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Forum Review

Mitochondrial Dysfunction in Aging and Alzheimer's Disease: Strategies to Protect Neurons

P. HEMACHANDRA REDDY

ABSTRACT

Recent structural and functional studies of mitochondria have revealed that abnormalities in mitochondria may lead to mitochondrial dysfunction in aged individuals and those with neurodegenerative diseases, including Alzheimer's disease (AD). Molecular, cellular, and biochemical studies of animal models of aging and AD have provided compelling evidence that mitochondria are involved in AD development and progression. Further, a role for mitochondrial dysfunction in AD is supported by studies of neurons from autopsy specimens of patients with AD, transgenic AD mice, and neuronal cells expressing human AD mutation, which have revealed that amyloid beta (Aβ) enters mitochondria early in the disease process and disrupts the electron-transport chain, generates reactive oxygen species, and inhibits the production of cellular ATP, which in turn prevents neurons from functioning normally. Although AD researchers are actively involved in understanding Aβ toxicity and trying to develop strategies to reduce Aβ toxicity, one route they have yet to take is to investigate the molecules that activate nonamyloidogenic α-secretase activity that may reduce Aβ production and toxicity. In addition, it may be worthwhile to develop mitochondrially targeted antioxidants to treat AD. This article discusses critical issues of mitochondria causing dysfunction in aging and AD and discusses the strategies to protect neurons caused by mitochondrial dysfunction. *Antioxid. Redox Signal.* 9, 1647–1658.

INTRODUCTION

INCREASING EVIDENCE SUGGESTS that mitochondria play a key role in the etiology of a number of age-related neurological diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and Friedreich's ataxia (38, 64). Mitochondria are the major source of energy or adenosine triphosphate (ATP) for the normal functioning of eukaryotic brain cells. Dysfunction of mitochondria is known to generate reactive oxygen species (ROS), impaired intracellular calcium levels, and reduced mitochondrial ATP production (6). Increased generation of ROS with compromised mitochondrial function ultimately kills neurons in neurodegenerative diseases. This article describes the structure and function of mitochondria and critical issues relating to the role of mitochondrial dysfunction in aging and AD. This article also discusses strategies that are under development to treat neurons damaged by mitochondrial dysfunction.

MITOCHONDRIAL STRUCTURE, FUNCTION, AND PHYSIOLOGY

Mitochondria are cytoplasmic organelles that arise from a symbiotic association between glycolytic protoeukaryotic cells and oxidative bacteria (64). Several features of mitochondria that reflect their endosymbiotic origin are their double-membrane structure and their circular genome with mitochondria-specific transcription, translation, and protein-assembly systems. Mitochondria have adapted to their new intracellular environment by reducing their genome size to ~16.5 kb DNA

Neurogenetics Laboratory, Neurological Sciences Institute, Oregon Health & Science University, Beaverton, Oregon.

(90). This reduction increases the rate at which mitochondria replicate. This reduction in genome size is assumed to be accomplished by the deletion of nonessential genes from and the transfer of many essential genes to the nucleus, where the proteins are transcribed into mRNA, translated onto cytoplasmic ribosomes and selectively imported back into the mitochondrion (71).

A mitochondrion is compartmentalized into two lipid membranes: the inner mitochondrial membrane and the outer mitochondrial membrane (68). The inner membrane houses the mitochondrial respiratory chain (Fig. 1) and provides a highly efficient barrier to ionic flow. It also covers the mitochondrial matrix, which contains the components of tricarboxylic acid cycle and beta oxidation. The outer membrane is basically porous, allowing low-molecular-weight substances between the cytosol and the intermembrane space (68).

Mitochondria are involved in several important cell functions: producing ATP and regulating intracellular Ca^{2+}, releasing proteins that activate the caspase family of proteases, and altering the reduction–oxidation potential of cells (6, 68). Disruption of the electron-transport chain (ETC) of mitochondria has been recognized as an early characteristic of apoptotic cell death. ETC involves the reduction of hydrogen peroxide (H_2O_2) to H_2O and O_2 by catalase or glutathione peroxidase–accepting electrons donated by the NADH and $FADH_2$, and then the yielding of energy to generate ATP from adenosine diphosphate and inorganic phosphate (Fig. 2) (67, 68).

