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression. Hum. Mol. Genet. 15, 1437 – 1449.
20 Devi, L., Prabhu, B. M., Galati, D. F., Avadhani, N. G. and Anandatheerthavarada, H. K. (2006) Accumulation of amyloid precursor protein in the mitochondrial import channels of human Alzheimer's disease brain is associated with mitochondrial dysfunction. J. Neurosci. 26, 9057 – 9068.
21 Seshadri, S., Beiser, A., Selhub, J., Jacques, P. F., Rosenberg, I. H., D'Agostino, R. B., Wilson, P. W. and Wolf, P. A. (2002) Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N. Engl. J. Med. 346, 476 – 483.
22 Streck, E. L., Matte, C., Vieira, P. S., Calcagnotto, T., Wannmacher, C. M., Wajner, M. and Wyse, A. T. (2003) Impairment of energy metabolism in hippocampus of rats subjected to chemically-induced hyperhomocysteinemia. Biochim. Biophys. Acta 1637, 187 – 192.
23 Connor, J. R., Milward, E. A., Moalem, S., Sampietro, M., Boyer, P., Percy, M. E., Vergani, C., Scott, R. J. and Chorney, M. (2001) Is hemochromatosis a risk factor for Alzheimer's disease? J. Alzheimers Dis. 3, 471 – 477.
24 Smith, M. A., Harris, P. L., Sayre, L. M. and Perry, G. (1997) Iron accumulation in Alzheimer disease is a source of redox-generated free radicals. Proc. Natl. Acad. Sci., USA 94, 9866 – 9868.
25 Lovell, M. A., Robertson, J. D., Teesdale, W. J., Campbell, J. L. and Markesbery, W. R. (1998) Copper, iron and zinc in Alzheimer's disease senile plaques., J. Neurol. Sci. 158, 47 – 52.
26 Casadesus, G., Smith, M. A., Zhu, X., Aliev, G., Cash, A. D., Honda, K., Petersen, R. B. and Perry, G. (2004) Alzheimer disease: evidence for a central pathogenic role of iron-mediated reactive oxygen species. J. Alzheimers Dis. 6, 165 – 169.
27 Honda, K., Smith, M. A., Zhu, X., Baus, D., Merrick, W. C., Tartakoff, A. M., Hattier, T., Harris, P. L., Siedlak, S. L., Fujioka, H. et al. (2005) Ribosomal RNA in Alzheimer disease is oxidized by bound redox-active iron., J. Biol. Chem. 280, 20978 – 20986.
28 Loeffler, D. A., LeWitt, P. A., Juneau, P. L., Sima, A. A., Nguyen, H. U., DeMaggio, A. J., Brickman, C. M., Brewer, G. J., Dick, R. D., Troyer, M. D. et al. (1996) Increased regional brain concentrations of ceruloplasmin in neurodegenerative disorders. Brain Res. 738, 265 – 274.
29 Castellani, R. J., Smith, M. A., Nunomura, A., Harris, P. L. and Perry, G. (1999) Is increased redox-active iron in Alzheimer disease a failure of the copper-binding protein ceruloplasmin? Free Radic. Biol. Med. 26, 1508 – 1512.
