ANTIOXIDANTS & REDOX SIGNALING
Volume 9, Number 10, 2007

DOI: 10.1089/ars.2007.1763

Forum Review

Mitochondrial Dysfunction: The First Domino in Brain Aging and Alzheimer's Disease?

KRISTINA LEUNER,[1]* SUSANNE HAUPTMANN,[1]* REHAM ABDEL-KADER,[1] ISABEL SCHERPING,[1] UTA KEIL,[1] JOHANNA B. STROSZNAJDER,[3] ANNE ECKERT,[2] and WALTER E. MÜLLER[1]

ABSTRACT

With the increasing average life span of humans and with decreasing cognitive function in elderly individuals, age-related cognitive disorders including dementia have become a major health problem in society. Aging-related mitochondrial dysfunction underlies many common neurodegenerative disorders diseases, including Alzheimer's disease (AD). AD is characterized by two major histopathological hallmarks, initially intracellular and with the progression of the disease extracellular accumulation of oligomeric and fibrillar β-amyloid (Aβ) peptides and intracellular neurofibrillary tangles (NFT) composed of hyperphosphorylated tau protein. In this review, the authors focus on the latest findings in AD animal models indicating that these histopathological alterations induce deficits in the function of the complexes of the respiratory chain and therefore consecutively result in mitochondrial dysfunction. This parameter is intrinsically tied to oxidative stress. Both are early events in aging and especially in the pathogenesis of aging-related severe neurodegeneration. *Ginkgo biloba* extract seems to be of therapeutic benefit in the treatment of mild to moderate dementia of different etiology, although the data are quite heterogeneous. Herein, the authors suggest that mitochondrial protection and subsequent reduction of oxidative stress are important components of the neuroprotective activity of *Ginkgo biloba* extract. *Antioxid. Redox Signal.* 9, 1659–1675.

AGING

The increase in the individual life span and the elevation of the average age of our population is concomitantly linked to a progressive increase in the number of people suffering from aging-related neurodegenerative disease such as Alzheimer's disease (AD) or Parkinson's disease. As in other differentiated tissues, cells in the central nervous system are affected by aging and react to aging, as indicated by a decline of several physiological abilities including sensory, motor, or cognitive functions (71, 109). Aging cells are affected by increasing amounts of oxidative stress, perturbed energy homeostasis, accumulation of damaged proteins, and lesions in their nucleic acids. These changes are significantly attenuated in neurodegenerative disorders. Cell organelles playing an important role in aging itself and in aging-related neurodegenerative disorders are the mitochondria.

MITOCHONDRIAL DYSFUNCTION AND AGING

Mitochondria were brought to attention in aging biology due to their central role in producing ATP and the decline of basal metabolic rate during aging. It is widely recognized that mito-

[1]Department of Pharmacology, Zafes, Biocenter, University of Frankfurt, Germany.
[2]Neurobiology Research Laboratory, Psychiatric University Clinic, Basel, Switzerland.
[3]Department of Cellular Signalling, Polish Academy of Science, Warzawa, Poland.
*These authors contributed equally to the article.

chondrial function becomes less efficient during aging. For instance, many studies have shown that old mitochondria are morphologically altered and functionally produce more oxidants and less ATP (153). For example, in a study comparing *C. elegans* and *Drosophila melanogaster,* there was a twofold decrease in a large set of genes involved in ATP synthesis in both species (111). The alterations of mitochondrial efficiency and function are mostly related to alterations in concentration and efficiency of the constituents of the respiratory chain. The mitochondrial respiratory chain generates energy through the flow of electrons down the respiratory chain. The respiratory chain is located in the inner mitochondrial membrane and consists of five membrane-spanning enzyme complexes that transfer electrons through a series of oxidation and reduction reactions, culminating in the reduction of oxygen to produce water (Fig. 1). NADH, generated by associated Krebs cycle dehydrogenase, is initially oxidized at complex I. The electrons from NADH are transferred to the first mobile electron acceptor, oxidized Coenzyme Q (CoQ). CoQ can also accept electrons from complex II donated by FADH. Coenzyme Q donates electrons in the next step to cytochrome b of complex III. In complex III, electrons are transferred to cytochrome c1 with the ejection of protons. Cytochrome c1 passes its electron to the second mobile electron acceptor, cytochrome c. This in turn reduces molecular oxygen to water in complex IV. The oxidation–reduction reactions are coupled to transfer of protons across the inner mitochondrial membrane, and this proton efflux creates a proton electrochemical gradient, consisting of the mitochondrial membrane potential and the pH gradient. The mitochondrial membrane potential is maintained at −150–180 mV negative to the cytosol and provides the force that drives an influx of protons and calcium into the mitochondria, and also determines the generation of reactive oxygen species and reactive nitrogen species. This potential energy is in turn used to phosphorylate ADP to ATP via complex V (F1-F0 ATPase).

Complexes II and III of the respiratory chain are almost unaffected by the aging process. In contrast, the complexes I and IV show significantly decreased enzymatic activities in mitochondria isolated from rat and mice liver, brain, heart, and kidney upon aging (11, 88, 93, 106, 116, 119, 121–123, 187). The decreased enzymatic activities of complexes I and IV could be a consequence either of an enzyme inhibition by aging-produced inhibitors, or of aging-mediated enzyme modification, or of decreased protein expression (120). Northern blot analysis of the respiratory complexes in mice brain mitochondria, however, revealed an increased expression of mitochondrial-encoded genes for complexes I, III, IV, and V in 12- and 18-month-old mice compared to 2-month-old mice, whereas the mRNA expression of all genes was decreased in 24-month-old mice. The upregulation in 12- and 18-month-old mice suggests a compensatory mechanism by the overproduction of electron transfer proteins, which cannot be sustained for a long time, resulting in a downregulation in the late stage of aging (103). In addition, as the amount of mitochondrial enzymes changes with age, the number of cells lacking cytochrome oxidase increases (39). Furthermore, uncoupling of oxidative phosphorylation

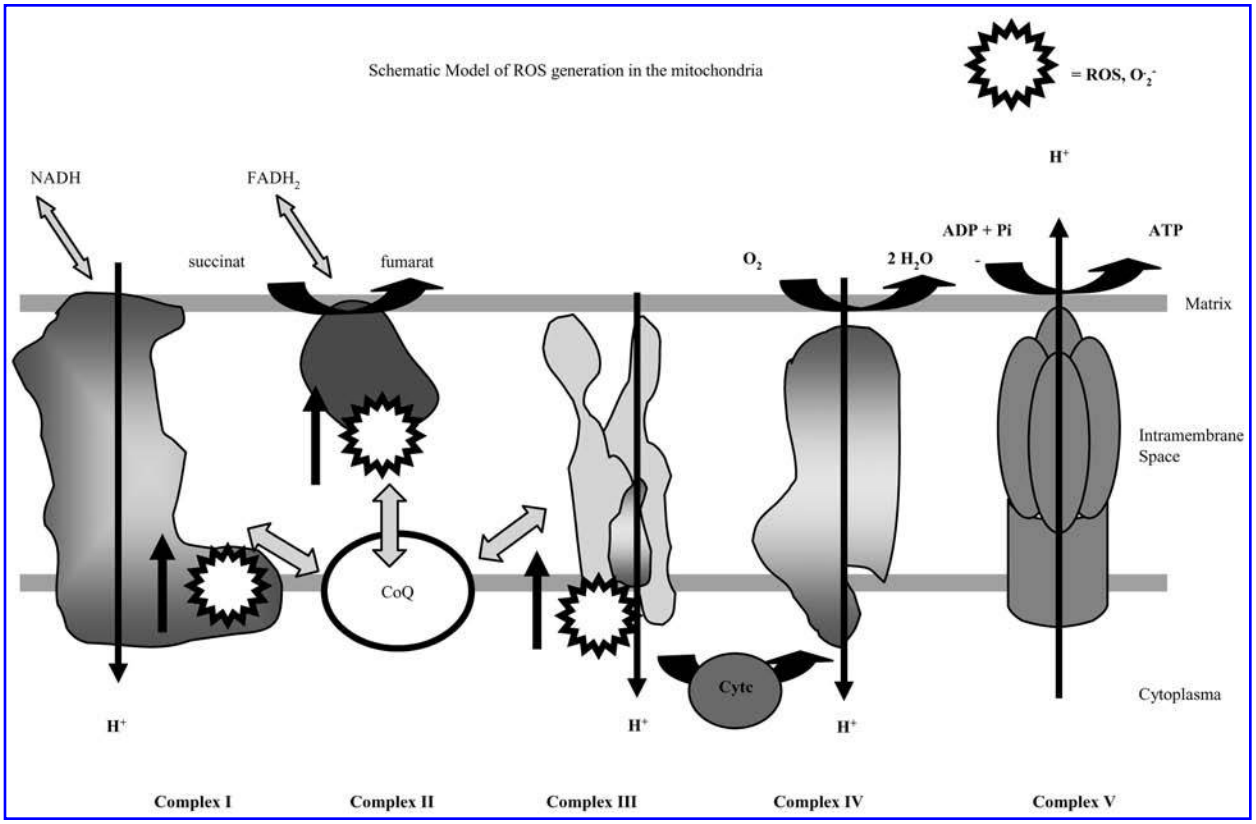
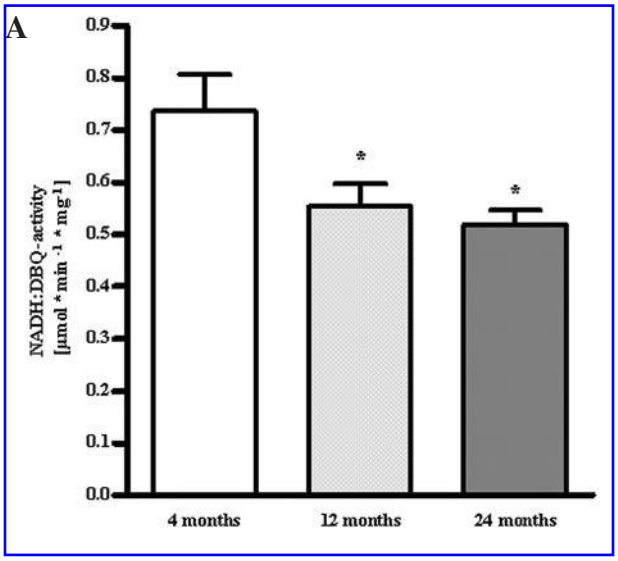
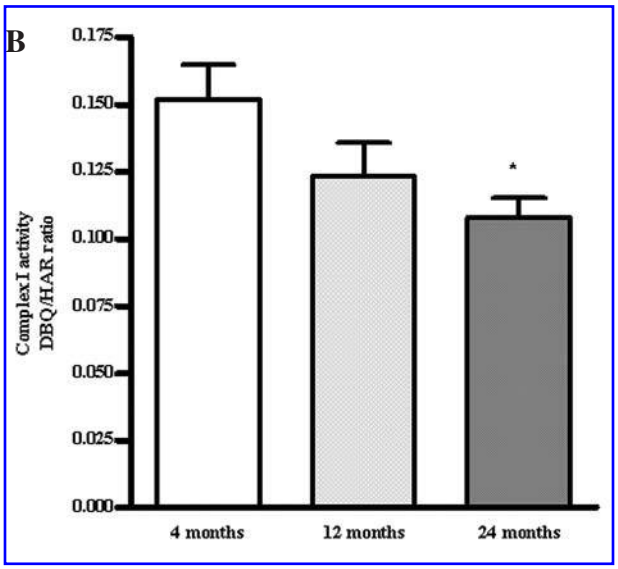
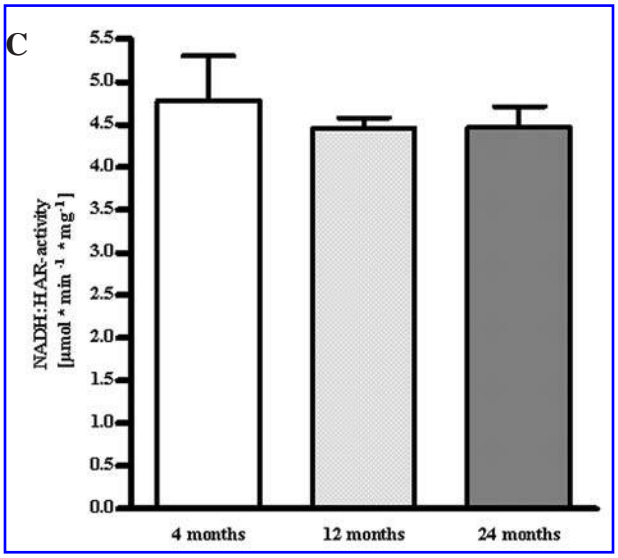


FIG. 1. A schematic model of the energy transfer down the mitochondrial respiratory chain and ROS generation in mitochondria. The mitochondrial respiratory chain generates energy through the flow of electrons down the respiratory chain composed of five complexes. Complexes I, II, and III are involved in the generation of ROS.







with an increase in state 4 respiration, a process that indicates increased passive proton permeability, and decreases in respiratory control ratio and membrane potential have been reported (116). In accordance, for aged NMRI mice used in our experiments we could confirm a significantly decreased complex I activity in isolated brain mitochondria (Fig. 2), using a direct measurement of the NADH-ubiquinone reductase activity and a significantly decreased basal mitochondrial membrane potential (data not shown). Furthermore, we observed a reduced respiratory control ratio using the complex I linked substrates malate/glutamate in aged mice (Fig. 3). There are two further enzymatic activities, which have been reported to be selectively decreased on aging: on the one hand, adenine nucleotide translocase, which catalyzes the fast ADP/ATP exchange between cytosol and mitochondria (183) and on the other hand, acyl carnitine transferase, that catalyzes the fatty acid transport to the mitochondrial matrix (97). Moreover, aging increases the vulnerability of mitochondria to toxins such as 3-nitropropionic acid (84).

In addition, it is well established that mitochondrial DNA (mtDNA) mutations accumulate with aging. Although most mitochondrial proteins are encoded by the nuclear genome, mitochondria contain many copies of their own DNA (*e.g.*, encoding for 13 polypeptide complexes of the respiratory chain). Aging-dependent increase in the level of damaged DNA can be detected through biomarkers [*e.g.*, the formation of 8-oxo-2′-deoxyguanosine (oxo^{8}dG)]. The levels of oxo^{8}dG were found to be significantly higher in mtDNA compared to nuclear DNA (139). These differences can be explained by the proximity of mtDNA to oxidative stress generated by the mitochondrial respiratory chain itself, the lack of any protective histone covering, and a deficient repair mechanism compared to nuclear DNA. Therefore, mitochondria themselves are extremely sensitive to oxidative stress.

OXIDATIVE STRESS AND AGING

Oxidizing and reducing equivalents are tightly controlled in the human body. Oxidants consist of reactive oxygen and nitrogen species (ROS and RNS) either of free radical ($^{\cdot}$OH, hydroxyl radical; $^{\cdot}$OOH, hydroxyperoxyl; $O_2^{\cdot -}$, superoxide radical) or nonradical nature (*e.g.*, $ONOO^-$, peroxynitrite; H_2O_2, hydrogenperoxide). To prevent oxidative damage, the cell has evolved a number of synergistic defense mechanisms (146). The

FIG. 2. Reduced mitochondrial complex I activity in aged NMRI-mice. Complex I activity in cerebral mitochondria from 4-, 12-, and 24-month-old NMRI-mice. (**A**) Reduced NADH-ubiquinone oxidoreductase (NADH:DBQ) activity in 24-month old NMRI-mice (*$p < 0.05$ *vs.* 4-month-old mice, Student's *t* test). (**B**) Unaltered NADH:HAR activity. (n.s. *vs.* non-tg littermate mice, Student's *t* test.) All values represent the means ± S.E.M., $n = 6$–8 animals/group. (**C**) Complex I activity was normalized to the complex I content of the mitochondrial preparation and is expressed as the DBQ/HAR ratio. Unpublished data from our laboratory (*$p < 0.05$ *vs.* 4-month-old mice, Student's *t* test).