Mitochondrial ATP is generated *via* oxidative phosphorylation (OXPHOS). Five polypeptide complexes (I–V), localized in the inner mitochondrial membrane and responsible for OXPHOS, use flavins, nicotinamides, cytochromes, and iron-sulfur centers. In complex IV, these complexes use copper ions to transfer electrons in a series of oxidation and reduction steps. Electrons pass along the mitochondrial ETC complexes and generate an electrochemical gradient by fueling the extrusion of protons from mitochondrial matrix across the inner mitochondrial membrane at complexes I, III, and IV. ATP is then generated by the dissipation of this proton gradient through complex V (see Figs. 1 and 2) (68). Mitochondria are critical in the metabolism of all the eukaryotic cells, including brain neurons and abnormalities in mitochondrial structure, and their function may lead to age-related neurodegenerative diseases (6, 38).

Mammalian mitochondrial DNA (mtDNA) consists of a 16.5-kb, double-stranded circular DNA molecule (6, 64, 90). Each mitochondrion contains from two to 10 copies of mtDNA. The mtDNA contains 13 polypeptide genes, all of which encode essential components of the ETC. All 13 polypeptide genes in the mtDNA are involved in producing components of mitochondrial complexes (6, 64, 90). The mtDNA also encodes the 12S and 16S rRNA genes and the 22 tRNA genes, which are required for mitochondrial protein synthesis. mtDNA encodes seven subunits (ND1, 2, 3, 4, 4L, 5, and 6) of the 43 subunits of complex I, one (cytochrome *b*) of 11 subunits of complex III, three (COX1, COX2, and COX3) of 13 subunits of complex IV, and two (ATPase 6 and ATPase 8) of 17 subunits of complex V. Nuclear genes encode the remaining mitochondrial proteins, the metabolic enzymes, the DNA and RNA polymerases, the ribosomal proteins, and the mtDNA regulatory factors, such as mitochondrial transcription factor A (90). mtDNA replication of the outer and inner strands occurs from separate sites and is under nuclear DNA control. mtDNA transcripts serve as primers that initiate the replication of the heavy strand. DNA polymerase is responsible for mtDNA replication and is stimulated by the binding of mitochondrial, single-stranded binding proteins to the exposed, single-stranded mtDNA (64, 90).

Mitochondria are transmitted through the cytoplasm of an oocyte and, therefore, are maternally inherited. However, in rare instances, paternal inheritance and a recombination of mtDNA have been reported (25). Mitochondria contain no protective histones and have a mutation rate that is 17 times greater than that of the nuclear genome (64). When a mutation occurs in mtDNA within a cell, mutant and normal molecules coexist in the cell, a state known as heteroplasmy (17, 64). Because of the maternal inheritance of mtDNA, the mutant and normal