30 Mezzetti, A., Pierdomenico, S. D., Costantini, F., Romano, F., De Cesare, D., Cuccurullo, F., Imbastaro, T., Riario-Sforza, G., Di Giacomo, F., Zuliani, G. et al. (1998) Copper/zinc ratio and systemic oxidant load: effect of aging and aging-related degenerative diseases. Free Radic. Biol. Med. 25, 676 – 681.
31 Smith, M. A., Casadesus, G., Joseph, J. A. and Perry, G. (2002) Amyloid-beta and tau serve antioxidant functions in the aging and Alzheimer brain. Free Radic. Biol. Med. 33, 1194 – 1199.
32 Seubert, P., Vigo-Pelfrey, C., Esch, F., Lee, M., Dovey, H., Davis, D., Sinha, S., Schlossmacher, M., Whaley, J., Swindlehurst, C. et al. (1992) Isolation and quantification of soluble Alzheimer's beta-peptide from biological fluids. Nature 359, 325 – 327.
33 Kamenetz, F., Tomita, T., Hsieh, H., Seabrook, G., Borchelt, D., Iwatsubo, T., Sisodia, S. and Malinow, R. (2003) APP processing and synaptic function. Neuron 37, 925 – 937.
34 Ramsden, M., Henderson, Z. and Pearson, H. A. (2002) Modulation of Ca2+ channel currents in primary cultures of rat cortical neurones by amyloid beta protein (1 – 40) is dependent on solubility status. Brain Res. 956, 254 – 261.
35 Ramsden, M., Plant, L. D., Webster, N. J., Vaughan, P. F., Henderson, Z. and Pearson, H. A. (2001) Differential effects of unaggregated and aggregated amyloid beta protein (1 – 40) on K(+) channel currents in primary cultures of rat cerebellar granule and cortical neurones., J. Neurochem. 79, 699 – 712.
36 Nunomura, A., Perry, G., Hirai, K., Aliev, G., Takeda, A., Chiba, S. and Smith, M. A. (1999) Neuronal RNA oxidation in Alzheimer's disease and Down's syndrome. Ann. N. Y. Acad. Sci. 893, 362 – 364.
37 Nunomura, A., Perry, G., Pappolla, M. A., Wade, R., Hirai, K., Chiba, S. and Smith, M. A. (1999) RNA oxidation is a prominent feature of vulnerable neurons in Alzheimer's disease. J. Neurosci. 19, 1959 – 1964.
38 Nunomura, A., Perry, G., Pappolla, M. A., Friedland, R. P., Hirai, K., Chiba, S. and Smith, M. A. (2000) Neuronal oxidative stress precedes amyloid-beta deposition in Down syndrome. J. Neuropathol. Exp. Neurol. 59, 1011 – 1017.
39 Lee, H. G., Casadesus, G., Zhu, X., Takeda, A., Perry, G. and Smith, M. A. (2004) Challenging the amyloid cascade hypothesis: senile plaques and amyloid-beta as protective adaptations to Alzheimer disease. Ann. N. Y. Acad. Sci. 1019, 1 – 4.