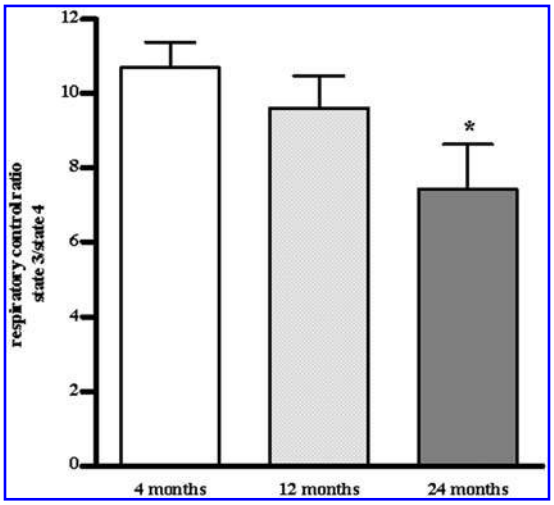


FIG. 3. Reduced respiratory control ratio with aging. Reduced respiratory control ratio in 24-month-old NMRI mitochondria (*$p < 0.05$ *vs.* 4-month-old NMRI mice, Student's *t* test), indicating an impaired efficiency of electron transport in aging. Values represent mean ± S.E.M., $n = 5$ animals/group. All experiments were done in duplicates. Unpublished data from our laboratory.

antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR) act in concert to remove ROS or RNS. Further antioxidant support comes from endogenous (such as GSH or uric acid) and exogenous antioxidants (*e.g.*, vitamin C or secondary plant metabolites) (for review, see Ref. (146)). Some species of ROS are not immediately removed because they perform important biological functions such as defence against infection and coordination of inflammatory response. If an imbalance in the formation and removal of ROS and RNS occur, the formation of ROS and RNS increases. This can injure human tissues through several events such as loss of specific protein function, abnormal protein clearance, depletion of cellular redox balance, and interference with cell cycle, and ultimately to neuronal death. However, this usually happens in old age when repair mechanisms tend to fail too. ROS are generated in multiple compartments and by multiple enzymes within the cell. Important contributors are proteins localized in the plasma membrane such as the growing family of NADPH oxidases or lipid metabolism within the peroxisomes and the activity of several cytosolic enzymes such as cyclooxygenases. Although all these different sources contribute to the overall oxidative burden, mitochondria are the major source of oxidants and at the same time the key targets of their deleterious effects. Approximately 90% of cellular ROS can be traced back to mitochondria. Mitochondrial ROS are generated as a consequence of oxidative phosphorylation, a process that uses the controlled oxidation of NADH or FADH to generate a potential energy for proteins, the mitochondrial membrane potential, across the inner mitochondrial membrane. The resulting energy is in turn used to phosphorylate ADP via complex V (Fig.1). At several sides along the cytochrome chain, electrons derived from NADH or FADH can directly react with oxygen or other electron acceptors and generate ROS (for review, see ref. 10). Three complexes of the respiratory chain are believed to be important for ROS generation: complex I and III, where large changes in the potential energy of electrons occur, and complex II. In experiments manipulating the redox potential of complex I and III activity ROS generation increases (33, 89) (Fig. 1). The radical superoxide ($O_2^{\cdot -}$), for example, is formed when electrons are transferred from complex III and complex I of the respiratory chain to oxygen. Additionally, reverse electron flow might also contribute to high ROS generation occurring with fatty acid oxidation that also generates electrons for complex II via FADH. ROS can further react with transition metals such as iron or copper which convert less reactive to more reactive species. For example, they accelerate lipid-peroxidation by converting H_2O_2 to the hxdroxyl radical.

Therefore, mitochondrial insult, including oxidative damage itself, can cause an imbalance between ROS production and removal, resulting in net ROS production (8). Mitochondrial membrane lipids are highly susceptible to oxidative damage, especially the long chain polyunsaturated fatty acid components. Furthermore, the inner mitochondrial membrane proteins are themselves directly susceptible for effects of oxidative stress. Damage to the inner membrane proteins and/or lipids can lead to membrane depolarization and subsequently impaired mitochondrial function (66). The resultant oxidative damage to mitochondria may increase oxidized proteins with age which, in turn, may cause further mitochondrial decline in energy transfer, perhaps due, in part, to altered conformation of critical enzymes. Concluding, electrons leaking from the electron transport chain (ETC) produce ROS and these molecules can then damage ETC components and mtDNA, leading to further increases in intracellular ROS levels and a decline in mitochondrial function (173). Therefore, mitochondria became the focal point of the controversially discussed free radical theory first proposed by Harman (65). The importance of mitochondrial ROS production in aging is supported by several findings that enhancing mitochondrial antioxidant defense such as overexpression of the manganese superoxide dismutase (MnSOD) in *Drosophila melanogaster* (162) or overexpression of catalase in mice (148), results in an increased life-span.

Although there is a debate on whether oxidative stress is causative for aging or only an effect in aging, there is no doubt about the increase in oxidative stress during aging (10, 94, 96). Reduced levels of antioxidants, as well as increased markers of oxidative stress, were found in the cerebral cortex of aged animals (26; 138) and in the plasma of humans (152; 185). Similarly, substantially higher levels of lipid peroxidation products (*e.g.*, MDA, 4-HNE and F_2-isoprostanes) have been observed in aged compared with young organism in tissues, such as kidney (131, 176), brain (134, 142, 181), liver (131, 176), lung (92, 181), and muscle (75, 132).

Keeping in mind that our brain is especially vulnerable to free radical damage, brain aging seems to be closely associated with ROS (126). This vulnerability can be explained by its high content of easily peroxidizable unsaturated fatty acids, the high number of neuronal mitochondria implicating high oxygen consumption rate, and relative paucity of antioxidant enzymes in comparison with other organs (41, 53, 108). Several studies using ROS- and RNS-dependent biomarkers (*e.g.*, MDA or nitrotyrosine), indicate an increase in vulnerability to oxidative

stress with aging. In brains from 24- to 29-month-old rats, a significantly elevated nitrotyrosine immunoreactive cell number was detected compared to 4- to 6-month-old rats (154). Leutner *et al*. (94) found steadily increasing amounts of MDA in young, adult, and aged mice, suggesting an age effect on lipid peroxidation in the brain of female NMRI mice. These results are supported by studies using rat brain or brain from C57BL mice (113, 167). Moreover, changes in the efficiency of the endogenous antioxidant network were reported, such as modifications in the activity of antioxidant enzymes (*e.g.*, SOD, GPx, and GR) (9, 94, 169). These modifications in the antioxidant network and in the accumulation of oxidative biomarkers are even increased in aging-related neurodegenerative diseases, such as AD.

ALZHEIMER`S DISEASE

AD is a progressive disorder that leads to dementia and affects ~10% of the population older than 65 years of age. The clinical symptoms of AD include a progressive loss of memory and impairment of cognitive ability. The AD brain is marked by severe neurodegenerative alterations, such as the loss of synapses and neurons, atrophy, and the selective depletion of neurotransmitter systems (*e.g.*, acetylcholine) in the hippocampus and cerebral cortex. Such defects are mainly observed in the late stage of the disease, and have also been partially demonstrated using transgenic animal models of AD (67).

AD can be classified into two broad types, the sporadic AD and the familial AD. The sporadic AD is by far the most common form, and aging itself is the only important risk factor known. The other type is called familial AD (FAD), which affects a small subset of patients of younger age, usually before their fifties. It has a strong genetic component. Mutations in the following genes have been described to be causative for FAD: presenilin 1 gene on chromosome 14, presenilin 2 gene on chromosome 1, and amyloid precursor protein (APP) gene on chromosome 21 (54, 143). Patients with either sporadic AD or FAD share common clinical and neuropathological features, including synaptic and neuritic loss and the two major histopathological hallmarks, the accumulation of diffuse and neuritic plaques, mainly comprised of the amyloid-β peptide (Aβ), and neurofibrillary tangles, which consist of hyperphosphorylated tau protein and finally, profound neurodegeneration in many but not all brain regions. Since the discovery of the 4 kDa Aβ peptide, much research has focused on understanding Aβ toxicity and its relationship to AD progression and pathogenesis (64, 155, 174, 175).

Several hypotheses have been set forth to explain the pathophysiology of AD. The main hypothesis concerning the origin of the disease is the so-called amyloid cascade hypothesis. It states that the dysregulation of APP processing and Aβ production are the major causes for neuronal death and dysfunction leading to dementia in AD (64). APP is an ubiquitously expressed type I integral membrane glycoprotein with various isoforms. It is abundantly expressed in several tissues, and APP processing is a normal event in nearly all neuronal and non-neuronal cells. Proteolytic processing of APP is mediated by the secretases. This process can be divided in two different pathways, the nonamyloidogenic and the amyloidogenic pathway. In the amyloidogenic pathway, full-length APP is first processed by BACE (β-secretase) and afterwards cleaved by the γ-secretase complex. The γ-secretase complex is composed of Presenilin 1 (PS1), PS 2, Nicastrin, and APH1 and PEN2 (61, 85, 164). The cut of the γ-secretase complex is variable that releases $A\beta_{1-38}$ and the most common forms $A\beta_{1-40}$ and $A\beta_{1-42}$. The $A\beta_{1-42}$ isoform is insoluble and more capable of aggregating into Aβ plaques. $A\beta_{1-42}$ exists initially as a monomer which further oligomerizes into larger forms such as large oligomers, protofibrils, and fibrils. Recent years of AD research focused on the fibrillar Aβ known as senile plaques. But many researchers have questioned the relevance of these plaques to AD pathogenesis because there was no clear correlation between Aβ plaques and cognitive decline. Therefore, research focused on soluble Aβ, including soluble oligomers (62) which correlate much better with the presence and the degree of cognitive deficits than simple plaque counts (99, 118). We will also address the question whether oligomeric or fibrillar Aβ cause mitochondrial dysfunction and oxidative stress in AD.

MITOCHONDRIAL DYSFUNCTION AND AD

Mitochondrial dysfunction is observed in AD brain (70) and has been proposed as an underlying mechanism of disease pathogenesis since defective energy metabolism is a fundamental component of AD (104, 170). Furthermore, early defects in glucose utilization in the brain of AD patients suggest possible abnormalities in mitochondrial function (19, 72). Interestingly, the activities of those enzymes that are reduced in the brains of AD patients, such as α-ketoglutarate dehydrogenase and pyruvate dehydrogenase, are inhibited by Aβ (27). The most consistent defect in mitochondrial electron transport enzymes in AD is a deficiency in cytochrome c oxidase (COX), which was reported in both AD platelets and postmortem brain samples (25, 86). Histochemical analyses revealed a significant reduction of COX activity in the dentate gyrus, and other subfields of the hippocampus of AD patients. In situ hybridization studies also showed decreased mRNA levels of the mitochondrial DNA (mtDNA)-encoded subunit II, but not the nuclear DNA-encoded subunit IV, of COX in AD brain (40). Furthermore, a correlation was reported between decreased COX activity and deficits in cognitive abilities (4, 12, 23). COX dysfunction increases ROS production, reduces energy stores, and disturbs energy metabolism (115).

To address the possible contributions of Aβ and aging for mitochondrial dysfunction in AD, we studied Thy-1-APP_{751}SL mice at different ages (49). These mice express the mutant human APP_{751} with the Swedish and the London mutation, regulated by the neuronal murine Thy-1 promoter. This leads to an overexpression of the mutated human APP, resulting in the development of typical Aβ depositions in the form of amyloid plaques at the age of 6 months, whereas only a moderately elevated intracellular Aβ load can be detected at an age of 3 months (17). Using isolated mitochondria from 3-month-old

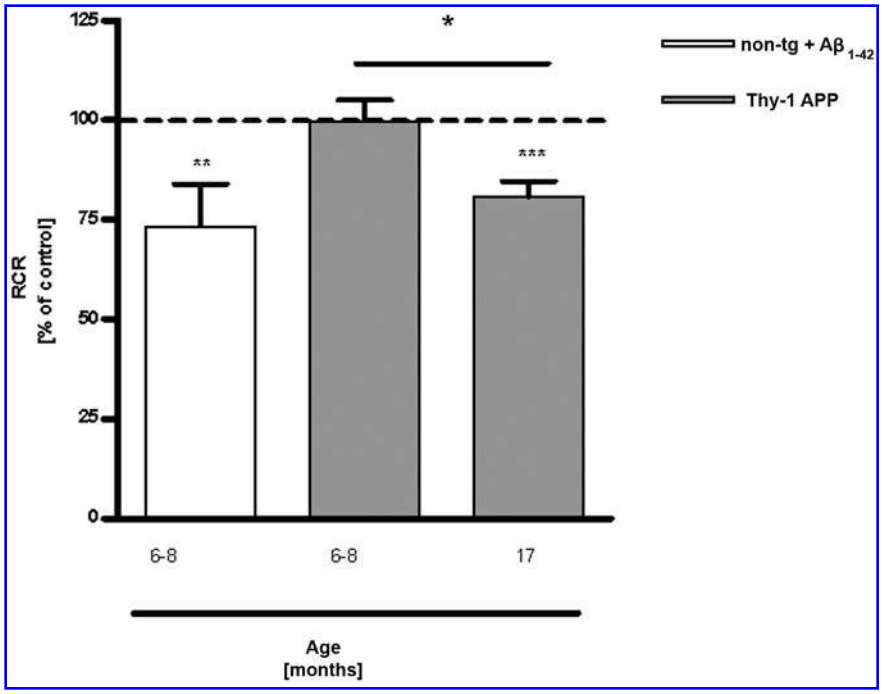


FIG. 4. Reduced respiratory control ratio of the young non-tg mitochondria after stimulation with A$\beta_{1–42}$ and in aged Thy-1 APP mice. Reduced respiratory control ratio after stimulation with A$\beta_{1–42}$ in 6- to 8-month-old non-tg animals and in 17-month-old Thy-1 APP mitochondria (**$p < 0.01$; ***$p < 0.001$ *vs.* untreated control and non-tg animals, respectively, Student's *t*-test), indicating an impaired efficiency of the electron transport. The values represent the mean ± S.E.M., $n = 8$ animals/group. All experiments were done in duplicate. The data are presented as the percentage of untreated non-tg mice or non-tg mice in comparison to Thy-1 APP mice (*$p < 0.05$ 6- to 8-month-old Thy-1 APP *vs.* 17-month-old Thy-1 APP, Student's *t* test) (66).