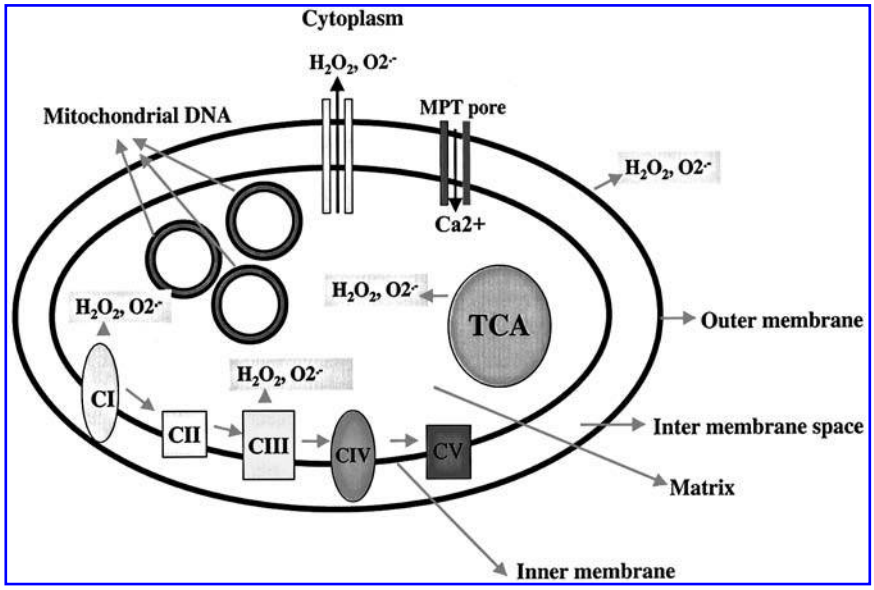

FIG. 1. Structure of mitochondria and the sites of free radical generation. Mitochondrion is compartmentalized with two lipid membranes: the inner mitochondrial membrane and the outer mitochondrial membrane. The inner mitochondrial membrane houses the mitochondrial respiratory chain and provides a highly efficient barrier to ionic flow. In the respiratory chain, complexes I, III leak electrons to oxygen, producing primarily superoxide radicals, and superoxide radicals are dismutated by manganese superoxide dismutase and produce H_2O_2. These radicals are carried to the cytoplasm *via* voltage-dependent anion channels.

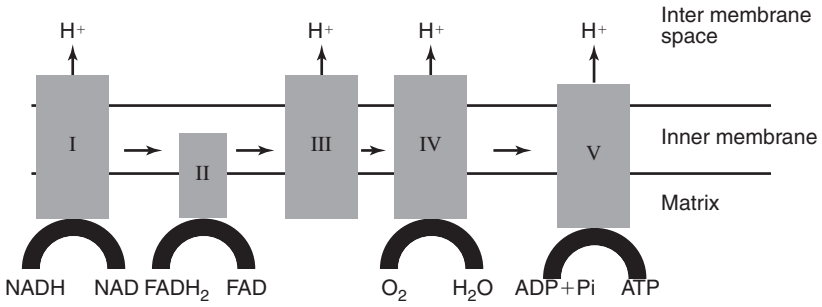

FIG. 2. The electron-transport chain and ATP synthesis on the inner mitochondrial membrane.

mtDNAs are randomly distributed into daughter cells. Over many generations, the mtDNA genotype of a cellular lineage can drift toward predominantly mutant or wild-type mtDNA (homoplasmy), a process known as replicative segregation (64, 90). As the percentage of mutant mtDNAs increases, the energy capacity of the cell declines until the capacity falls below the bioenergetic threshold, which is the minimal energy output necessary for a cell or tissue to function normally (64, 90).

MITOCHONDRIAL FUSION AND FISSION

Eukaryotic cells maintain their mitochondrial shape by balancing two opposing processes: mitochondrial fusion and mitochondrial fission. Mitochondrial fission leads to mitochondrial fragmentation, and mitochondrial fusion leads to elongated mitochondria. These two processes control the shape, structure, and function of mitochondria. Both mitochondrial fusion and fission are controlled by evolutionarily conserved, large GTPases belonging to the dynamin family (13). Dynamins are large, ubiquitous enzymes that use the free energy generated by guanine 5′-triphosphate hydrolysis. The prototype dynamin I regulates the dynamic changes of intracellular membranes, including mitochondria (61). In mammalian cells, Opa1, mitofusin 1, and mitofusin 2 regulate mitochondrial fusion, whereas dynamin-related protein 1 (Drp1) and fission 1 (Fis1) are involved in mitochondrial fission (70).

Mitochondrial fusion is the joining of two mitochondria (Fig. 3) (15). In a healthy cell, mitochondrial fusion and fission constantly change the shape (boundaries) of the mitochondria. Therefore, mitochondria are not autonomous organelles, and their boundaries are constantly being altered (13). However, in cells without mitochondrial-fusion capability, a mitochondrion becomes an autonomous organelle that is unable to interact with neighbors. In such cases, mitochondrial defects, including depletion of mtDNA or metabolites or both, is known to lead to mitochondrial dysfunction (13).

Mitochondrial fusion may protect cells from the toxic effects of mtDNA mutations by allowing functional complementation of mtDNA gene products (proteins). Cell hybrids formed by fusing parental cells carrying different pathogenic mtDNA mutations have been found to restore ETC activity (56). In addition to controlling the shape of mitochondria, mitochondrial fusion is important for their bioenergetic function (14). Mitochondria within individual cells show heterogeneity in membrane potential and a compromised oxygen consumption. It is possible that mitochondrial fusion is minimal at synaptic terminals because isolated mitochondria are localized at synaptic terminals. The absence of mitochondrial fusion in brain cells may lead to increased production of ROS and low ATP, and ultimately may lead to decreased neurotransmission, particularly in a diseased state.