40 Smith, M. A., Nunomura, A., Zhu, X., Takeda, A. and Perry, G. (2000) Metabolic, metallic, and mitotic sources of oxidative stress in Alzheimer disease. Antioxid. Redox Signal. 2, 413 – 420.
41 Rottkamp, C. A., Atwood, C. S., Joseph, J. A., Nunomura, A., Perry, G. and Smith, M. A. (2002) The state versus amyloid-beta: the trial of the most wanted criminal in Alzheimer disease. Peptides 23, 1333 – 1341.
42 Rottkamp, C. A., Raina, A. K., Zhu, X., Gaier, E., Bush, A. I., Atwood, C. S., Chevion, M., Perry, G. and Smith, M. A. (2001) Redox-active iron mediates amyloid-beta toxicity. Free Radic. Biol. Med. 30, 447 – 450.
43 Unnikrishnan, M. K. and Rao, M. N. (1990) Antiinflammatory activity of methionine, methionine sulfoxide and methionine sulfone. Agents Actions 31, 110 – 112.
44 Hiller, K. O. and Asmus, K. D. (1981) Tl2+ and Ag2+ metal-ion-induced oxidation of methionine in aqueous solution: a pulse radiolysis study. Int. J. Radiat. Biol. Relat. Stud. Phys. Chem. Med. 40, 597 – 604.
45 Varadarajan, S., Yatin, S., Aksenova, M. and Butterfield, D. A. (2000) Review: Alzheimer's amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity. J. Struct. Biol. 130, 184 – 208.
46 Kontush, A., Berndt, C., Weber, W., Akopyan, V., Arlt, S., Schippling, S. and Beisiegel, U. (2001) Amyloid-beta is an antioxidant for lipoproteins in cerebrospinal fluid and plasma. Free Radic. Biol. Med. 30, 119 – 128.
47 Behl, C., Davis, J. B., Lesley, R. and Schubert, D. (1994) Hydrogen peroxide mediates amyloid beta protein toxicity. Cell 77, 817 – 827.
48 Mark, R. J., Lovell, M. A., Markesbery, W. R., Uchida, K. and Mattson, M. P. (1997) A role for 4-hydroxynonenal, an aldehydic product of lipid peroxidation, in disruption of ion homeostasis and neuronal death induced by amyloid beta-peptide. J. Neurochem. 68, 255 – 264.
49 Xu, J., Chen, S., Ahmed, S. H., Chen, H., Ku, G., Goldberg, M. P. and Hsu, C. Y. (2001) Amyloid-beta peptides are cytotoxic to oligodendrocytes. J. Neurosci. 21, RC118.
50 Mark, R. J., Pang, Z., Geddes, J. W., Uchida, K. and Mattson, M. P. (1997) Amyloid beta-peptide impairs glucose transport in hippocampal and cortical neurons: involvement of membrane lipid peroxidation. J. Neurosci. 17, 1046 – 1054.
51 Iversen, L. L., Mortishire-Smith, R. J., Pollack, S. J. and Shearman, M. S. (1995) The toxicity in vitro of beta-amyloid protein. Biochem. J. 311 (Pt. 1), 1 – 16.
52 Kontush, A. (2001) Amyloid-beta: an antioxidant that becomes a pro-oxidant and critically contributes to Alzheimer's disease. Free Radic. Biol. Med. 31, 1120 – 1131.
53 Bondy, S. C., Guo-Ross, S. X. and Truong, A. T. (1998) Promotion of transition metal-induced reactive oxygen species formation by beta-amyloid. Brain Res. 799, 91 – 96.
54 Schubert, D. and Chevion, M. (1995) The role of iron in beta amyloid toxicity. Biochem. Biophys. Res. Commun. 216, 702 – 707.
55 Huang, X., Atwood, C. S., Hartshorn, M. A., Multhaup, G., Goldstein, L. E., Scarpa, R. C., Cuajungco, M. P., Gray, D. N., Lim, J., Moir, R. D. et al. (1999) The A beta peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction. Biochemistry (Mosc). 38, 7609 – 7616.
56 Walter, M. F., Mason, P. E. and Mason, R. P. (1997) Alzheimer's disease amyloid beta peptide 25 – 35 inhibits lipid peroxidation as a result of its membrane interactions. Biochem. Biophys. Res. Commun. 233, 760 – 764.
57 Butterfield, D. A. and Bush, A. I. (2004) Alzheimer's amyloid beta-peptide (1 – 42): involvement of methionine residue 35 in the oxidative stress and neurotoxicity properties of this peptide. Neurobiol. Aging 25, 563 – 568.
58 Soriani, M., Pietraforte, D. and Minetti, M. (1994) Antioxidant potential of anaerobic human plasma: role of serum albumin and thiols as scavengers of carbon radicals. Arch. Biochem. Biophys. 312, 180 – 188.