and 6-month-old APP transgenic (tg) mice and nontransgenic (non-tg) littermate control animals, we found decreased basal levels of mitochondrial membrane potential in tgAPP mice compared to littermate non-tg control mice, similar to the decrease in dissociated cells. Our data indicate that the increased Aβ production by APP transgenic mice might trigger the dysfunction of the mitochondrial respiratory chain. Importantly, we found decreased levels of mitochondrial membrane potential in 3-month-old mice where no Aβ plaques could be detected. The result points to an involvement of soluble Aβ in Aβ-mediated mitochondrial dysfunction in 3-month-old mice. When tracing mitochondrial dysfunction at the level of the respiratory chain, we detected an enhanced depolarization in the mitochondria obtained from the 6-month-old Thy-1 APP mice after treatment with the complex IV inhibitor sodium azide. In agreement, we also demonstrated a decrease in the complex IV activity using a direct measurement of COX activity. This observed phenotype may comprise: (a) increased H^+ permeability of the inner mitochondrial membrane; (b) decreased complex IV content; (c) decreased complex IV activity; or (d) a combination of these effects. Moreover, treatment with extracellular Aβ led to a significant decrease in state 3 respiration and FCCP-uncoupled respiration in non-tg mice. Calculation of the respiratory control ratio (RCR) showed a significant effect of Aβ on the coupling of mitochondrial respiration, indicating that the relative efficiency of metabolic coupling of the electron chain complexes is impaired after extracellular stimulation with Aβ. Furthermore, we detect differences between the mitochondrial respiratory chain using 17-month-old littermates compared to tg-APP transgenic mice, notable in a significantly reduced state 3 respiration with the NADH-generating, and therefore complex I-linked substrates malate/glutamate as well as an impaired efficiency of coupling between the mitochondrial respiratory chain complexes (Fig. 4). These differences were only detected in old Thy-1 APP transgenic mice, suggesting that the subtle phenotype in young Thy-1 APP mice is probably due to compensatory effects mediated by the other respiratory chain enzymes (Fig. 5). Therefore, we conclude that Aβ-related mitochondrial dysfunction is exacerbated by aging and may be one of the mechanisms explaining the pronounced accumulation of AD pathology with aging. In agreement, Caspersen *et al.* (28) used isolated mitochondria from Tg mAPP mice, observed comparable oxygen consumption at 4 months in tg mAPP and non-tg littermates, a trend toward lower levels in tg mAPP mice at 8 months that achieved statistical significance at the age of 12 months (28). Furthermore, Aleardi *et al.* (6) reported the inhibition of the respiratory chain complexes depending on the Aβ concentration by using isolated rat mitochondria. In addition, the authors demonstrated an increase in mitochondrial membrane viscosity with a concomitant decrease in ATP/O (6). In addition, impairment of mitochondrial oxidative phosphorylation was also extensively reported in the brain of AD patients (31), as well as that the degree of impairment being proportional to the clinical disability (18). Our results, together with these observations, disclose a clear relationship between Aβ toxicity, aging, and mitochondrial respiratory defects. This conclusion is further supported by recent observations showing, for instance, that Aβ progressively accumulates in mitochondria and that Aβ is associated with diminished enzymatic activity of respiratory chain complexes (28). In addition, Lustbader *et al*. (101) demonstrated that Aβ-binding alcohol dehydrogenase (ABAD) is a direct molecular link between Aβ and mitochondrial toxicity. They found that Aβ interacts with ABAD in the mitochondria of AD patients and APP transgenic mice (101). Recently, Anandatheerthavarada *et al*. (7) studied the relationship between mutant APP and mitochondrial dysfunction in neuronal cells of Tg2576 mice. This work demonstrated that APP can accumulate in mitochondrial membranes (7). Two

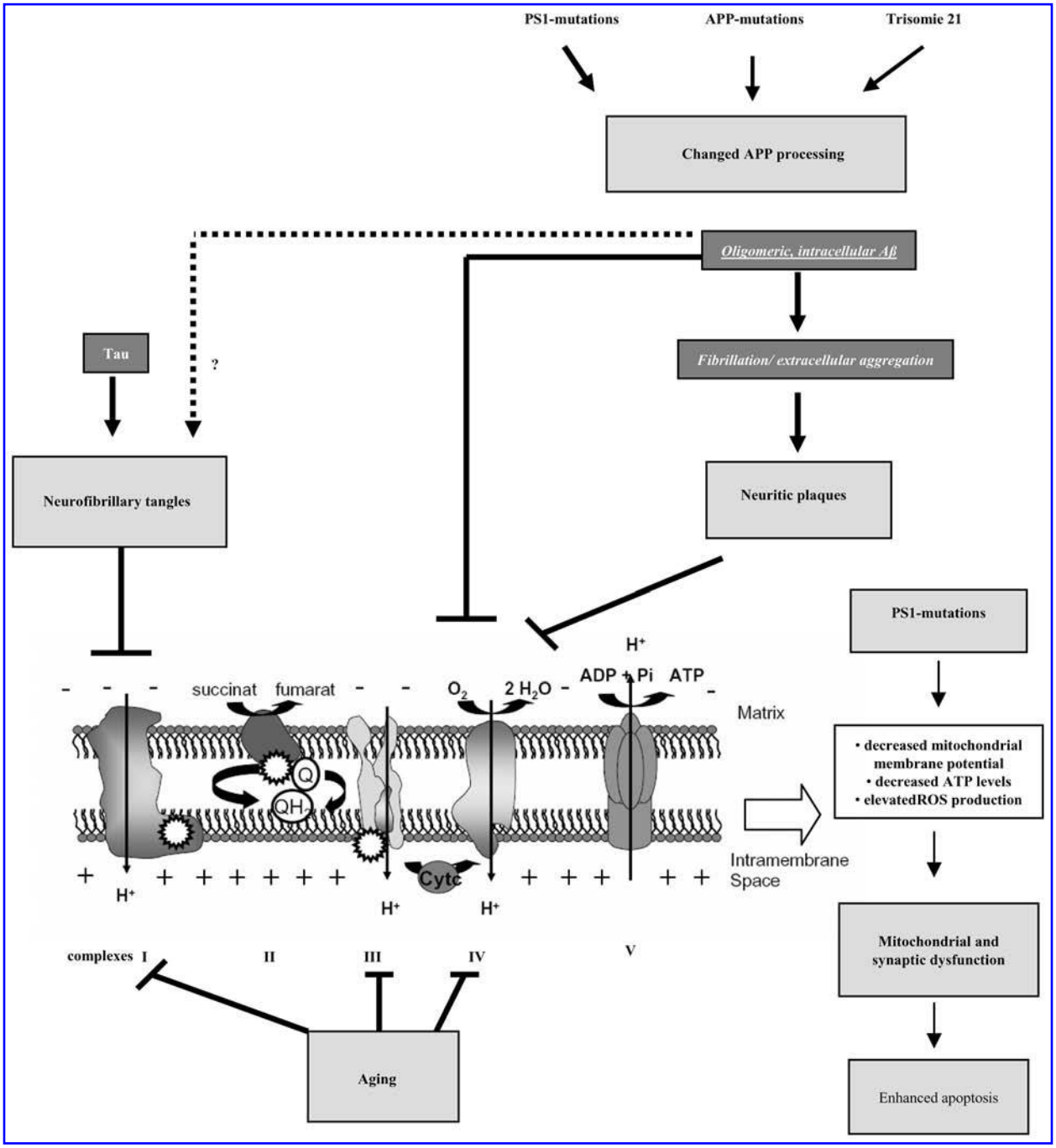


FIG. 5. Role of aging and Aβ in mitochondrial dysfunction. Mitochondrial dysfunction is an early common pathological pathway in aging, Complexes I, III, and IV activity is decreased in aging. In addition, Aβ pathology results in a decrease of complex IV activity. In addition, tau pathology may impair complex I activity. All these pathogenic changes cumulate together with PS1-induced reduction of mitochondrial function independently of the Aβ cascade. Therefore, we conclude that Aβ-related mitochondrial dysfunction is exacerbated by aging and lead to decreased mitochondrial membrane potential, decreased ATP levels, enhanced ROS production, and finally to synaptic dysfunction, apoptosis, and neurodegeneration. APP, amyloid precursor protein; PS1, presenilin 1; ROS, reactive oxygen species.

other groups have also reported that Aβ interacts with mitochondria, inhibiting cytochrome c oxidase activity, and increasing free radical generation (42, 102).

Beside APP mutations, mutations in the presenilins PS1 and PS2 account for the majority of FAD cases, and clinical onset in some carriers of PS1 mutations is extremely early, occasionally as soon as in the third decade of life (24). Presenilins are a component of the γ-secretase complex which is involved in the formation of Aβ from APP. Several different PS mutations have been shown to alter γ-secretase processing of APP

to yield higher levels of A$\beta_{1\text{-}42}$ isoform and a higher production of A$\beta_{1\text{-}42}$ correlated with an earlier onset of Alzheimer dementia in carriers of PS1 mutations (98). Therefore, the increased formation of A$\beta_{1–42}$ formation is proposed to be a major causative mechanism for neurotoxicity induced by PS mutations. Consistent with this hypothesis, proapoptotic effects are induced by expression of mutant PS1 in cell culture systems (60, 178, 179) and transgenic mice (59). Similarly, in primary cultured neurons of transgenic rats expressing wild-type PS1, increased apoptosis correlated with the amount of PS1 expression (44). Moreover, mice transgenic for human PS1 with FAD mutations display increased formation of rodent A$\beta_{1–42}$ and neural degeneration (36, 144) and show cognitive deficits. Furthermore, in human brain sections bearing a PS1 mutation, abnormal morphologic changes in mitochondria have been reported (172). More importantly, several studies demonstrated that neuronal cells carrying mutant PS1 had decreased mitochondrial membrane potential, reduced permeability transition (81, 83), and altered mitochondrial function (74). Furthermore, studies have shown that FAD PS mutations sensitize cells to die by apoptosis after mitochondrial failure (81). Therefore, PS1-mutations may in addition directly impair mitochondrial function independently of the Aβ cascade.

In addition, the appearance of neurofibrillary tangles, primarily composed of aggregated hyperphosphorylated tau protein within specific neuronal populations, is a known neuropathological feature in several diseases known as tauopathies, such as AD. Little is known about the distinct intracellular mechanism underlying the consequences of tau pathology. Some data suggest that tau plays a key role in the pathogenic cascades. For example, neurons from tau-knockout mice are resistant to Aβ-induced neurotoxicity (137) and the expression of pseudophosphorylated tau constructs in cells is toxic (52). Using transgenic mice overexpressing the P301L mutant human tau protein, we could demonstrate mitochondrial dysfunction by proteomic and functional analyses in these mice (45). The P301L transgenic mice express the human pathogenic mutation P301L of tau together with the longest human brain tau isoform under control of the neuron-specific mThy1.2 promoter (56). This isoform contains exons 2 and 3 as well as four microtubule-binding repeats. P301L tau transgenic mice show tau hyperphosphorylation already at 3 months and NFT formation starts at 6 months of age (56, 57).

Our functional analysis demonstrated reduced NADH-ubiquinone oxidoreductase (complex I) activity and, with age, impaired mitochondrial respiration and ATP synthesis in P301L tau mice. In particular, the reduction in state 3 respiration reflects a reduced capacity of mitochondria to metabolize oxygen and the complex I substrates in the presence of a limited quantity of ADP (45). In addition, mitochondrial dysfunction was associated with higher levels of reactive oxygen species in aged transgenic mice. Furthermore, P301L tau mitochondria displayed increased vulnerability towards Aβ peptide insult, suggesting a synergistic action of tau and Aβ pathology on the mitochondria. Together, this evidence supports a role of tau pathology in mitochondrial and metabolic dysfunction. However, it remains unclear how tau accumulation mediates these changes. Although it is uncertain exactly how tau mechanistically affects mitochondrial function, we can postulate that the mutant tau acts either indirectly by modifying microtubule stability, axonal transport, and mitochondrial network, or directly by inhibiting energy production through complex I of the respiratory chain.

As in aging, there is some evidence that mtDNA may be involved in the mitochondrial dysfunction in AD. When AD patient DNA is transferred to mtDNA-deficient cell lines, the resulting cybrids reproduce the respiratory enzyme deficiency seen in the brain and other tissues (163). These results suggest in part that the deficit is carried by mtDNA. However, until today research failed to provide conclusive proof for, or against, a specific role of mtDNA mutations in the AD disease process (51, 171).

In conclusion, the exact mechanism related to the impairment of mitochondrial dysfunction to AD remains unclear. AD is most certainly a complex and multifactorial disorder. There are many interacting components contributing to its occurrence, some of which we are just starting to identify. Finally, tau and Aβ accumulation probably act in synergy on oxidative stress and mitochondrial dysfunction.

OXIDATIVE STRESS IN AD

Again, oxidative stress is not only associated with aging but also with the development of neurodegenerative disease such as AD or Parkinson's disease. In addition to an increased production of ROS due to aging, AD brain is exposed to even more oxidative stress. Postmortem tissues provide strong evidence for increased levels of cellular oxidative stress in vulnerable regions of AD brains compared to aged controls (34, 43, 63, 107). Increased protein oxidation, protein nitration, and lipid peroxidation were detected in brain areas showing neurofibrillary tangles and amyloid plaques (133). Further evidence comes from studies investigating peroxidation products such as HNE in cerebrospinal fluid of AD patients. Here, elevated HNE levels were detected. These products of membrane lipid peroxidation such as HNE or MDA are particularly devastating for neuronal function. They impair the function of membrane ion motive ATPases and glucose and glutamate transporters. These changes consecutively lead to a disruption of cellular calcium homeostasis. Additionally, alteration in levels of antioxidant enzymes such as catalase, Cu/Zn-SOD, and Mn-SOD support the evidence for increased oxidative stress in Alzheimer postmortem tissue and AD animal models (5, 149, 150). In other studies, oxidatively modified brain proteins were detected in AD patients with redox proteomics (22, 29, 30, 125, 161). For example, in patients carrying PS1 mutations, oxidative modifications of ubiquitin carboxyl-terminal hydrolase, gamma enolase, actin, and dimethylarginin were detected (22). Importantly, only in the hippocampus and not in the cerebellum oxidative modification were found, consistent with the lack of pathology in this brain region in AD (160).

Several recent studies in transgenic animals, postmortem brains, and biological fluids from subjects with AD or mild cognitive impairment support the strong relationship between mitochondrial dysfunction and oxidative stress in AD and the early involvement of these two parameters in the pathology of AD. Nunomura *et al.* (127) found that oxidative damage was more pronounced in AD subjects with lesser amount of Aβ plaques.

Importantly, individuals with MCI or very mild AD showed elevated levels of lipid peroxidation and nucleic acid oxidation in postmortem brain tissue (82) and increased levels of lipid peroxidation and nucleic acid oxidation in the cerebrospinal fluid, plasma, urine, and peripheral leukocytes (112, 135), compared to patients suffering from severe AD. Furthermore, decreased levels of plasma antioxidants and total plasma antioxidant activity were observed (58, 140). These results are supported by studies conducted in AD animal models (47, 136, 150). Schüssel *et al*. (151) demonstrated that 3-month-old APP transgenic mice showed increased levels of HNE before Aβ plaques can be detected. These increased HNE levels were accompanied by reduced activity of Cu/Zn-superoxide dismutase. This suggests that impaired antioxidant defense is causally responsible for increased formation of HNE (150). In addition, another study revealed an increase in mitochondrial as well as cytosolic ROS (149).

The mechanism of how oxidative stress increases in AD is still unknown but several findings suggest a link between Aβ toxicity and the generation of reactive oxygen species (2). In AD brain, protein oxidation occurs in Aβ-rich regions, such as inferior parietal lobule, cortex, and hippocampus, but not in cerebellum where Aβ levels are negligible (69). This hypothesis is supported by a co-localization of mouse brain Aβ deposits with a variety of oxidative stress markers (158). Furthermore, lipid membrane damage is promoted by Aβ aggregates (114, 149) and enhanced ROS were found as a consequence of Aβ-mediated mitochondrial dysfunction (77, 105). In addition, we demonstrated in cell culture experiments that extracellular Aβ causes oxidative stress (78). Expression of APPsw rendered PC12 cells vulnerable to the induction of cell death after exposure to oxidative stress (50, 95). Moreover, Aβ has been shown to generate free radicals *in vitro* (68). These results are in agreement with the hypothesis that Aβ is a metalloenzyme that is capable of generating hydrogen peroxide through its superoxide dismutase activity (130). It has been further suggested that oxidative stress may actually promote the amyloidogenic pathway (124). The resulting increase in Aβ can in turn generate hydrogen peroxide leading to further oxidative damage. A cyclic and vicious pathway of excessive Aβ promoting oxidative damage which promotes further Aβ production would result in increased neurotoxicity and subsequently enhance AD progression (130). Backwards, oxidative stress increases the expression of β-secretase and therefore enhances the amyloidogenic pathway (165). Several recent publications point to the toxicity of intracellular oligomeric Aβ species (37, 128, 129). Therefore, we propose the following hypothetical sequence of pathogenetic steps linking sporadic AD, oligomeric and fibrillar Aβ, tau, mitochondrial dysfunction, and oxidative stress (Fig. 5). In an early phase of AD, intracellular Aβ and tau cause mitochondrial dysfunction by impairing complex IV activity. Consequently, mitochondrial membrane potential is reduced, ATP levels are decreased, and ROS generation/oxidative stress are enhanced. Mitochondrial dysfunction and increased oxidative stress result via a pathogenic cascade in enhanced apoptosis and cell death (67, 80).