Mitochondrial fission is the fragmentation of a mitochondrion (see Fig. 3). Mitochondrial fission plays an important

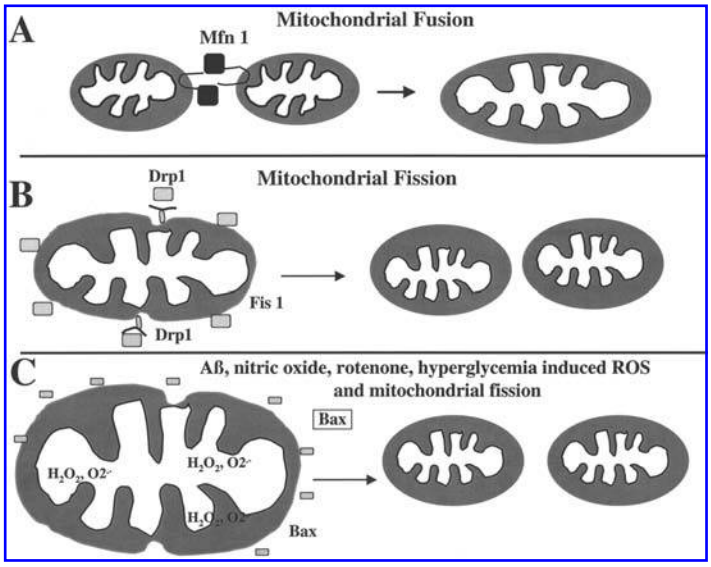

FIG. 3. Mitochondrial fusion and fission molecules. (**A**) Mitochondrial fusion. Mfn 1 is an outer mitochondrial membrane protein with a cytosolic GTPase domain. The C-terminal coil mediates oligomerization between Mfn molecules on adjacent mitochondria facilitate two mitochondria fuse together become single elongated mitochondrion. (**B**) Mitochondrial fission. Fis 1 protein is localized to the outer mitochondrial membrane, and Drp1 is localized in the cytoplasm. Drp 1 has punctate spots on mitochondria, and these punctate constriction spots lead to mitochondrial fission. (**C**) Mitochondrial fission caused by Aβ peptide, nitric oxide, rotenone, and hyperglycemia. Aβ peptide, nitric oxide, rotenone, and hyperglycemia induce ROS production and activate Drp1, which may lead to mitochondrial fission.

role in apoptosis and has been identified as an early apoptotic event (9, 17). Mitochondrial fission occurs before caspase is activated and at the time when BAX (an apoptotic gene) translocates to mitochondria. The level of mitochondrial fragmentation depends on the activity of Drp1 and Fis1. The inhibition of Drp1 and Fis1 activities reduces mitochondrial fission and apoptosis (9, 17, 41). Mitochondrial fission plays a proapoptotic role, and mitochondrial fusion protects cells from death. Mitochondrial fusion is reduced after the induction of apoptosis (33), and the overexpression of mitofusins can reduce apoptosis (79).

REACTIVE OXYGEN SPECIES PRODUCTION AND MITOCHONDRIAL FISSION

An important aspect of ETC is the generation of ROS, which is a physiologically important by-product of respiration (64). During the transfer of electrons to molecular oxygen, an estimated 1–5% of electrons in the ETC lose their way and participate in the formation of superoxide radicals ($O_2^{\bullet -}$). The production of mitochondrial $O_2^{\bullet -}$ occurs primarily at discrete points in the ETC at complexes I and III, and in components of TCA, including α-ketoglutarate dehydrogenase (27, 78). $O_2^{\bullet -}$ are also generated by the outer mitochondrial membrane. Monoamine oxidase is localized on the outer mitochondrial membrane and catalyzes the oxidative deamination of primary aromatic amines. This deamination is a primary source of H_2O_2 that contributes to an increase in the steady-state concentrations of ROS in both the mitochondrial matrix and the cytosol (31). H_2O_2, produced during the oxidative deamination of catecholamines, has been identified as likely being involved in neurodegenerative disorders, such as AD and PD, presumably *via* oxidative damage to the mitochondrial membranes (26).