59 Lynch, S. M. and Frei, B. (1997) Physiological thiol compounds exert pro- and anti-oxidant effects, respectively, on iron- and copper-dependent oxidation of human low-density lipoprotein. Biochim. Biophys. Acta 1345, 215 – 221.
60 Harrington, C. R. and Colaco, C. A. (1994) Alzheimer's disease: a glycation connection. Nature 370, 247 – 248.
61 Munch, G., Thome, J., Foley, P., Schinzel, R. and Riederer, P. (1997) Advanced glycation endproducts in ageing and Alzheimer's disease. Brain Res. Brain Res. Rev. 23, 134 – 143.
62 Thome, J., Munch, G., Muller, R., Schinzel, R., Kornhuber, J., Blum-Degen, D., Sitzmann, L., Rosler, M., Heidland, A. and Riederer, P. (1996) Advanced glycation endproducts-associated parameters in the peripheral blood of patients with Alzheimer's disease. Life Sci. 59, 679 – 685.
63 Munch, G., Schinzel, R., Loske, C., Wong, A., Durany, N., Li, J. J., Vlassara, H., Smith, M. A., Perry, G. and Riederer, P. (1998) Alzheimer's disease – synergistic effects of glucose deficit, oxidative stress and advanced glycation endproducts. J. Neural. Transm. 105, 439 – 461.
64 Reddy, V. P., Obrenovich, M. E., Atwood, C. S., Perry, G. and Smith, M. A. (2002) Involvement of Maillard reactions in Alzheimer disease. Neurotox. Res. 4, 191 – 209.
65 Smith, M. A., Sayre, L. M., Monnier, V. M. and Perry, G. (1995) Radical AGEing in Alzheimer's disease. Trends Neurosci. 18, 172 – 176.
66 Smith, M. A., Richey, P. L., Taneda, S., Kutty, R. K., Sayre, L. M., Monnier, V. M. and Perry, G. (1994) Advanced Maillard reaction end products, free radicals, and protein oxidation in Alzheimer's disease. Ann. N. Y. Acad. Sci. 738, 447 – 454.
67 Vitek, M. P., Bhattacharya, K., Glendening, J. M., Stopa, E., Vlassara, H., Bucala, R., Manogue, K. and Cerami, A. (1994) Advanced glycation end products contribute to amyloidosis in Alzheimer disease. Proc. Natl. Acad. Sci. USA 91, 4766 – 4770.
68 Smith, M. A., Rudnicka-Nawrot, M., Richey, P. L., Praprotnik, D., Mulvihill, P., Miller, C. A., Sayre, L. M. and Perry, G. (1995) Carbonyl-related posttranslational modification of neurofilament protein in the neurofibrillary pathology of Alzheimer's disease. J. Neurochem. 64, 2660 – 2666.
69 Shuvaev, V. V., Laffont, I., Serot, J. M., Fujii, J., Taniguchi, N. and Siest, G. (2001) Increased protein glycation in cerebrospinal fluid of Alzheimer's disease. Neurobiol. Aging 22, 397 – 402.
70 Smith, M. A., Taneda, S., Richey, P. L., Miyata, S., Yan, S. D., Stern, D., Sayre, L. M., Monnier, V. M. and Perry, G. (1994) Advanced Maillard reaction end products are associated with Alzheimer disease pathology. Proc. Natl. Acad. Sci. USA 91, 5710 – 5714.
71 Li, J. J., Surini, M., Catsicas, S., Kawashima, E. and Bouras, C. (1995) Age-dependent accumulation of advanced glycosylation end products in human neurons. Neurobiol. Aging 16, 69 – 76.
72 Ko, L. W., Ko, E. C., Nacharaju, P., Liu, W. K., Chang, E., Kenessey, A. and Yen, S. H. (1999) An immunochemical study on tau glycation in paired helical filaments. Brain Res. 830, 301 – 313.
73 Castellani, R. J., Harris, P. L., Sayre, L. M., Fujii, J., Taniguchi, N., Vitek, M. P., Founds, H., Atwood, C. S., Perry, G. and Smith, M. A. (2001) Active glycation in neurofibrillary pathology of Alzheimer disease: N(epsilon)-(carboxymethyl) lysine and hexitol-lysine. Free Radic. Biol. Med. 31, 175 – 180.
74 Mruthinti, S., Sood, A., Humphrey, C. L., Swamy-Mruthinti, S. and Buccafusco, J. J. (2006) The induction of surface beta-amyloid binding proteins and enhanced cytotoxicity in cultured PC-12 and IMR-32 cells by advanced glycation end products. Neuroscience 142, 463 – 473.
75 Yan, S. D., Roher, A., Chaney, M., Zlokovic, B., Schmidt, A. M. and Stern, D. (2000) Cellular cofactors potentiating induction of stress and cytotoxicity by amyloid beta-peptide. Biochim. Biophys. Acta 1502, 145 – 157.