Aside from Aβ, redox metal ions, inflammation, and microglia activation are important in AD. Excessive deposits of zinc, iron, and/or copper catalyze the formation of OH from H_2O_2 as well as the formation of advanced glycation end products. In the presence of transition metals, these products can undergo redox cycling with consequent ROS and RNS production. Microglia co-localized with Aβ plaques produce ROS and RNS (*e.g.*, superoxide anion or NO). This increased production of ROS and RNS is explained by the expression of a membrane-bound NADPH oxidase and an inducible nitric oxide synthase (iNOS). When activated, these enzymes and their products contribute to the generation of ROS and RNS (3, 38).

Another hypothesis reviewed by Nunomura *et al*. (126) suggests that AD pathology may represent a response to oxidative stress. They propose that Aβ acts as an antioxidant in AD pathology. This hypothesis is supported by findings that neurons respond to oxidative stress, both *in vitro* and *in vivo*, by increasing Aβ production (165, 184). Recently, the antioxidant activity of fibrillar Aβ was demonstrated in several recent *in vitro* and *in vivo* studies (16, 87).

Not only Aβ, but also tau, seem to be involved in this scenario. Recent data indicate that tau is also a protective antioxidant response, because oxidative damage is reduced in neurons with most cytopathology. In addition, oxidative stress activates several kinases, including glycogen synthase kinase-3 and mitogen-activated protein kinase, both involved in the phosphorylation of tau. Once phosphorylated, tau becomes vulnerable to oxidative modification and consecutively aggregates to fibrils. Therefore, NFT formation is considered to be a result of neuronal oxidation.

GINKGO BILOBA EXTRACT

In line with the neuropathological findings described above, drugs with antioxidant and mitochondrial protecting properties such as *Ginkgo biloba* extract attract increasing interest regarding beneficial effects in aging and AD pathology. The standardized *Ginkgo biloba* extract (EGb 761) has been used for many years as a prescription drug in many countries and as a dietary supplement in the United States to treat aging-related cognitive disorders, including AD (35). EGb 761 contains 24% flavonoids and 6% terpenens. The terpene lactones are represented by the Ginkgolides A, B, C, J, and M, and bilobalide. The flavonoid fraction is composed of quercetin, kaempferol, and isorhamnetin. Several clinical trials provided evidence of efficacy in the treatment of mild to moderate dementia of different etiology (13, 14, 90, 91, 117), even comparable with donepezil in one study (110). However, a recent metaanalysis conducted by the Cochrane Collaboration including many heterogeneous reports concludes that the evidence for Ginkgo's clinically significant benefit for people with dementia or cognitive impairment is inconsistent (15). Nevertheless, substantial experimental data suggests that EGb 761 has relevant neuroprotective and neuromodulatory effects (46, 48, 100, 177, 186). This review focuses on the antioxidant effects of EGb 761 and on its protective effects on mitochondrial function in respect to the important role of these two parameters for aging and aging-related neurodegenerative disorders like AD.

Mitochondria-protecting effects of EGb 761 have been described in several publications. Our group showed protection of mitochondrial function in a neuronal-like cell line and in dissociated brain cells and isolated mitochondria of EGb 761

TABLE 1. EFFECTS OF EGB 761 ON MITOCHONDRIAL FUNCTION IN PC12 CELLS, DISSOCIATED BRAIN CELLS, AND ISOLATED MITOCHONDRIA FROM NMRI MICE

	Stressors	*PC12 cells Egb 761 10 μg/ml*	*Dissociated brain cells In vitro EGb 761 0.5 mg/ml*	*Isolataec mitochondria Ex vivo EGb 761 100 mg/kg*
ATP	SNP	↑*		
MMP	SNP	↑†	↑†	↑*
MMP	Complex I Rotenone	↑*	↑*	↑*
	Complex II Thenoyltrifluoroaceton	↑†	↑†	
	Complex III Antimycin	↑*	↑*	↑*
	Complex IV Natriumazide	↑†	↑†	
	Complex V Oligomycin	↑*	↑*	↑*

Data published in refs. 1 and 48.

*$p < 0.05$, †$p < 0.01$ compared to PC12 cells, dissociated brain cells *in vitro*, and isolated mitochondria *ex vivo*, respectively, only stressed with SNP or complex inhibitors.

treated animals (Table 1, Fig. 6) (1, 48). Progressive NO elevation has been found in AD models (79, 141). Therefore, in our study we stressed PC12 cells, a neuronal-like cell line, with sodium nitroprusside (SNP), a NO donor. EGb 761 treatment reduced SNP-induced drop in ATP levels and mitochondrial membrane potential at a concentration of 5 and 10 μg/ml, respectively (Table 1). In addition, EGb 761 protected complexes I, II, IV, and IV of the mitochondrial respiratory chain after stimulation with specific complex inhibitors in a concentration of 10 μg/ml (Table 1, Fig. 6). Data from Tendi *et al*. (166) and Chandrasekaran *et al*. (32) support our findings in PC12 cells. Tendi *et al*. (166) found a significant increase in the mRNA levels of complex I in PC12 cells treated for 48 or 72 h with EGb 761 (100 μg/ml) or bilobalide (10 μg/ml). They also evaluated state 3 and state 4 respiration and found a significant decrease in state 4 respiration, resulting in an increase in respiratory control ratio.

Similar effects as in PC12 cells were detected in dissociated brain cells of female 3-month-old NMRI mice. EGb 761 prevented SNP- and H_2O_2-induced decrease of mitochondrial membrane potential in dissociated brain cells *in vitro* (Table 1, Fig. 6). In addition, EGb 761 showed protective effects on complexes I, II, III, IV, and V of the respiratory chain in dissociated brain cells *in vitro* (0.5 mg/ml). To evaluate the effects of *Ginkgo biloba* extract *ex vivo*, NMRI mice were treated per os with 100 mg/kg for 14 days. In isolated mitochondria and in dissociated brain cells from EGb 761-treated animals, a significant protection against SNP-induced decrease of mitochondrial membrane potential could be observed (Table 1, Fig. 6). Furthermore, EGb 761 showed significant protective effects on complexes I, IV, and V in isolated mitochondria of aged mice (15 months) and no effects in young mice (3 months). In accordance with our data, treatment with EGb 761 prevented age-associated changes in mitochondrial morphology, mitochondrial glutathione levels, and respiratory function of rat brain mitochondria (145). In addition, mitochondrial numeric density was significantly increased in EGb 761 (100 mg/kg BW) treated vitamin E-deficient rats. In another study, *Ginkgo biloba* extract increased state 2 respiratory rate in a dose-dependent manner in concentrations over 4 μg/ml in rat heart mitochondria *in vitro* (168). *Ex vivo*, Janssen *et al*. (73) investigated the effect of bilobalide on ischemia-induced alterations of the mitochondrial respiratory chain. Bilobalide was found to allow mitochondria to maintain their respiratory activity in ischemic conditions by protecting complex I and probably complex III activities.

Several studies provide evidence for the antioxidant properties of EGb 761. It can scavenge ROS, such as hxdroxy radicals, peroxy radicals, superoxide anions as well as nitric oxide (46, 157). Schindowski *et al*. (147) showed a significant reduction of ROS-induced apoptosis by EGb 761 in T-lymphocytes. Three- and 24-month-old female NMRI mice were treated with 100 mg/kg BW EGb 761 per os over a period of 2 weeks. This dose has been previously shown to improve learning deficits in aged mice (159). *Ex vivo* ROS-induced apoptosis in isolated T-lymphocytes triggered by treatment with d-ribose was significantly reduced in young and old mice. Interestingly, lymphocytes from old animals revealed a significantly higher protection by EGb 761 than cells from young mice. In line with our experiments, Wu *et al*. (182) found increased resistance to oxidative stress in EGb 761-treated wild type *C. elegans* worms. Furthermore, EGb 761 extended the median life span of these worms by 8%. In prematurely aging mutant worms, *Ginkgo biloba* extract also increased the resistance to oxidative stress. In another study with *C. elegans*, EGb 761 protected worms by increasing the resistance to oxidative stress and the attenuation of ROS accumulation (76). Moreover, an increase in catalase and SOD activities in the hippocampus, striatum, and substantia nigra of rats could be detected and lipid peroxidation was decreased in the hippocampus of rats after the treatment with EGb 761 (21). In addition, in AD-relevant models like a neuroblastoma cell line stably expressing Sw APP695/PS1 mutations as well as transgenic *C. elegans* constitutively expressing human Aβ, EGb 761 attenuates basal as well as the induced levels of H_2O_2-related ROS (156).The extract's flavonoid fraction was implicated in these protections. Smith and Luo (156) showed a direct attenuation of ROS by the flavonoid fraction of EGb 761. The extract scavenges directly and preferentially hydroxyl radicals (188). Additional antioxidant properties of EGb 761 can be explained by flavonoids chelating prooxidant transitional metal ions (*e.g.*, Fe^{2+}) (55) and therefore consequently inhibiting the generation of new hydroxyl radicals. Other results indicate an involvement of antioxidant enzymes. The flavonoids attenuate the expres-

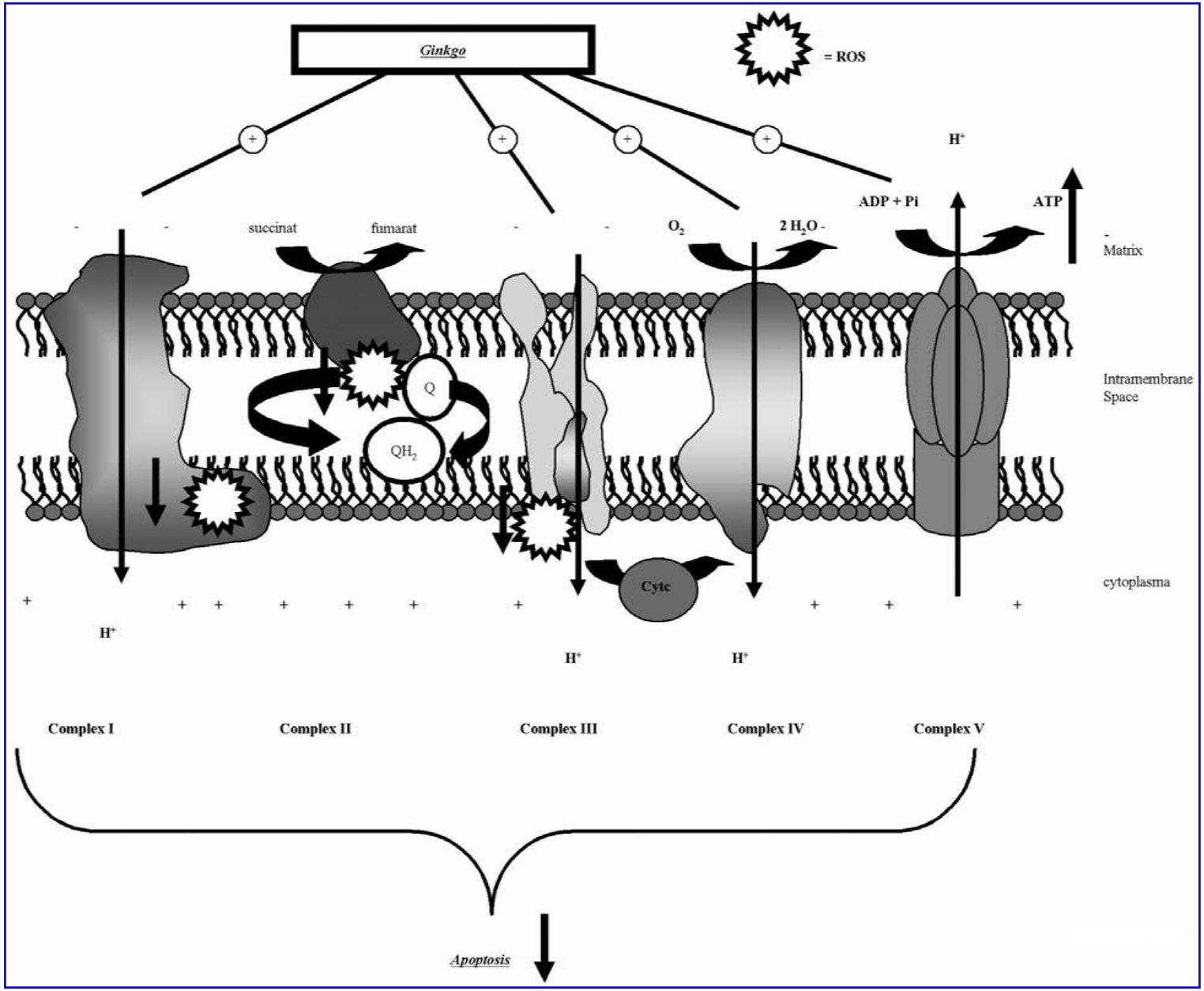


FIG. 6. Effect of EGb 761 on mitochondrial dysfunction and oxidative stress *in vitro*. EGb 761 protects all five complexes of the respiratory chain in PC12 cells (10 μg/ml) and dissociated brain cells (0.5 mg/ml). These effects probably lead to a decrease in ROS and a reduction in apoptosis (1, 48).

sion of SOD and increase antioxidant metabolites such as glutathione (55). Furthermore, Ginkgo inhibits the age-dependent generation of NO via iNos in mouse microglia (180).

CONCLUSION AND FURTHER PERSPECTIVE

Impaired mitochondrial metabolism associated with respiratory chain dysfunction and the consequent oxidative stress is being considered as a possible pathogenic mechanism in a number of neurodegenerative diseases, including AD. In contrast to Aβ plaques and tau tangles seen in the late stage of AD, mitochondrial dysfunction and oxidative stress are two early events in the pathology of AD, cumulating with aging-associated changes in mitochondrial function and oxidative stress. Aβ-mediated complex IV impairment, together with complex I, III, and IV reduced activities in aging, lead to severe changes in mitochondrial energy supply. The changes result in a vicious cycle inducing electrons leakage from the ETC leading to enhanced production of ROS. These elevated levels of ROS themselves damage ETC components and mtDNA and further increase mitochondrial dysfunction and oxidative stress. When phenotypic threshold and severe energy deprivation is reached, neuronal and synaptic dysfunction can appear. Thus, both mitochondrial dysfunction and oxidative stress clearly play an important role in the pathogenesis of AD. Nevertheless, the precise mechanism of events in AD pathogenesis still remains uncertain.