Increasing evidence suggests that increased mitochondrial ROS is responsible for changes in mitochondrial morphology and mitochondrial fission (3, 7, 94) (see Fig. 3). Recently, Bernard and colleagues studied the connection between mitochondrial morphology and mitochondrial function in human cells. They determined the effect of mitochondrial fission on ATP production by using small, interfering RNA that target Drp1 (critical for mitochondrial fission) and revealed the importance of membrane fluidity to control bioenergetics. Bernard and colleagues (7) also studied the effect of rotenone, a specific inhibitor of ETC complex I, which causes large structural changes after a threshold is reached. They investigated human cells that had been treated with modulators of OXPHOS and measured the generation of ROS in two patients with a mitochondrial disease. They monitored changes in the patients' mitochondrial network configuration and found increased ROS production and decreased ATP. These findings suggest that increased ROS production and/or genes that regulate mitochondrial fission may alter ATP production and mitochondrial decay (7).

Yoon *et al*. (94) studied mitochondrial fission and high glucose-induced overproduction of ROS. In this study, after cells were exposed to high glucose concentrations, mitochondrial fragmentation occurred, as did ROS production. Neither an increase in ROS nor mitochondrial fission was observed after cells were integrated with the nonmetabolizable stereoisomer L-glucose. However, the inhibition of mitochondrial pyruvate uptake, which is known to stop the increase of ROS, did not prevent mitochondrial fragmentation in high-glucose conditions. Yoon and colleagues (94) found that mitochondrial fragmentation mediated by mitochondrial fission is a necessary process that increases high-glucose–induced respiration and ROS production. Inhibition of mitochondrial fission prevented periodic fluctuation of ROS production in high-glucose conditions. These results suggest that the dynamic change of mitochondrial morphology in high-glucose conditions contributes to ROS overproduction and that mitochondrial fission/fusion mechanisms may be targeted to control acute and chronic ROS production in hyperglycemia-related disorders (94).

Recently, Barsoum *et al.* (3) investigated the connection among mitochondrial fission, nitric oxide, amyloid beta (Aβ) peptides (25–35), and rotenone. They found that mitochondria undergo fission in response to nitric oxide, rotenone, and Aβ peptide in cortical neurons of primary cultures. Mitochondrial fission by nitric oxide occurs long before neurite injury and neuronal cell death and is accompanied by ultrastructural damage of the mitochondria, autophagy, ATP decline, and generation of ROS. Strikingly, mitochondrial fission is an early event in ischemic stroke *in vivo*. Mitofusin 1 or dominant-negative Drp1 inhibits mitochondrial fission induced by nitric oxide, rotenone, and Aβ peptide. Conversely, overexpression of Drp1 or Fis1 elicits fission and increases neuronal loss, suggesting that ROS inducers may cause mitochondrial fragmentation (3). Findings from these studies suggest that ROS production is induced by nitric oxide and that Aβ peptide and rotenone may be responsible for mitochondrial fragmentation and apoptosis in neurodegenerative diseases. It is also possible that in late-onset AD, increased ROS production may cause mitochondrial fragmentation and subsequent mitochondrial dysfunction and neuronal cell death.

MITOCHONDRIAL DYSFUNCTION AND AGING

Mitochondrial dysfunction has been well documented in aging and age-related neurodegenerative diseases (38, 64). In aging, mitochondrial dysfunction is caused by an accumulation of mtDNA defects and an increased production of ROS. Mitochondrial ETC is responsible for the transfer of electrons from NADH or FADH, to electron acceptors, and to oxygen, the final transfer of which leads to the production of H_2O (see Fig. 2). These biochemical events lead to a small amount (1–5%) of electron leakage and, subsequently, to ROS production (64).

MtDNA is localized close to the source of ROS production and may be vulnerable to DNA damage. Oxidized guanosine levels are higher in mtDNA relative to nuclear DNA (69). It has been reported that several DNA repair mechanisms may operate within mitochondria, but one such repair mechanism—nucleotide excision repair—may be absent in mtDNA, leaving mtDNA vulnerable to a number of DNA changes (40). MtDNA defects that reduce the accuracy of electron transfer may in-

crease the production of ROS and decrease the production of ATP. An increase in the production of ROS may further damage mtDNA (67, 68).