76 Yan, S. D., Chen, X., Fu, J., Chen, M., Zhu, H., Roher, A., Slattery, T., Zhao, L., Nagashima, M., Morser, J. et al. (1996) RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. Nature 382, 685 – 691.

77 El Khoury, J., Hickman, S. E., Thomas, C. A., Cao, L., Silverstein, S. C. and Loike, J. D. (1996) Scavenger receptor-mediated adhesion of microglia to beta-amyloid fibrils. Nature 382, 716 – 719.

78 Eikelenboom, P. andVeerhuis, R. (1996) The role of complement and activated microglia in the pathogenesis of Alzheimer's disease. Neurobiol. Aging 17, 673 – 680.

79 Mrak, R. E., Sheng, J. G. and Griffin, W. S. (1996) Correlation of astrocytic S100 beta expression with dystrophic neurites in amyloid plaques of Alzheimer's disease. J Neuropathol. Exp. Neurol. 55, 273 – 279.

80 Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G. M., Cooper, N. R., Eikelenboom, P., Emmerling, M., Fiebich, B. L. et al.(2000) Inflammation and Alzheimer's disease. Neurobiol. Aging 21, 383 – 421.

81 Van Muiswinkel, F. L., Veerhuis, R. and Eikelenboom, P. (1996) Amyloid beta protein primes cultured rat microglial cells for an enhanced phorbol 12-myristate 13-acetate-induced respiratory burst activity. J. Neurochem. 66, 2468 – 2476.

82 Klegeris, A. and McGeer, P. L. (1997) beta-amyloid protein enhances macrophage production of oxygen free radicals and glutamate. J. Neurosci. Res. 49, 229 – 235.

83 Good, P. F., Werner, P., Hsu, A., Olanow, C. W. and Perl, D. P. (1996) Evidence of neuronal oxidative damage in Alzheimer's disease. Am. J. Pathol. 149, 21 – 28.

84 Smith, M. A., Richey Harris, P. L., Sayre, L. M., Beckman, J. S. and Perry, G. (1997) Widespread peroxynitrite-mediated damage in Alzheimer's disease. J. Neurosci. 17, 2653 – 2657.

85 Luth, H. J., Munch, G. and Arendt, T. (2002) Aberrant expression of NOS isoforms in Alzheimer's disease is structurally related to nitrotyrosine formation. Brain Res. 953, 135 – 143.

86 Luth, H. J., Holzer, M., Gartner, U., Staufenbiel, M. and Arendt, T. (2001) Expression of endothelial and inducible NOS-isoforms is increased in Alzheimer's disease, in APP23 transgenic mice and after experimental brain lesion in rat: evidence for an induction by amyloid pathology. Brain Res. 913, 57 – 67.

87 Reynolds, W. F., Rhees, J., Maciejewski, D., Paladino, T., Sieburg, H., Maki, R. A. and Masliah, E. (1999) Myeloperoxidase polymorphism is associated with gender specific risk for Alzheimer's disease. Exp. Neurol. 155, 31 – 41.

88 Podrez, E. A., Schmitt, D., Hoff, H. F. and Hazen, S. L. (1999) Myeloperoxidase-generated reactive nitrogen species convert LDL into an atherogenic form in vitro. J. Clin. Invest. 103, 1547 – 1560.

89 Anderson, M. M., Requena, J. R., Crowley, J. R., Thorpe, S. R. and Heinecke, J. W. (1999) The myeloperoxidase system of human phagocytes generates Nepsilon-(carboxymethyl)-lysine on proteins: a mechanism for producing advanced glycation end products at sites of inflammation. J. Clin. Invest. 104, 103 – 113.

90 Glickman, M. H. and Ciechanover, A. (2002) The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction. Physiol. Rev. 82, 373 – 428.

91 Reinheckel, T., Ullrich, O., Sitte, N. and Grune, T. (2000) Differential impairment of 20S and 26S proteasome activities in human hematopoietic K562 cells during oxidative stress. Arch. Biochem. Biophys. 377, 65 – 68.

92 Keller, J. N., Gee, J. and Ding, Q. (2002) The proteasome in brain aging. Ageing Res. Rev. 1, 279 – 293.

93 Perry, G., Friedman, R., Shaw, G. and Chau, V. (1987) Ubiquitin is detected in neurofibrillary tangles and senile plaque neurites of Alzheimer disease brains. Proc. Natl. Acad. Sci. USA 84, 3033 – 3036.

94 Hol, E. M., van Leeuwen, F. W. and Fischer, D. F. (2005) The proteasome in Alzheimer's disease and Parkinson's disease: lessons from ubiquitin B+1. Trends Mol. Med. 11, 488 – 495.

95 Keller, J. N., Hanni, K. B. and Markesbery, W. R. (2000) Impaired proteasome function in Alzheimer's disease. J. Neurochem. 75, 436 – 439.