Current available drug treatment for AD is symptomatic with no beneficial effect on progressive underlying disease processes. Growing evidence for the existence of oxidative stress and the accumulation of free radicals in the brains of AD patients has led to the notion of antioxidants as a potential treatment. Antioxidant therapies hold promise for improving mitochondrial performance; however, medicine still has large gaps in its knowledge of which types and ratios of antioxidants, and in which forms, will result in the best outcomes. *In vitro* and animal model studies support the potential beneficial role of various antioxidant compounds such as *Ginkgo biloba* extract in neurologic disease. Our own results and several other studies show that EGb 761 acts as a scavenger of ROS. In addition, further experiments demonstrated that *Ginkgo biloba* extract stabilizes mitochondrial function in aging and AD. This effect can be explained by the protection of different respiratory chain complexes. Current data on the impact of pure antioxidant supplements (*e.g.*, vitamin E or C) showed only very moderate efficacy in the treatment and the prevention of AD (20). Therefore, we propose that mitochondrial protecting properties of *Ginkgo biloba* extract are more important for the treatment of different forms of dementia and that treatment with *Ginkgo biloba* extract in an early stage of the disease could be a promising concept for AD prevention and treatment.

ABBREVIATIONS

Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; CAT, catalase; COX, cytochrome c oxidase; CoQ, coenzyme Q; oxo^{8}dG, 8-oxo-2′-deoxyguanosine; FAD, familial Alzheimer's disease; GPx, glutathione peroxidase; GR, glutathione reductase; HNE, 4-hydroxynonenal; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde; MnSOD, manganese superoxide dismutase; mtDNA, mitochondrial DNA; PS, presenilin; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; SNP, sodium nitroprusside.

REFERENCES

1. Abdel–Kader RM, Scherping I, Hauptmann S, Keil U, and Müller WE. Protective effects of *Ginkgo biloba* extract in different animal models. *Naunyn Schmiedebergs Arch Exp Pathol Pharmakol* 372: 294, 2006.
2. Abdul HM, Sultana R, Keller JN, St Clair DK, Markesbery WR, and Butterfield DA. Mutations in amyloid precursor protein and presenilin-1 genes increase the basal oxidative stress in murine neuronal cells and lead to increased sensitivity to oxidative stress mediated by amyloid beta-peptide (1-42), H2O2 and kainic acid: implications for Alzheimer's disease. *J Neurochem* 96: 1322–1335, 2006.
3. Adams DO and Hamilton TA. The cell biology of macrophage activation. *Annu Rev Immunol* 2: 283–318, 1984.
4. Agin V, Chicher R, and Chichery MP. Effects of learning on cytochrome oxidase activity in cuttlefish brain. *Neuroreport* 12: 113–116, 2001.
5. Aksenov MY, Tucker HM, Nair P, Aksenova MV, Butterfield DA, Estus S, and Markesbery WR. The expression of key oxidative stress-handling genes in different brain regions in Alzheimer's disease. *J Mol Neurosci* 11: 151–164, 1998.
6. Aleardi AM, Benard G, Augereau O, Malgat M, Talbot JC, Mazat JP, Letellier T, Dachary–Prigent J, Solaini GC, and Rossignol R. Gradual alteration of mitochondrial structure and function by beta-amyloids: importance of membrane viscosity changes, energy deprivation, reactive oxygen species production, and cytochrome c release. *J Bioenerg Biomembr* 37: 207–225, 2005.
7. Anandatheerthavarada HK, Biswas G, Robin MA, and Avadhani NG. Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. *J Cell Biol* 161: 41–54, 2003.
8. Andreyev AI, Kushnareva YE, and Starkov AA. Mitochondrial metabolism of reactive oxygen species. *Biochemistry-Moscow* 70: 200–214, 2005.
9. Baek BS, Kwon HJ, Lee KH, Yoo MA, Kim KW, Ikeno Y, Yu BP, and Chung HY. Regional difference of ROS generation, lipid peroxidation, and antioxidant enzyme activity in rat brain and their dietary modulation. *Arch Pharm Res* 22: 361–366, 1999.
10. Balaban RS, Nemoto S, and Finkel T. Mitochondria, oxidants, and aging. *Cell* 120: 483–495, 2005.
11. Benzi G, Pastoris O, Marzatico F, Villa RF, Dagani F, and Curti D. The mitochondrial electron transfer alteration as a factor involved in the brain aging. *Neurobiol Aging* 13: 361–368, 1992.
12. Berndt JD, Callaway NL, and Gonzalez–Lima F. Effects of chronic sodium azide on brain and muscle cytochrome oxidase activity: a potential model to investigate environmental contributions to neurodegenerative diseases. *J Toxicol Environ Health A* 63: 67–77, 2001.
13. Birks J. Is *Ginkgo biloba* effective and safe for dementia and cognitive impairment? *Neuroepidemiology* 23: 150, 2004.
14. Birks J, Grimley EV, and Van Dongen M. *Ginkgo biloba* for cognitive impairment and dementia. *Cochrane Database Syst Rev* CD003120, 2002.
15. Birks J and Grimley EJ. *Ginkgo biloba* for cognitive impairment and dementia. *Cochrane Database Syst Rev* CD003120, 2007.
16. Bishop GM and Robinson SR. Human Abeta1-42 reduces iron-induced toxicity in rat cerebral cortex. *J Neurosci Res* 73: 316–323, 2003.
17. Blanchard V, Moussaoui S, Czech C, Touchet N, Bonici B, Planche M, Canton T, Jedidi I, Gohin M, Wirths O, Bayer TA,

Langui D, Duyckaerts C, Tremp G, and Pradier L. Time sequence of maturation of dystrophic neurites associated with A beta deposits in APP/PS1 transgenic mice. *Exp Neurol* 184: 247–263, 2003.
18. Blass JP. Cerebrometabolic abnormalities in Alzheimer's disease. *Neurol Res* 25: 556–566, 2003.
19. Blass JP, Gibson GE, and Hoyer S. The role of the metabolic lesion in Alzheimer's disease. *J Alzheimers Dis* 4: 225–232, 2002.
20. Boothby LA and Doering PL. Vitamin C and vitamin E for Alzheimer's disease. *Ann Pharmacother* 39: 2073–2080, 2005.
21. Bridi R, Crossetti FP, Steffen VM, and Henriques AT. The antioxidant activity of standardized extract of *Ginkgo biloba* (EGb 761) in rats. *Phytother Res* 15: 449–451, 2001.
22. Butterfield DA, Poon HF, Clair DS, Keller JN, Pierce WM, Klein JB, and Markesbery WR. Redox proteomics identification of oxidatively modified hippocampal proteins in mild cognitive impairment: Insights into the development of Alzheimer's disease. *Neurobiol Dis* 22: 223–232, 2006.
23. Cada A, Gonzalez–Lima F, Rose GM, and Bennett MC. Regional brain effects of sodium azide treatment on cytochrome oxidase activity: a quantitative histochemical study. *Metab Brain Dis* 10: 303–320, 1995.
24. Campion D, Flaman JM, Brice A, Hannequin D, Dubois B, Martin C, Moreau V, Charbonnier F, Didierjean O, Tardieu S, Penet C, Puel M, Pasquier F, Ledoze F, Bellis G, Calenda A, Heilig R, Martinez M, Mallet J, Bellis M, Clergetdarpoux F, Agid Y, and Frebourg T. Mutations of the presenilin-I gene in families with early-onset Alzheimers disease. *Hum Mol Genet* 4: 2373–2377, 1995.
25. Cardoso SM, Proenca MT, Santos S, Santana I, and Oliveira CR. Cytochrome c oxidase is decreased in Alzheimer's disease platelets. *Neurobiol Aging* 25: 105–110, 2004.
26. Carney JM, Starke–Reed PE, Oliver CN, Landum RW, Cheng MS, Wu JF, and Floyd RA. Reversal of age-related increase in brain protein oxidation, decrease in enzyme activity, and loss in temporal and spatial memory by chronic administration of the spin-trapping compound N-tert-butyl-alpha-phenylnitrone. *Proc Natl Acad Sci USA* 88: 3633–3636, 1991.
27. Casley CS, Canevari L, Land JM, Clark JB, and Sharpe MA. beta-Amyloid inhibits integrated mitochondrial respiration and key enzyme activities. *J Neurochem* 80: 91–100, 2002.
28. Caspersen C, Wang N, Yao J, Sosunov A, Chen X, Lustbader JW, Xu HW, Stern D, McKhann G, and Yan SD. Mitochondrial Abeta: a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. *FASEB J* 19: 2040–2041, 2005.
29. Castegna A, Aksenov M, Aksenova M, Thongboonkerd V, Klein JB, Pierce WM, Booze R, Markesbery WR, and Butterfield DA. Proteomic identification of oxidatively modified proteins in Alzheimer's disease brain. Part 1: Creatine kinase bb, glutamine synthase, and ubiquitin carboxy-terminal hydrolase L-1. *Free Radical Biol Med* 33: 562–571, 2002.
30. Castegna A, Aksenov M, Thongboonkerd V, Klein JB, Pierce WM, Booze R, Markesbery WR, and Butterfield DA. Proteomic identification of oxidatively modified proteins in Alzheimer's disease brain. Part II: dihydropyrimidinase-related protein 2, alpha-enolase and heat shock cognate 71. *J Neurochem* 82: 1524–1532, 2002.
31. Chagnon P, Betard C, Robitaille Y, Cholette A, and Gauvreau D. Distribution of brain cytochrome oxidase activity in various neurodegenerative diseases. *Neuroreport* 6: 711–715, 1995.
32. Chandrasekaran K, Mehrabian Z, Spinnewyn B, Chinopoulos C, Drieu K, and Fiskum G. Bilobalide, a component of the *Ginkgo biloba* extract (EGb 761), protects against neuronal death in global brain ischemia and in glutamate-induced excitotoxicity. *Cell Mol Biol* 48: 663–669, 2002.
33. Chen Q, Vazquez EJ, Moghaddas S, Hoppel CL, and Lesnefsky EJ. Production of reactive oxygen species by mitochondria: central role of complex III. *J Biol Chem* 278: 36027–36031, 2003.
34. Chong ZZ, Li FQ, and Maiese K. Oxidative stress in the brain: Novel cellular targets that govern survival during neurodegenerative disease. *Progr Neurobiol* 75: 207–246, 2005.
35. Christen Y and Maixent JM. What is *Ginkgo biloba* extract EGb 761? An overview—From molecular biology to clinical medicine. *Cell Mol Biol* 48: 601–611, 2002.
36. Chui DH, Tanahashi H, Ozawa K, Ikeda S, Checler F, Ueda O, Suzuki H, Araki W, Inoue H, Shirotani K, Takahashi K, Gallyas F, and Tabira T. Transgenic mice with Alzheimer presenilin 1 mutations show accelerated neurodegeneration without amyloid plaque formation. *Nat Med* 5: 560–564, 1999.
37. Cleary JP, Walsh DM, Hofmeister JJ, Shankar GM, Kuskowski MA, Selkoe DJ, and Ashe KH. Natural oligomers of the amyloid-protein specifically disrupt cognitive function. *Nat Neurosci* 8: 79–84, 2005.
38. Colton CA, Chernyshev ON, Gilbert DL, and Vitek MP. Microglial contribution to oxidative stress in Alzheimer's disease. *Ann NY Acad Sci* 899: 292–307, 2000.
39. Cortopassi GA and Wong A. Mitochondria in organismal aging and degeneration. *Biochim Biophys Acta* 1410: 183–193, 1999.
40. Cottrell DA, Borthwick GM, Johnson MA, Ince PG, and Turnbull DM. The role of cytochrome c oxidase deficient hippocampal neurones in Alzheimer's disease. *Neuropathol Appl Neurobiol* 28: 390–396, 2002.
41. Coyle JT and Puttfarcken P. Oxidative stress, glutamate, and neurodegenerative disorders. *Science* 262: 689–695, 1993.
42. Crouch PJ, Blake R, Duce JA, Ciccotosto GD, Li QX, Barnham KJ, Curtain CC, Cherny RA, Cappai R, Dyrks T, Masters CL, and Trounce IA. Copper-dependent inhibition of human cytochrome c oxidase by a dimeric conformer of amyloid-beta1-42. *J Neurosci* 25: 672–679, 2005.
43. Culmsee C and Landshamer S. Molecular insights into mechanisms of the cell death program: role in the progression of neurodegenerative disorders. *Curr Alzheimer Res* 3: 269–283, 2006.
44. Czech C, Lesort M, Tremp G, Terro F, Blanchard V, Schombert B, Carpentier N, Dreisler S, Bonici B, Takashima A, Moussaoui S, Hugon J, and Pradier L. Characterization of human presenilin 1 transgenic rats: Increased sensitivity to apoptosis in primary neuronal cultures. *Neuroscience* 87: 325–336, 1998.
45. David DC, Hauptmann S, Scherping I, Schuessel K, Keil U, Rizzu P, Ravid R, Drose S, Brandt U, Muller WE, Eckert A, and Gotz J. Proteomic and functional analyses reveal a mitochondrial dysfunction in P301L Tau transgenic mice. *J Biol Chem* 280: 23802–23814, 2005.
46. Defeudis FV and Drieu K. *Ginkgo biloba* extract (EGb 761) and CNS functions: basic studies and clinical applications. *Curr Drug Targets* 1: 25–58, 2000.
47. Drake J, Link CD, and Butterfield DA. Oxidative stress precedes fibrillar deposition of Alzheimer's disease amyloid beta-peptide (1–42) in a transgenic Caenorhabditis elegans model. *Neurobiol Aging* 24: 415–420, 2003.
48. Eckert A, Keil U, Scherping I, Hauptmann S, and Muller WE. Stabilization of mitochondrial membrane potential and improvement of neuronal energy metabolism by *Ginkgo biloba* extract EGb 761. *Ann NY Acad Sci* 1056: 474–485, 2005.
49. Eckert A, Scherping I, Bonert A, Hauptmann S, Müller-Spahn F, Müller WE. Effects of age-related accumulation of amyloid on mitochondrial failure in APP transgenic mice. Program No. 206.1/2005 Abstract Viewer/Itinerary Planner./Washington, DC: Society for Neuroscience, 2005.
50. Eckert A, Steiner B, Marques C, Leutz S, Romig H, Haass C, and Muller WE. Elevated vulnerability to oxidative stress-induced cell death and activation of caspase-3 by the Swedish amyloid precursor protein mutation. *J Neurosci Res* 64: 183–192, 2001.
51. Elson JL, Herrnstadt C, Preston G, Thal L, Morris CM, Edwardson JA, Beal MF, Turnbull DM, and Howell N. Does the mitochondrial genome play a role in the etiology of Alzheimer's disease? *Hum Genet* 119: 241–254, 2006.
52. Fath T, Eidenmuller J, and Brandt R. Tau-mediated cytotoxicity in a pseudohyperphosphorylation model of Alzheimer's disease. *J Neurosci* 22: 9733–9741, 2002.
53. Floyd RA and Hensley K. Oxidative stress in brain aging. Implications for therapeutics of neurodegenerative diseases. *Neurobiol Aging* 23: 795–807, 2002.
54. Goate A, Chartier–Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 349: 704–706, 1991.
55. Gohil K and Packer L. Bioflavonoid-rich botanical extracts show