Further, an age-dependent increase of Ca^{2+} has been found to induce ROS production within mitochondria (68). Recently, Brown and colleagues (10) studied Ca^{2+} influx and ROS production in mitochondria isolated from Fischer 344 rats, ranging in age from 4 to 25 months. Mitochondria isolated from the cortex of the 25-month-old rat brain exhibited greater rates of ROS production and mitochondrial swelling in response to increasing Ca^{2+} loads than did mitochondria isolated from younger (4- and 13-month) animals, suggesting that increased mitochondrial swelling may be indicative of the opening of the mitochondrial permeability transition pore in aged animals (10).

Mitochondrial DNA changes and aging

It is well documented that mtDNA changes are responsible for aging phenotypes (18, 32, 33, 36, 89). Many tissues from aged individuals have lower respiratory function compared with those from younger individuals (18). Both mtDNA single-nucleotide mutations and deletions are highly prevalent in aged cells. Evidence suggests that 8-hydroxy-2-deoxyguanosine (DNA damage marker) is more prevalent in aged tissues (33).

To help elucidate the role of mitochondrial mutations in aging, two investigators independently created mouse lines containing a point mutation in the proofreading region of DNA polymerase gene, the catalytic subunit of mtDNA polymerase (36, 89). The mutant DNA polymerase-γ mice were found to have normal DNA polymerase activity but to lack the exonuclease activity necessary for proofreading. Homozygous mutant mice showed a three- to eightfold increase in mtDNA point mutations in several tissues. These homozygous mutated mice had reduced life spans and showed an early onset of age-associated features, including weight loss, reduction in subcutaneous fat, hair loss, curvature of the spine, and osteoporosis. The findings from these studies suggest that mtDNA changes are critical in the aging process (36, 89).

Further, a recent mitochondrially targeted catalase transgenic mice study supports the involvement of mitochondria in aging process and longevity (72). To determine the protective effects of catalase (antioxidant), Schriner *et al*. (72) created transgenic mouse lines that overexpress human catalase localized to peroxisomes, nuclei, and mitochondria. Catalase is found mainly in peroxisomes and rapidly converts toxic H_2O_2 into H_2O and O_2. Schriner and colleagues (72) found that the transgenic mice that targeted to mitochondria showed about a 20% increase in median and maximal life span (on average, 5.5 months) compared with the life span of nontransgenic, age-matched wild-type littermates. The ability of catalase to increase longevity was most apparent when the enzyme was targeted to mitochondria. Nuclear catalase (NCAT) expression (in NCAT mice) had no effect on either the median or the maximal life span of the mice.

Overall, findings from these aging studies suggest that mtDNA mutations are involved in the aging phenotype. From these aging studies, it is also clear that mitochondrially generated ROS (including H_2O_2 and superoxide radicals) are critical factors in determining longevity.

MITOCHONDRIAL DYSFUNCTION AND ALZHEIMER'S DISEASE

AD is a late-onset, progressive, age-dependent neurodegenerative disorder, characterized clinically by the impairment of cognitive functions and changes in behavior and personality (48, 66, 73). AD is associated with the presence of intracellular neurofibrillary tangles and extracellular Aβ plaques, mitochondrial oxidative damage, a loss of neuronal subpopulations, synaptophysin immunoreactivity of presynaptic terminals, cholinergic fibers, and the proliferation of reactive astrocytes and microglia (64, 66, 67, 68). With the life span of humans increasing and with decreasing cognitive function in elderly individuals with AD-related dementia, AD has become a major health problem in society. Therapeutic interventions are urgently needed to minimize the ill effects of this devastating disease.

Familial AD constitutes only 2% of AD patients. It is caused by mutations in the amyloid precursor protein (APP), presenilin 1, and presenilin 2 (64, 66, 73). In contrast, causal factors are still unknown for the vast majority of sporadic (late-onset) AD patients. Much research has been done on FAD in terms of pathophysiology and cellular changes that regulate AD progression, but much more research is needed to understand causal factors, pathophysiology, and cellular changes in late-onset AD.