96 Keller, J. N. and Markesbery, W. R. (2000) Proteasome inhibition results in increased poly-ADP-ribosylation: implications for neuron death. J. Neurosci. Res. 61, 436 – 442.

97 McNaught, K. S., Mytilineou, C., Jnobaptiste, R., Yabut, J., Shashidharan, P., Jennert, P. and Olanow, C. W. (2002) Impairment of the ubiquitin-proteasome system causes dopaminergic cell death and inclusion body formation in ventral mesencephalic cultures. J. Neurochem. 81, 301 – 306.

98 Sullivan, P. G., Dragicevic, N. B., Deng, J. H., Bai, Y., Dimayuga, E., Ding, Q., Chen, Q., Bruce-Keller, A. J. and Keller, J. N. (2004) Proteasome inhibition alters neural mitochondrial homeostasis and mitochondria turnover. J. Biol. Chem. 279, 20699 – 20707.

99 Ding, Q., Dimayuga, E., Martin, S., Bruce-Keller, A. J., Nukala, V., Cuervo, A. M. and Keller, J. N. (2003) Characterization of chronic low-level proteasome inhibition on neural homeostasis. J. Neurochem. 86, 489 – 497.

100 Ding, Q., Reinacker, K., Dimayuga, E., Nukala, V., Drake, J., Butterfield, D. A., Dunn, J. C., Martin, S., Bruce-Keller, A. J. and Keller, J. N. (2003) Role of the proteasome in protein oxidation and neural viability following low-level oxidative stress. FEBS Lett. 546, 228 – 232.

101 Radisky, D. C. and Kaplan, J. (1998) Iron in cytosolic ferritin can be recycled through lysosomal degradation in human fibroblasts. Biochem. J. 336 (Pt 1), 201 – 205.

102 Brunk, U. T., Neuzil, J. and Eaton, J. W. (2001) Lysosomal involvement in apoptosis. Redox Rep. 6, 91 – 97.

103 Zhao, M., Antunes, F., Eaton, J. W. and Brunk, U. T. (2003) Lysosomal enzymes promote mitochondrial oxidant production, cytochrome c release and apoptosis. Eur. J. Biochem. 270, 3778 – 3786.

104 Nakamura, Y., Takeda, M., Suzuki, H., Hattori, H., Tada, K., Hariguchi, S., Hashimoto, S. and Nishimura, T. (1991) Abnormal distribution of cathepsins in the brain of patients with Alzheimer's disease. Neurosci. Lett. 130, 195 – 198.

105 Cataldo, A. M., Thayer, C. Y., Bird, E. D., Wheelock, T. R. and Nixon, R. A. (1990) Lysosomal proteinase antigens are prominently localized within senile plaques of Alzheimer's disease: evidence for a neuronal origin. Brain Res. 513, 181 – 192.

106 Cataldo, A. M., Hamilton, D. J. and Nixon, R. A. (1994) Lysosomal abnormalities in degenerating neurons link neuronal compromise to senile plaque development in Alzheimer disease. Brain Res. 640, 68 – 80.

107 Cataldo, A. M., Paskevich, P. A., Kominami, E. and Nixon, R. A. (1991) Lysosomal hydrolases of different classes are abnormally distributed in brains of patients with Alzheimer disease. Proc. Natl. Acad. Sci., USA 88, 10998 – 11002.

108 Bernstein, H. G., Kirschke, H., Wiederanders, B., Schmidt, D. and Rinne, A. (1990) Antigenic expression of cathepsin B in aged human brain. Brain Res. Bull. 24, 543 – 549.

109 Nixon, R. A., Wegiel, J., Kumar, A., Yu, W. H., Peterhoff, C., Cataldo, A. and Cuervo, A. M. (2005) Extensive involvement of autophagy in Alzheimer disease: an immuno-electron microscopy study. J. Neuropathol. Exp. Neurol. 64, 113 – 122.

110 Gray, D. A. and Woulfe, J. (2005) Lipofuscin and aging: a matter of toxic waste. Sci Aging Knowledge Environ 2005, re1.

111 Brunk, U. T. and Terman, A. (2002) The mitochondrial-lysosomal axis theory of aging: accumulation of damaged mitochondria as a result of imperfect autophagocytosis. Eur. J. Biochem. 269, 1996 – 2002.