antioxidant and gene regulatory activity. *Ann NY Acad Sci* 957: 70–77, 2002.
56. Gotz J, Chen F, Barmettler R, and Nitsch RM. Tau filament formation in transgenic mice expressing P301L tau. *J Biol Chem* 276: 529–534, 2001.
57. Gotz J, Chen F, van Dorpe J, and Nitsch RM. Formation of neurofibrillary tangles in P301l tau transgenic mice induced by Abeta 42 fibrils. *Science* 293: 1491–1495, 2001.
58. Guidi I, Galimberti D, Lonati S, Novembrino C, Bamonti F, Tiriticco M, Fenoglio C, Venturelli E, Baron P, Bresolin N, and Scarpini E. Oxidative imbalance in patients with mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 27: 262–269, 2006.
59. Guo Q, Sebastian L, Sopher BL, Miller MW, Ware CB, Martin GM, and Mattson MP. Increased vulnerability of hippocampal neurons from presenilin-1 mutant knock-in mice to amyloid beta-peptide toxicity: Central roles of superoxide production and caspase activation. *J Neurochem* 72: 1019–1029, 1999.
60. Guo Q, Sopher BL, Furukawa K, Pham DG, Robinson N, Martin GM, and Mattson MP. Alzheimer's presenilin mutation sensitizes neural cells to apoptosis induced by trophic factor withdrawal and amyloid beta-peptide: Involvement of calcium and oxyradicals. *J Neurosci* 17: 4212–4222, 1997.
61. Haass C. Take five–-BACE and the gamma-secretase quartet conduct Alzheimer's amyloid beta-peptide generation. *EMBO J* 23: 483–488, 2004.
62. Haass C and Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. *Nat Rev Mol Cell Biol* 8: 101–112, 2007.
63. Halliwell B. Oxidative stress and neurodegeneration: where are we now? *J Neurochem* 97: 1634–1658, 2006.
64. Hardy J and Selkoe DJ. Medicine–-The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. *Science* 297: 353–356, 2002.
65. Harman D. Aging–-a theory based on free-radical and radiation chemistry. *J Gerontol* 11: 298–300, 1956.
66. Harper ME, Bevilacqua L, Hagopian K, Weindruch R, and Ramsey JJ. Ageing, oxidative stress, and mitochondrial uncoupling. *Acta Physiol Scand* 182: 321–331, 2004.
67. Hauptmann S, Keil U, Scherping I, Bonert A, Eckert A, and Muller WE. Mitochondrial dysfunction in sporadic and genetic Alzheimer's disease. *Exp Gerontol* 41: 668–673, 2006.
68. Hensley K, Carney JM, Mattson MP, Aksenova M, Harris M, Wu JF, Floyd RA, and Butterfield DA. A model for beta-amyloid aggregation and neurotoxicity based on free-radical generation by the peptide, Relevance to Alzheimer-disease. *Proc Natl Acad Sci USA* 91: 3270–3274, 1994.
69. Hensley K, Hall N, Subramaniam R, Cole P, Harris M, Aksenov M, Aksenova M, Gabbita SP, Wu JF, Carney JM, Lovell M, Markesbery WR, and Butterfield DA. Brain regional correspondence between Alzheimers disease histopathology and biomarkers of protein oxidation. *J Neurochem* 65: 2146–2156, 1995.
70. Hirai K, Aliev G, Nunomura A, Fujioka H, Russell RL, Atwood CS, Johnson AB, Kress Y, Vinters HV, Tabaton M, Shimohama S, Cash AD, Siedlak SL, Harris PLR, Jones PK, Petersen RB, Perry G, and Smith MA. Mitochondrial abnormalities in Alzheimer's disease. *J Neurosci* 21: 3017–3023, 2001.
71. Hofer SM, Berg S, and Era P. Evaluating the interdependence of aging-related changes in visual and auditory acuity, balance, and cognitive functioning. *Psychol Aging* 18: 285–305, 2003.
72. Hoyer S. Brain glucose and energy metabolism abnormalities in sporadic Alzheimer disease. Causes and consequences: an update. *Exp Gerontol* 35: 1363–1372, 2000.
73. Janssens D, Delaive E, Remacle J, and Michiels C. Protection by bilobalide of the ischaemia-induced alterations of the mitochondrial respiratory activity. *Fundam Clin Pharmacol* 14: 193–201, 2000.
74. Johnston JM, Burnett P, Thomas AP, and Tezapsidis N. Calcium oscillations in type-1 astrocytes, the effect of a presenilin 1 (PS1) mutation. *Neurosci Lett* 395: 159–164, 2006.
75. Judge S, Jang YM, Smith A, Hagen T, and Leeuwenburgh C. Age-associated increases in oxidative stress and antioxidant enzyme activities in cardiac interfibrillar mitochondria: implications for the mitochondrial theory of aging. *FASEB J* 19: 419–421, 2005.
76. Kampkotter A, Pielarski T, Rohrig R, Timpel C, Chovolou Y, Watjen W, and Kahl R. The *Ginkgo biloba* extract EGb761 reduces stress sensitivity, ROS accumulation and expression of catalase and glutathione S-transferase 4 in Caenorhabditis elegans. *Pharmacol Res* 55: 139–147, 2007.
77. Keil U, Bonert A, Marques CA, Scherping I, Weyermann J, Strosznajder JB, Muller-Spahn F, Haass C, Czech C, Pradier L, Muller WE, and Eckert A. Amyloid beta-induced changes in nitric oxide production and mitochondrial activity lead to apoptosis. *J Biol Chem* 279: 50310–50320, 2004.
78. Keil U, Bonert A, Marques CA, Scherping I, Weyermann JR, Strosznajder JB, Muller–Spahn F, Haass C, Czech C, Pradier L, Muller WE, and Eckert A. Amyloid beta-induced changes in nitric oxide production and mitochondrial activity lead to apoptosis. *J Biol Chem* 279: 50310–50320, 2004.
79. Keil U, Bonert A, Marques CA, Strosznajder JB, Muller–Spahn F, Muller WE, and Eckert A. Elevated nitric oxide production mediates beta-amyloid-induced mitochondria failure. *Pol J Pharmacol* 56: 631–634, 2004.
80. Keil U, Hauptmann S, Bonert A, Scherping I, Eckert A, and Muller WE. Mitochondrial dysfunction induced by disease relevant A beta PP and tau protein mutations. *J Alzheimers Dis* 9: 139–146, 2006.
81. Keller JN, Guo Q, Holtsberg FW, Bruce–Keller AJ, and Mattson MP. Increased sensitivity to mitochondrial toxin-induced apoptosis in neural cells expressing mutant presenilin-1 is linked to perturbed calcium homeostasis and enhanced oxyradical production. *Journal of Neuroscience* 18: 4439–4450, 1998.
82. Keller JN, Schmitt FA, Scheff SW, Ding Q, Chen Q, Butterfield DA, and Markesbery WR. Evidence of increased oxidative damage in subjects with mild cognitive impairment. *Neurology* 64: 1152–1156, 2005.
83. Kilb W, Hartmann D, Saftig P, and Luhmann HJ. Altered morphological and electrophysiological properties of Cajal–Retzius cells in cerebral cortex of embryonic Presenilin-1 knockout mice. *Eur J Neurosci* 20: 2749–2756, 2004.
84. Kim GW and Chan PH. Oxidative stress and neuronal DNA fragmentation mediate age-dependent vulnerability to the mitochondrial toxin, 3-nitropropionic acid, in the mouse striatum. *Neurobiol Dis* 8: 114–126, 2001.
85. Kimberly WT, Lavoie MJ, Ostaszewski BL, Ye WJ, Wolfe MS, and Selkoe DJ. gamma-secretase is a membrane protein complex comprised of presenilin, nicastrin, aph-1, and pen-2. *Proc Natl Acad Sci U S A* 100: 6382–6387, 2003.
86. Kish SJ, Bergeron C, Rajput A, Dozic S, Mastrogiacomo F, Chang LJ, Wilson JM, DiStefano LM, and Nobrega JN. Brain cytochrome oxidase in Alzheimer's disease. *J Neurochem* 59: 776–779, 1992.
87. Kontush A, Donarski N, and Beisiegel U. Resistance of human cerebrospinal fluid to in vitro oxidation is directly related to its amyloid-beta content. *Free Radic Res* 35: 507–517, 2001.
88. Kumaran S, Subathra M, Balu M, and Panneerselvam C. Supplementation of L-carnitine improves mitochondrial enzymes in heart and skeletal muscle of aged rats. *Exp Aging Res* 31: 55–67, 2005.
89. Kushnareva Y, Murphy AN, and Andreyev A. Complex I-mediated reactive oxygen species generation: modulation by cytochrome c and NAD(P)+ oxidation-reduction state. *Biochem J* 368: 545–553, 2002.
90. Le Bars PL. Magnitude of effect and special approach to *Ginkgo biloba* extract EGb 761 in cognitive disorders. *Pharmacopsychiatry* 36 Suppl 1: S44–S49, 2003.
91. Le Bars PL, Katz MM, Berman N, Itil TM, Freedman AM, and Schatzberg AF. A placebo-controlled, double-blind, randomized trial of an extract of *Ginkgo biloba* for dementia. North American EGb Study Group. *JAMA* 278: 1327–1332, 1997.
92. Lee HC, Lim ML, Lu CY, Liu VW, Fahn HJ, Zhang C, Nagley P, and Wei YH. Concurrent increase of oxidative DNA damage and lipid peroxidation together with mitochondrial DNA mutation in human lung tissues during aging–-smoking enhances oxidative stress on the aged tissues. *Arch Biochem Biophys* 362: 309–316, 1999.
93. Lenaz G, Bovina C, Castelluccio C, Fato R, Formiggini G, Genova ML, Marchetti M, Pich MM, Pallotti F, Parenti CG, and Bi-

agini G. Mitochondrial complex I defects in aging. *Mol Cell Biochem* 174: 329–333, 1997.
94. Leutner S, Eckert A, and Muller WE. ROS generation, lipid peroxidation and antioxidant enzyme activities in the aging brain. *J Neural Transm* 108: 955–967, 2001.
95. Leutz S, Steiner B, Marques CA, Haass C, Muller WE, and Eckert A. Reduction of trophic support enhances apoptosis in PC12 cells expressing Alzheimer's APP mutation and sensitizes cells to staurosporine-induced cell death. *J Mol Neurosci* 18: 189–201, 2002.
96. Lin MT and Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 443: 787–795, 2006.
97. Liu J, Killilea DW, and Ames BN. Age-associated mitochondrial oxidative decay: improvement of carnitine acetyltransferase substrate-binding affinity and activity in brain by feeding old rats acetyl-L-carnitine and/or R-alpha-lipoic acid. *Proc Natl Acad Sci USA* 99: 1876–1881, 2002.
98. Lleo A, Berezovska O, Growdon JH, and Hyman BT. Clinical, pathological, and biochemical spectrum of Alzheimer disease associated with PS-1 mutations. *Am J Geriatr Psychiatry* 12: 146–156, 2004.
99. Lue LF, Kuo YM, Roher AE, Brachova L, Shen Y, Sue L, Beach T, Kurth JH, Rydel RE, and Rogers J. Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease. *Am J Pathol* 155: 853-862, 1999.
100. Luo Y. *Ginkgo biloba* neuroprotection: Therapeutic implications in Alzheimer's disease. *J Alzheimers Dis* 3: 401-407, 2001.
101. Lustbader JW, Cirilli M, Lin C, Xu HW, Takuma K, Wang N, Caspersen C, Chen X, Pollak S, Chaney M, Trinchese F, Liu S, Gunn-Moore F, Lue LF, Walker DG, Kuppusamy P, Zewier ZL, Arancio O, Stern D, Yan SS, and Wu H. ABAD directly links Abeta to mitochondrial toxicity in Alzheimer's disease. *Science* 304: 448–452, 2004.
102. Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, and Reddy PH. 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, 2006.
103. Manczak M, Jung Y, Park BS, Partovi D, and Reddy PH. Time-course of mitochondrial gene expressions in mice brains: implications for mitochondrial dysfunction, oxidative damage, and cytochrome c in aging. *J Neurochem* 92: 494–504, 2005.
104. Manczak M, Park BS, Jung Y, and Reddy PH. Differential expression of oxidative phosphorylation genes in patients with Alzheimer's disease: implications for early mitochondrial dysfunction and oxidative damage. *Neuromolecular Med* 5: 147–162, 2004.
105. Marques CA, Keil U, Bonert A, Steiner B, Haass C, Muller WE, and Eckert A. Neurotoxic mechanisms caused by the Alzheimer's disease-linked Swedish amyloid precursor protein mutation—Oxidative stress, caspases, and the JNK pathway. *J Biol Chem* 278: 28294–28302, 2003.
106. Martinez M, Ferrandiz ML, De Juan E, and Miquel J. Age-related changes in glutathione and lipid peroxide content in mouse synaptic mitochondria: relationship to cytochrome c oxidase decline. *Neurosci Lett* 170: 121–124, 1994.
107. Mattson MP. Pathways towards and away from Alzheimer's disease (vol 430, pg 631, 2004). *Nature* 431: 107, 2004.
108. Mattson MP, Chan SL, and Duan WZ. Modification of brain aging and neurodegenerative disorders by genes, diet, and behavior. *Physiol Rev* 82: 637–672, 2002.
109. Mattson MP and Magnus T. Ageing and neuronal vulnerability. *Nat Rev Neurosci* 7: 278–294, 2006.
110. Mazza M, Capuano A, Bria P, and Mazza S. *Ginkgo biloba* and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. *Eur J Neurol* 13: 981-985, 2006.
111. McCarroll SA, Murphy CT, Zou S, Pletcher SD, Chin CS, Jan YN, Kenyon C, Bargmann CI, and Li H. Comparing genomic expression patterns across species identifies shared transcriptional profile in aging. *Nat Genet* 36: 197–204, 2004.
112. Migliore L, Fontana I, Trippi F, Colognato R, Coppede F, Tognoni G, Nucciarone B, and Siciliano G. Oxidative DNA damage in peripheral leukocytes of mild cognitive impairment and AD patients. *Neurobiol Aging* 26: 567–573, 2005.
113. Mo JQ, Hom DG, and Andersen JK. Decreases in protective enzymes correlates with increased oxidative damage in the aging mouse brain. *Mech Ageing Dev* 81: 73–82, 1995.
114. Murray IVJ, Sindoni ME, and Axelsen PH. Promotion of oxidative lipid membrane damage by amyloid beta proteins. *Biochemistry* 44: 12606–12613, 2005.
115. Mutisya EM, Bowling AC, and Beal MF. Cortical cytochrome oxidase activity is reduced in Alzheimer's disease. *J Neurochem* 63: 2179–2184, 1994.
116. Nakahara H, Kanno T, Inai Y, Utsumi K, Hiramatsu M, Mori A, and Packer L. Mitochondrial dysfunction in the senescence accelerated mouse (SAM). *Free Radic Biol Med* 24: 85–92, 1998.
117. Napryeyenko O and Borzenko I. *Ginkgo biloba* special extract in dementia with neuropsychiatric features. A randomised, placebo-controlled, double-blind clinical trial. *Arzneimittelforschung* 57: 4–11, 2007.
118. Naslund J, Haroutunian V, Mohs R, Davis KL, Davies P, Greengard P, and Buxbaum JD. Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline. *JAMA* 283: 1571–1577, 2000.
119. Navarro A and Boveris A. Rat brain and liver mitochondria develop oxidative stress and lose enzymatic activities on aging. *Am J Physiol Regul Integr Comp Physiol* 287: R1244–R1249, 2004.
120. Navarro A and Boveris A. The mitochondrial energy transduction system and the aging process. *Am J Physiol Cell Physiol* 292: C670–C686, 2007.
121. Navarro A, Gomez C, Lopez-Cepero JM, and Boveris A. Beneficial effects of moderate exercise on mice aging: survival, behavior, oxidative stress, and mitochondrial electron transfer. *Am J Physiol Regul Integr Comp Physiol* 286: R505–R511, 2004.
122. Navarro A, Gomez C, Sanchez–Pino MJ, Gonzalez H, Bandez MJ, Boveris AD, and Boveris A. Vitamin E at high doses improves survival, neurological performance, and brain mitochondrial function in aging male mice. *Am J Physiol Regul Integr Comp Physiol* 289: R1392–R1399, 2005.
123. Navarro A, Sanchez Del Pino MJ, Gomez C, Peralta JL, and Boveris A. Behavioral dysfunction, brain oxidative stress, and impaired mitochondrial electron transfer in aging mice. *Am J Physiol Regul Integr Comp Physiol* 282: R985–R992, 2002.
124. Newman M, Musgrave FI, and Lardelli M. Alzheimer disease: Amyloidogenesis, the presenilins and animal models. *Biochim Biophys Acta* 1772: 285–297, 2007.
125. Newman SF, Sultana R, Perluigi M, Coccia R, Cai J, Pierce WM, Klein JB, Turner DM, and Butterfield DA. An increase in S-glutathionylated proteins in the Alzheimer's disease inferior parietal lobule, a proteomics approach. *J Neurosci Res* 85: 1506–1514, 2007.
126. Nunomura A, Castellani RJ, Zhu XW, Moreira PI, Perry G, and Smith MA. Involvement of oxidative stress in Alzheimer disease. *J Neuropathol Exp Neurol* 65: 631–641, 2006.
127. Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, Jones PK, Ghanbari H, Wataya T, Shimohama S, Chiba S, Atwood CS, Petersen RB, and Smith MA. Oxidative damage is the earliest event in Alzheimer disease. *J Neuropathol Exp Neurol* 60: 759–767, 2001.
128. Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, and LaFerla FM. Triple-transgenic model of Alzheimer's disease with plaques and tangles: Intracellular A beta and synaptic dysfunction. *Neuron* 39: 409–421, 2003.
129. Oddo S, Caccamo A, Tran L, Lambert MP, Glabe CG, Klein WL, and LaFerla FM. Temporal profile of amyloid-beta (Abeta) oligomerization in an in vivo model of Alzheimer disease. A link between Abeta and tau pathology. *J Biol Chem* 281: 1599–1604, 2006.
130. Opazo C, Huang X, Cherny RA, Moir RD, Roher AE, White AR, Cappai R, Masters CL, Tanzi RE, Inestrosa NC, and Bush AI. Metalloenzyme-like activity of Alzheimer's disease beta-amyloid. Cu-dependent catalytic conversion of dopamine, cholesterol, and