112 Brunk, U. T., Jones, C. B. and Sohal, R. S. (1992) A novel hypothesis of lipofuscinogenesis and cellular aging based on interactions between oxidative stress and autophagocytosis. Mutat. Res. 275, 395 – 403.

113 Smith, M. A., Taneda, S., Richey, P. L., Miyata, S., Yan, S. D., Stern, D., Sayre, L. M., Monnier, V. M. and Perry, G. (1994) Advanced Maillard reaction end products are associated with Alzheimer disease pathology. Proc. Natl. Acad. Sci. USA 91, 5710 – 5714.
114 Castegna, A., Thongboonkerd, V., Klein, J. B., Lynn, B., Markesbery, W. R. and Butterfield, D. A. (2003) Proteomic identification of nitrated proteins in Alzheimer's disease brain. J. Neurochem. 85, 1394 – 1401.
115 Williamson, K. S., Gabbita, S. P., Mou, S., West, M., Pye, Q. N., Markesbery, W. R., Cooney, R. V., Grammas, P., Reimann-Philipp, U., Floyd, R. A. and Hensley, K. (2002) The nitration product 5-nitro-gamma-tocopherol is increased in the Alzheimer brain. Nitric Oxide 6, 221 – 227.
116 Butterfield, D. A., Drake, J., Pocernich, C. and Castegna, A. (2001) Evidence of oxidative damage in Alzheimer's disease brain: central role for amyloid beta-peptide. Trends Mol. Med. 7, 548 – 554.
117 Markesbery, W. R. and Lovell, M. A. (1998) Four-hydroxynonenal, a product of lipid peroxidation, is increased in the brain in Alzheimer's disease. Neurobiol. Aging 19, 33 – 36.
118 Lovell, M. A., Ehmann, W. D., Butler, S. M. and Markesbery, W. R. (1995) Elevated thiobarbituric acid-reactive substances and antioxidant enzyme activity in the brain in Alzheimer's disease. Neurology 45, 1594 – 1601.
119 Tamaoka, A., Miyatake, F., Matsuno, S., Ishii, K., Nagase, S., Sahara, N., Ono, S., Mori, H., Wakabayashi, K., Tsuji, S. et al. (2000) Apolipoprotein E allele-dependent antioxidant activity in brains with Alzheimer's disease. Neurology 54, 2319 – 2321.
120 Palmer, A. M. and Burns, M. A. (1994) Selective increase in lipid peroxidation in the inferior temporal cortex in Alzheimer's disease. Brain Res. 645, 338 – 342.
121 Guan, Z., Wang, Y., Cairns, N. J., Lantos, P. L., Dallner, G. and Sindelar, P. J. (1999) Decrease and structural modifications of phosphatidylethanolamine plasmalogen in the brain with Alzheimer disease. J. Neuropathol. Exp. Neurol. 58, 740 – 747.
122 Sayre, L. M., Zelasko, D. A., Harris, P. L., Perry, G., Salomon, R. G. and Smith, M. A. (1997) 4-Hydroxynonenal-derived advanced lipid peroxidation end products are increased in Alzheimer's disease. J. Neurochem. 68, 2092 – 2097.
123 Smith, C. D., Carney, J. M., Starke-Reed, P. E., Oliver, C. N., Stadtman, E. R., Floyd, R. A. and Markesbery, W. R. (1991) Excess brain protein oxidation and enzyme dysfunction in normal aging and in Alzheimer disease. Proc. Natl. Acad. Sci. USA 88, 10540 – 10543.
124 Smith, M. A., Richey, P. L., Taneda, S., Kutty, R. K., Sayre, L. M., Monnier, V. M. and Perry, G. (1994) Advanced Maillard reaction end products, free radicals, and protein oxidation in Alzheimer's disease. Ann. N. Y. Acad. Sci. 738, 447 – 454.
125 Smith, M. A., Perry, G., Richey, P. L., Sayre, L. M., Anderson, V. E., Beal, M. F. and Kowall, N. (1996) Oxidative damage in Alzheimer's. Nature 382, 120 – 121.