biological reducing agents to neurotoxic H(2)O(2). *J Biol Chem* 277: 40302–40308, 2002.
131. Oxenkrug GF and Requintina PJ. Mating attenuates aging-associated increase of lipid peroxidation activity in C57BL/6J mice. *Ann NY Acad Sci* 993: 161–167, 2003.
132. Pansarasa O, Bertorelli L, Vecchiet J, Felzani G, and Marzatico F. Age-dependent changes of antioxidant activities and markers of free radical damage in human skeletal muscle. *Free Radic Biol Med* 27: 617–622, 1999.
133. Perry G, Nunomura A, Hirai K, Takeda A, Aliev G, and Smith MA. Oxidative damage in Alzheimer's disease: the metabolic dimension. *Int J Dev Neurosci* 18: 417–421, 2000.
134. Poon HF, Calabrese V, Scapagnini G, and Butterfield DA. Free radicals and brain aging. *Clin Geriatr Med* 20: 329–359, 2004.
135. Pratico D. Peripheral biomarkers of oxidative damage in Alzheimer's disease: the road ahead. *Neurobiol Aging* 26: 581–583, 2005.
136. Pratico D, Uryu K, Leight S, Trojanoswki JQ, and Lee VM. Increased lipid peroxidation precedes amyloid plaque formation in an animal model of Alzheimer amyloidosis. *J Neurosci* 21: 4183–4187, 2001.
137. Rapoport M, Dawson HN, Binder LI, Vitek MP, and Ferreira A. Tau is essential to beta-amyloid-induced neurotoxicity. *Proc Natl Acad Sci USA* 99: 6364–6369, 2002.
138. Ravindranath V, Shivakumar BR, and Anandatheerthavarada HK. Low glutathione levels in brain regions of aged rats. *Neurosci Lett* 101: 187–190, 1989.
139. Richter C, Park JW, and Ames BN. Normal oxidative damage to mitochondrial and nuclear DNA is extensive. *Proc Natl Acad Sci USA* 85: 6465–6467, 1988.
140. Rinaldi P, Polidori MC, Metastasio A, Mariani E, Mattioli P, Cherubini A, Catani M, Cecchetti R, Senin U, and Mecocci P. Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease. *Neurobiol Aging* 24: 915–919, 2003.
141. Rodrigo J, Fernandez–Vizarra P, Castro–Blanco S, Bentura ML, Nieto M, Gomez–Isla T, Martinez–Murillo R, Martinez A, Serrano J, and Fernandez AP. Nitric oxide in the cerebral cortex of amyloid-precursor protein (SW) Tg2576 transgenic mice. *Neuroscience* 128: 73–89, 2004.
142. Rodrigues SI, Fochesatto C, da ST I, Dalmaz C, and Alexandre NC. Aging affects oxidative state in hippocampus, hypothalamus and adrenal glands of Wistar rats. *Life Sci* 78: 271–278, 2005.
143. Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, Chi H, Lin C, Holman K, Tsuda T, and Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* 376: 775–778, 1995.
144. Sadowski M, Pankiewicz J, Scholtzova H, Yong J, Quartermain D, Jensen CH, Duff K, Nixon RA, Gruen RJ, and Wisniewski T. Amyloid-beta deposition is associated with decreased hippocampal glucose metabolism and spatial memory impairment in APP/PS1 mice. *J Neuropathol Exp Neurol* 63: 418–428, 2004.
145. Sastre J, Millan A, delaAsuncion JG, Pla R, Juan G, Pallardo FV, OConnor E, Martin JA, Droy Lefaix MT, and Vina J. A *Ginkgo biloba* extract (EGb 761) prevents mitochondrial aging by protecting against oxidative stress. *Free Radic Biol Med* 24: 298–304, 1998.
146. Schaffer S, Eckert GP, Schmitt–Schillig S, and Muller WE. Plant foods and brain aging: a critical appraisal. *Forum Nutr* 59: 86–115, 2006.
147. Schindowski K, Leutner S, Kressmann S, Eckert A, and Muller WE. Age-related increase of oxidative stress-induced apoptosis in mice—Prevention by *Ginkgo biloba* extract (EGb761). *J Neural Transm* 108: 969–978, 2001.
148. Schriner SE, Linford NJ, Martin GM, Treuting P, Ogburn CE, Emond M, Coskun PE, Ladiges W, Wolf N, Van Remmen H, Wallace DC, and Rabinovitch PS. Extension of murine life span by overexpression of catalase targeted to mitochondria. *Science* 308: 1909–1911, 2005.
149. Schuessel K, Frey C, Jourdan C, Keil U, Weber CC, Muller–Spahn F, Muller WE, and Eckert A. Aging sensitizes toward ROS formation and lipid peroxidation in PS1M146L transgenic mice. *Free Radic Biol Med* 40: 850–862, 2006.
150. Schuessel K, Schafer S, Bayer TA, Czech C, Pradier L, Muller–Spahn F, Muller WE, and Eckert A. Impaired Cu/Zn-SOD activity contributes to increased oxidative damage in APP transgenic mice. *Neurobiol Dis* 18: 89–99, 2005.
151. Schussel K, Leutner S, Cairns NJ, Czech C, Pradier L, Muller WE, and Eckert A. Antioxidative defence capacity in sporadic Alzheimer's disease and in transgenic mice overexpressing amyloid-beta. *Naunyn-Schmiedebergs Archives Pharmacol* 367: R87, 2003.
152. Shemyakov SE and Mikhailova EV. The dynamics of morphological measures and lipid peroxidation during aging of the cerebral cortex in humans. *Neurosci Behav Physiol* 33: 195–197, 2003.
153. Shigenaga MK, Hagen TM, and Ames BN. Oxidative damage and mitochondrial decay in aging. *Proc Natl Acad Sci USA* 91: 10771–10778, 1994.
154. Shin CM, Chung YH, Kim MJ, Lee EY, Kim EG, and Cha CI. Age-related changes in the distribution of nitrotyrosine in the cerebral cortex and hippocampus of rats. *Brain Res* 931: 194–199, 2002.
155. Sisodia SS, Annaert W, Kim SH, and De Strooper B. Gamma-secretase: never more enigmatic. *Trends Neurosci* 24: S2–S6, 2001.
156. Smith JV and Luo Y. Elevation of oxidative free radicals in Alzheimer's disease models can be attenuated by *Ginkgo biloba* extract EGb 761. *J Alzheimers Dis* 5: 287–300, 2003.
157. Smith JV and Luo Y. Elevation of oxidative free radicals in Alzheimer's disease models can be attenuated by *Ginkgo biloba* extract EGb 761. *J Alzheimers Dis* 5: 287–300, 2003.
158. Smith MA, Hirai K, Hsiao K, Pappolla MA, Harris PL, Siedlak SL, Tabaton M, and Perry G. Amyloid-beta deposition in Alzheimer transgenic mice is associated with oxidative stress. *J Neurochem* 70: 2212–2215, 1998.
159. Stoll S, Scheuer K, Pohl O, and Muller WE. *Ginkgo biloba* extract (EGb 761) independently improves changes in passive avoidance learning and brain membrane fluidity in the aging mouse. *Pharmacopsychiatry* 29: 144–149, 1996.
160. Sultana R, Boyd–Kimball D, Poon HF, Cai J, Pierce WM, Klein JB, Merchant M, Markesbery WR, and Butterfield DA. Redox proteomics identification of oxidized proteins in Alzheimer's disease hippocampus and cerebellum: an approach to understand pathological and biochemical alterations in AD. *Neurobiol Aging* 27: 1564–1576, 2006.
161. Sultana R, Perluigi M, and Butterfield DA. Protein oxidation and lipid peroxidation in brain of subjects with Alzheimer's disease: Insights into mechanism of neuro degeneration from redox proteomics. *Antioxid Redox Signal* 8: 2021–2037, 2006.
162. Sun JT, Folk D, Bradley TJ, and Tower J. Induced overexpression of mitochondrial Mn-superoxide dismutase extends the life span of adult Drosophila melanogaster. *Genetics* 161: 661–672, 2002.
163. Swerdlow RH, Parks JK, Cassarino DS, Maguire DJ, Maguire RS, Bennett JP, Jr., Davis RE, and Parker WD, Jr. Cybrids in Alzheimer's disease: a cellular model of the disease? *Neurology* 49: 918–925, 1997.
164. Takasugi N, Tomita T, Hayashi I, Tsuruoka M, Niimura M, Takahashi Y, Thinakaran G, and Iwatsubo T. The role of presenilin cofactors in the gamma-secretase complex. *Nature* 422: 438–441, 2003.
165. Tamagno E, Parola M, Bardini P, Piccini A, Borghi R, Guglielmotto M, Santoro G, Davit A, Danni O, Smith MA, Perry G, and Tabaton M. Beta-site APP cleaving enzyme up-regulation induced by 4-hydroxynonenal is mediated by stress-activated protein kinases pathways. *J Neurochem* 92: 628–636, 2005.
166. Tendi EA, Bosetti F, DasGupta SF, Stella AMG, Drieu K, and Rapoport SI. *Ginkgo biloba* extracts EGb 761 and bilobalide increase NADH dehydrogenase mRNA level and mitochondrial respiratory control ratio in PC12 cells. *Neurochem Res* 27: 319–323, 2002.
167. Tian L, Cai Q, and Wei H. Alterations of antioxidant enzymes and oxidative damage to macromolecules in different organs of rats during aging. *Free Radic Biol Med* 24: 1477–1484, 1998.
168. Trumbeckaite S, Bernatoniene J, Majiene D, Jakstas V, Savickas

A, and Toleikis A. Effect of *Ginkgo biloba* extract on the rat heart mitochondrial function. *J Ethnopharmacol* 2006.
169. Tsay HJ, Wang P, Wang SL, and Ku HH. Age-associated changes of superoxide dismutase and catalase activities in the rat brain. *J Biomed Sci* 7: 466–474, 2000.
170. Valla J, Berndt JD, and Gonzalez–Lima F. Energy hypometabolism in posterior cingulate cortex of Alzheimer's patients: superficial laminar cytochrome oxidase associated with disease duration. *J Neurosci* 21: 4923–4930, 2001.
171. van der Walt JM, Dementieva YA, Martin ER, Scott WK, Nicodemus KK, Kroner CC, Welsh–Bohmer KA, Saunders AM, Roses AD, Small GW, Schmechel DE, Murali DP, Gilbert JR, Haines JL, Vance JM, and Pericak–Vance MA. Analysis of European mitochondrial haplogroups with Alzheimer disease risk. *Neurosci Lett* 365: 28–32, 2004.
172. Velez–Pardo C, Arroyave ST, Lopera F, Castano AD, and Jimenez DR. Ultrastructure evidence of necrotic neural cell death in familial Alzheimer's disease brains bearing presenilin-1 E280A mutation. *J Alzheimers Dis* 3: 409–415, 2001.
173. Wallace DC. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. *Annu Rev Genet* 39: 359–407, 2005.
174. Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, and Selkoe DJ. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. *Nature* 416: 535–539, 2002.
175. Walsh DM, Klyubin I, Fadeeva JV, Rowan MJ, and Selkoe DJ. Amyloid-beta oligomers: their production, toxicity and therapeutic inhibition. *Biochem Soc Trans* 30: 552–557, 2002.
176. Ward WF, Qi W, Van Remmen H, Zackert WE, Roberts LJ, and Richardson A. Effects of age and caloric restriction on lipid peroxidation: measurement of oxidative stress by F2-isoprostane levels. *J Gerontol A Biol Sci Med Sci* 60: 847–851, 2005.
177. Watanabe CM, Wolffram S, Ader P, Rimbach G, Packer L, Maguire JJ, Schultz PG, and Gohil K. The in vivo neuromodulatory effects of the herbal medicine *Ginkgo biloba*. *Proc Natl Acad Sci USA* 98: 6577–6580, 2001.
178. Weihl CC, Ghadge GD, Kennedy SG, Hay N, Miller RJ, and Roos RP. Mutant presenilin-1 induces apoptosis and downregulates Akt PKB. *J Neurosci* 19: 5360–5369, 1999.
179. Wolozin B, Alexander P, and Palacino J. Regulation of apoptosis by presenilin 1. *Neurobiol Aging* 19: S23–S27, 1998.
180. Wong A, Dukic–Stefanovic S, Gasic–Milenkovic J, Schinzel R, Wiesinger H, Riederer P, and Munch G. Anti-inflammatory antioxidants attenuate the expression of inducible nitric oxide synthase mediated by advanced glycation endproducts in murine microglia. *Eur J Neurosci* 14: 1961–1967, 2001.
181. Wozniak A, Drewa G, Wozniak B, and Schachtschabel DO. Activity of antioxidant enzymes and concentration of lipid peroxidation products in selected tissues of mice of different ages, both healthy and melanoma-bearing. *Z Gerontol Geriatr* 37: 184–189, 2004.
182. Wu Z, Smith JV, Paramasivam V, Butko P, Khan I, Cypser JR, and Luo Y. *Ginkgo biloba* extract EGb 761 increases stress resistance and extends life span of Caenorhabditis elegans. *Cell Mol Biol (Noisy-le-grand)* 48: 725–731, 2002.
183. Yan LJ and Sohal RS. Mitochondrial adenine nucleotide translocase is modified oxidatively during aging. *Proc Natl Acad Sci USA* 95: 12896–12901, 1998.
184. Yan SD, Yan SF, Chen X, Fu J, Chen M, Kuppusamy P, Smith MA, Perry G, Godman GC, Nawroth P, and Non-enzymatically glycated tau in Alzheimer's disease induces neuronal oxidant stress resulting in cytokine gene expression and release of amyloid beta-peptide. *Nat Med* 1: 693–699, 1995.
185. Yang CS, Chou ST, Liu L, Tsai PJ, and Kuo JS. Effect of ageing on human plasma glutathione concentrations as determined by high-performance liquid chromatography with fluorimetric detection. *J Chromatogr B Biomed Appl* 674: 23–30, 1995.
186. Yao Z, Drieu K, and Papadopoulos V. The *Ginkgo biloba* extract EGb 761 rescues the PC12 neuronal cells from beta-amyloid-induced cell death by inhibiting the formation of beta-amyloid-derived diffusible neurotoxic ligands. *Brain Res* 889: 181–190, 2001.
187. Zaobornyj T, Valdez LB, La Padula P, Costa LE, and Boveris A. Effect of sustained hypobaric hypoxia during maturation and aging on rat myocardium. II. mtNOS activity. *J Appl Physiol* 98: 2370–2375, 2005.
188. Zimmermann M, Colciaghi F, Cattabeni F, and Di Luca M. *Ginkgo biloba* extract: from molecular mechanisms to the treatment of Alzhelmer's disease. *Cell Mol Biol (Noisy-le-grand)* 48: 613–623, 2002.

Address reprint requests to:
Kristina Leuner
Department of Pharmacology
Max-von-Laue-Strasse 9
60438 Frankfurt, Germany

E-mail: Leuner@em.uni-frankfurt.de

Date of first submission to ARS Central, May 30, 2007; date of acceptance, June 3, 2007.

This article has been cited by:

1. Rukhsana Sultana, Marzia Perluigi, D. Allan Butterfield. 2012. Lipid Peroxidation Triggers Neurodegeneration: A Redox Proteomics View into the Alzheimer Disease Brain. *Free Radical Biology and Medicine* . [CrossRef]
2. Deep Raj Sharma, Willayat Yousuf Wani, Aditya Sunkaria, Ramesh J. L. Kandimalla, Deepika Verma, Swaranjit Singh Cameotra, Kiran Dip Gill. 2012. Quercetin Protects Against Chronic Aluminum-Induced Oxidative Stress and Ensuing Biochemical, Cholinergic, and Neurobehavioral Impairments in Rats. *Neurotoxicity Research* . [CrossRef]
3. Walter E. Müller, Jeanine Heiser, Kristina Leuner. 2012. Effects of the standardized Ginkgo biloba extract EGb 761® on neuroplasticity. *International Psychogeriatrics* **24**:S1, S21-S24. [CrossRef]
4. Zhao Zhong Chong, Yan Chen Shang, Shaohui Wang, Kenneth Maiese. 2012. Shedding new light on neurodegenerative diseases through the mammalian target of rapamycin. *Progress in Neurobiology* . [CrossRef]
5. Kathrin L. Schulz, Anne Eckert, Virginie Rhein, Sören Mai, Winfried Haase, Andreas S. Reichert, Marina Jendrach, Walter E. Müller, Kristina Leuner. 2012. A New Link to Mitochondrial Impairment in Tauopathies. *Molecular Neurobiology* **46**:1, 205-216. [CrossRef]
6. Gunter P. Eckert, Kathrin Renner, Schamim H. Eckert, Janett Eckmann, Stephanie Hagl, Reham M. Abdel-Kader, Christopher Kurz, Kristina Leuner, Walter E. Muller. 2012. Mitochondrial Dysfunction—A Pharmacological Target in Alzheimer's Disease. *Molecular Neurobiology* **46**:1, 136-150. [CrossRef]
7. Kristina Leuner, Walter E. Müller, Andreas S. Reichert. 2012. From Mitochondrial Dysfunction to Amyloid Beta Formation: Novel Insights into the Pathogenesis of Alzheimer's Disease. *Molecular Neurobiology* **46**:1, 186-193. [CrossRef]
8. Joanna B. Strosznajder, Grzegorz A. Czapski, Agata Adamczyk, Robert P. Strosznajder. 2012. Poly(ADP-ribose) Polymerase-1 in Amyloid Beta Toxicity and Alzheimer's Disease. *Molecular Neurobiology* **46**:1, 78-84. [CrossRef]
9. Rommy von Bernhardi , Jaime Eugenín . 2012. Alzheimer's Disease: Redox Dysregulation As a Common Denominator for Diverse Pathogenic Mechanisms. *Antioxidants & Redox Signaling* **16**:9, 974-1031. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links]
10. Elena Galea, Nathalie Launay, Manuel Portero-Otin, Montserrat Ruiz, Reinald Pamplona, Patrick Aubourg, Isidre Ferrer, Aurora Pujol. 2012. Oxidative stress underlying axonal degeneration in adrenoleukodystrophy: A paradigm for multifactorial neurodegenerative diseases?. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* . [CrossRef]
11. Jorge Galino , Montserrat Ruiz , Stéphane Fourcade , Agatha Schlüter , Jone López-Erauskin , Cristina Guilera , Mariona Jove , Alba Naudi , Elena García-Arumí , Antoni L. Andreu , Anatoly A. Starkov , Reinald Pamplona , Isidre Ferrer , Manuel Portero-Otin , Aurora Pujol . 2011. Oxidative Damage Compromises Energy Metabolism in the Axonal Degeneration Mouse Model of X-Adrenoleukodystrophy. *Antioxidants & Redox Signaling* **15**:8, 2095-2107. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links] [Supplemental material]
12. Peizhong Mao, P. Hemachandra Reddy. 2011. Aging and amyloid beta-induced oxidative DNA damage and mitochondrial dysfunction in Alzheimer's disease: Implications for early intervention and therapeutics. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* . [CrossRef]
13. Arne Ittner, Yazi D. Ke, Janet van Eersel, Amadeus Gladbach, Jürgen Götz, Lars M. Ittner. 2011. Brief update on different roles of tau in neurodegeneration. *IUBMB Life* **63**:7, 495-502. [CrossRef]
14. Jan Frank, Xiao Wei Dawn Chin, Charlotte Schrader, Gunter P. Eckert, Gerald Rimbach. 2011. Do tocotrienols have potential as neuroprotective dietary factors?. *Ageing Research Reviews* . [CrossRef]
15. Joanna B. Strosznajder, Magdalena Cieslik, Magdalena Cakala, Henryk Jesko, Anne Eckert, Robert P. Strosznajder. 2011. Lipoxygenases and Poly(ADP-Ribose) Polymerase in Amyloid Beta Cytotoxicity. *Neurochemical Research* **36**:5, 839-848. [CrossRef]
16. Aleksandra Maruszak, Cezary #ekanowski. 2011. Mitochondrial dysfunction and Alzheimer's disease. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **35**:2, 320-330. [CrossRef]
17. Micha M.M. Wilhelmus, Susanne M.A. van der Pol, Quentin Jansen, Maarten E. Witte, Paul van der Valk, Annemieke J.M. Rozemuller, Benjamin Drukarch, Helga E. de Vries, Jack Van Horssen. 2011. Association of Parkinson disease-related protein PINK1 with Alzheimer disease and multiple sclerosis brain lesions. *Free Radical Biology and Medicine* **50**:3, 469-476. [CrossRef]
18. Lucia Pagani, Anne Eckert. 2011. Amyloid-Beta Interaction with Mitochondria. *International Journal of Alzheimer's Disease* **2011**, 1-12. [CrossRef]

19. Masahiro Kawahara, Isao Ohtsuka, Shoko Yokoyama, Midori Kato-Negishi, Yutaka Sadakane. 2011. Membrane Incorporation, Channel Formation, and Disruption of Calcium Homeostasis by Alzheimer's #-Amyloid Protein. *International Journal of Alzheimer's Disease* **2011**, 1-17. [CrossRef]
20. Andrea M. Vincent, James L. Edwards, Lisa L. McLean, Yu Hong, Federica Cerri, Ignazio Lopez, Angelo Quattrini, Eva L. Feldman. 2010. Mitochondrial biogenesis and fission in axons in cell culture and animal models of diabetic neuropathy. *Acta Neuropathologica* **120**:4, 477-489. [CrossRef]
21. C. J. Martyniuk, K. J. Kroll, N. J. Doperalski, D. S. Barber, N. D. Denslow. 2010. Genomic and Proteomic Responses to Environmentally Relevant Exposures to Dieldrin: Indicators of Neurodegeneration?. *Toxicological Sciences* **117**:1, 190-199. [CrossRef]
22. Mohammad Ali Rezvanfar, Mohammad Amin Rezvanfar, Akram Ranjbar, Maryam Baeeri, Azadeh Mohammadirad, Mohammad Abdollahi. 2010. Biochemical evidence on positive effects of rolipram a phosphodiesterase-4 inhibitor in malathion-induced toxic stress in rat blood and brain mitochondria. *Pesticide Biochemistry and Physiology* **98**:1, 135-143. [CrossRef]
23. X. Gao, C.-Q. Lai, T. Scott, J. Shen, T. Cai, J. M. Ordovas, K. L. Tucker. 2010. Urinary 8-Hydroxy-2-deoxyguanosine and Cognitive Function in Puerto Rican Adults. *American Journal of Epidemiology* **172**:3, 271-278. [CrossRef]
24. Jinling Hou, Zhao Zhong Chong, Yan Chen Shang, Kenneth Maiese. 2010. FOXO3a governs early and late apoptotic endothelial programs during elevated glucose through mitochondrial and caspase signaling. *Molecular and Cellular Endocrinology* **321**:2, 194-206. [CrossRef]
25. Tamara Azarashvili, Rolf Stricker, Georg Reiser. 2010. The mitochondria permeability transition pore complex in the brain with interacting proteins – promising targets for protection in neurodegenerative diseases. *Biological Chemistry* **391**:6, 619-629. [CrossRef]
26. Walter E. Müller, Anne Eckert, Christopher Kurz, Gunter Peter Eckert, Kristina Leuner. 2010. Mitochondrial Dysfunction: Common Final Pathway in Brain Aging and Alzheimer's Disease—Therapeutic Aspects. *Molecular Neurobiology* **41**:2-3, 159-171. [CrossRef]
27. C Kurz, I Ungerer, U Lipka, S Kirr, T Schütt, A Eckert, K Leuner, WE Müller. 2010. The metabolic enhancer piracetam ameliorates the impairment of mitochondrial function and neurite outgrowth induced by ß-amyloid peptide. *British Journal of Pharmacology* **160**:2, 246-257. [CrossRef]
28. Yang Su, Hao Sun, Jie Fang, Gang Hu, Ming Xiao. 2010. Brain Mitochondrial Dysfunction in Ovariectomized Mice Injected with d-Galactose. *Neurochemical Research* **35**:3, 399-404. [CrossRef]
29. Antonella Bobba, Vito A. Petragallo, Ersilia Marra, Anna Atlante. 2010. Alzheimer's Proteins, Oxidative Stress, and Mitochondrial Dysfunction Interplay in a Neuronal Model of Alzheimer's Disease. *International Journal of Alzheimer's Disease* **2010**, 1-11. [CrossRef]
30. Victor L. Villemagne, Christopher C. Rowe. 2010. Amyloid PET Ligands for Dementia. *PET Clinics* **5**:1, 33-53. [CrossRef]
31. Vijay Kumar, Kiran Dip Gill. 2009. Aluminium neurotoxicity: neurobehavioural and oxidative aspects. *Archives of Toxicology* **83**:11, 965-978. [CrossRef]
32. S. Hauptmann, I. Scherping, S. Dröse, U. Brandt, K.L. Schulz, M. Jendrach, K. Leuner, A. Eckert, W.E. Müller. 2009. Mitochondrial dysfunction: An early event in Alzheimer pathology accumulates with age in AD transgenic mice. *Neurobiology of Aging* **30**:10, 1574-1586. [CrossRef]
33. Pavel F. Pavlov, Camilla Hansson Petersen, Elzbieta Glaser, Maria Ankarcrona. 2009. Mitochondrial accumulation of APP and A#: significance for Alzheimer disease pathogenesis. *Journal of Cellular and Molecular Medicine* **13**:10, 4137-4145. [CrossRef]
34. N. Widodo, N. Shah, D. Priyandoko, T. Ishii, S. C. Kaul, R. Wadhwa. 2009. Deceleration of Senescence in Normal Human Fibroblasts by Withanone Extracted From Ashwagandha Leaves. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* **64A**:10, 1031-1038. [CrossRef]
35. Michelle T. Fodero-Tavoletti, Roberto Cappai, Catriona A. McLean, Kerryn E. Pike, Paul A. Adlard, Tiffany Cowie, Andrea R. Connor, Colin L. Masters, Christopher C. Rowe, Victor L. Villemagne. 2009. Amyloid Imaging in Alzheimer's Disease and Other Dementias. *Brain Imaging and Behavior* **3**:3, 246-261. [CrossRef]
36. Walter E. Müller, Reham M. Abdel-Kader, Christian J. Fehske, Kristina Leuner. 2009. Grundlagen der therapeutischen Anwendung von EGb 761 ® . Wirkung auf die Kraftwerke der Zellen. *Pharmazie in unserer Zeit* **38**:5, 408-416. [CrossRef]
37. V. Rhein, G. Baysang, S. Rao, F. Meier, A. Bonert, F. Müller-Spahn, A. Eckert. 2009. Amyloid-beta Leads to Impaired Cellular Respiration, Energy Production and Mitochondrial Electron Chain Complex Activities in Human Neuroblastoma Cells. *Cellular and Molecular Neurobiology* **29**:6-7, 1063-1071. [CrossRef]

38. Kenneth Maiese, Zhao Zhong Chong, Yan Chen Shang, Jinling Hou. 2009. A “FOXO” in sight: Targeting Foxo proteins from conception to cancer. *Medicinal Research Reviews* **29**:3, 395-418. [CrossRef]
39. S. Zraika, R. L. Hull, J. Udayasankar, K. Aston-Mourney, S. L. Subramanian, R. Kisilevsky, W. A. Szarek, S. E. Kahn. 2009. Oxidative stress is induced by islet amyloid formation and time-dependently mediates amyloid-induced beta cell apoptosis. *Diabetologia* **52**:4, 626-635. [CrossRef]
40. V KUMAR, A BAL, K GILL. 2009. Susceptibility of mitochondrial superoxide dismutase to aluminium induced oxidative damage. *Toxicology* **255**:3, 117-123. [CrossRef]
41. Young-Sook Choi, Sang-Ho Kim. 2009. Mitochondrial Dysfunction and Apoptosis Related Gene Expression in A#25-35-Treated Human Neuroblastoma Cell Line, SK-N-SH. *Journal of the Korean Geriatrics Society* **13**:3, 142. [CrossRef]
42. Sukhdev Singh Kamboj, Vikas Kumar, Amit Kamboj, Rajat Sandhir. 2008. Mitochondrial Oxidative Stress and Dysfunction in Rat Brain Induced by Carbofuran Exposure. *Cellular and Molecular Neurobiology* **28**:7, 961-969. [CrossRef]
43. Imrich Blasko, Susanne Jungwirth, Kurt Jellinger, Georg Kemmler, Wolfgang Krampla, Silvia Weissgram, Ildiko Wichart, Karl Heinz Tragl, Hartmann Hinterhuber, Peter Fischer. 2008. Effects of medications on plasma amyloid beta (A#) 42: Longitudinal data from the VITA cohort. *Journal of Psychiatric Research* **42**:11, 946-955. [CrossRef]
44. Kenneth Maiese, Zhao Zhong Chong, Faqi Li, Yan Chen Shang. 2008. Erythropoietin: Elucidating new cellular targets that broaden therapeutic strategies. *Progress in Neurobiology* **85**:2, 194-213. [CrossRef]
45. Kenneth Maiese, Faqi Li, Zhao Zhong Chong, Yan Chen Shang. 2008. The Wnt signaling pathway: Aging gracefully as a protectionist?. *Pharmacology & Therapeutics* **118**:1, 58-81. [CrossRef]
46. K MAIESE. 2008. Triple play: Promoting neurovascular longevity with nicotinamide, WNT, and erythropoietin in diabetes mellitus. *Biomedicine & Pharmacotherapy* **62**:4, 218-232. [CrossRef]