Oxidative damage and Alzheimer's disease

Oxidative damage has been reported in aging and age-related neurodegenerative diseases, including AD (6, 22, 32, 45, 55, 58, 64, 81). Several recent articles reported that oxidative damage occurs in the AD brain before the onset of Aβ pathology. In addition, oxidative damage has been reported in the platelets and in fibroblast mitochondria from AD patients. Decreased levels of mitochondrial enzymes—including pyruvate dehydrogenase complex, α-ketoglutarate dehydrogenase complex, and cytochrome oxidase—have been reported (29). Markers of oxidative damage have been found in lesions not only in the brains of AD patients (8, 12, 22, 49, 77) but also in the brains of AD transgenic mice (1, 42, 45, 65, 76). Increased free-radical production and decreased cellular ATP have also been found in brain specimens from AD patients (22), suggesting that oxidative damage is an early and critical event in AD development and progression.

mtDNA changes, aging, and Alzheimer's disease

MtDNA defects (both deletions and point mutations) have been found in AD patients and in aged humans without AD (43) and have been associated with decreased cytochrome oxidase activity in these brains (57, 83). However, the effects of specific mtDNA change on cytochrome oxidase activity have not yet been studied. Defects in mitochondrial OXPHOS have frequently been associated with AD, and both inherited and somatic mutations have been reported in certain AD cases. Indeed, available data clearly indicate that in AD patients, age-related somatic mutations, including deletions, accumulate in mtDNA (64). These data support the hypothesis that mtDNA defects impair the ETC enzymes and ATP production below a threshold level, rendering low ATP levels incompatible with

normal cell function. To determine whether mtDNA mutations contribute to the etiology of AD, Coskun *et al.* (19) investigated brains from sporadic AD patients for the sequence of the mtDNA control region, for possible disease-causing mutations. They found that 65% of the AD brains harbored the T414G mutation and that this mutation was absent from all control brains. Moreover, cloning and sequencing of the mtDNA control region in AD and control brains revealed that all AD brains had an average 63% increase in mutations of the heteroplasmic mtDNA control region and that the brains from AD patients who were 80 years and older had a 130% increase in heteroplasmic control-region mutations. In addition, mtDNA mutations from AD patients preferentially altered known mtDNA regulatory elements (19). Overall, these findings suggest that somatic mutations in the control region may play a role in the etiology of sporadic AD patients.

Amyloid beta associated with mitochondria from AD neurons

Substantial research has focused on understanding Aβ toxicity ever since the Aβ peptide was discovered in brain samples from patients with sporadic AD (73). The Aβ peptide, 4 kDa, is a cleaved product of APP *via* sequential proteolysis of aspartyl beta secretase and presenilin-dependent gamma secretase (73). APP is synthesized in the cell bodies of neurons and is anterogradely transported within axons to nerve terminals in the brain (11, 35, 75). The localization of APP in nerve terminals suggests that nerve terminals are the major source of Aβ in Aβ plaques found in the brains of AD patients. It is now well established that after APP processing, Aβ forms oligomers in synaptic terminals. Oligomeric Aβ is hypothesized to enter other cell organelles, such as mitochondria and lysosomes, within cytoplasm because of their sharp morphology that penetrates membranes and their small size (oligomeric Aβ is ~10–50 kDa). Several studies have recently found both monomeric and oligomeric forms of Aβ in mitochondrial membranes (12, 45), supporting the hypothesis that Aβ enters mitochondria. Caspersen *et al*. (12) found Aβ in mitochondria taken from postmortem brain specimens from AD patients and in mitochondria taken from postmortem brain slices of transgenic mice that had targeted neuronal overexpression of mutant human APP. Recently, Manczak *et al*. (45) found a 4-kDa Aβ monomer in isolated mitochondria from the cerebral cortex of Tg2576 mice (45). By using mouse N2a cells expressing human mutant APP and human wild-type APP, Manczak *et al*. (45) found Aβ monomers and oligomers in the mitochondria, confirming a relation between Aβ and mitochondria. Overall, findings from recent molecular, cellular, and animal-model studies have revealed that mutant APP and Aβ enter mitochondria and interact with mitochondrial proteins (12), disrupt the ETC (12, 22, 45), and generate ROS (12, 22, 45), and that free radicals derived from molecular oxygen in the mitochondria inhibit the generation of cellular ATP (6, 68).

STRATEGIES TO PROTECT NEURONS FROM MITOCHONDRIAL TOXICITY IN AGING AND ALZHEIMER'S DISEASE INDIVIDUALS

With the number of cases of mitochondrial diseases increasing, including AD, mitochondrial dysfunction is a major health concern (6, 64). It is critical to develop therapeutics that treat mitochondrial illnesses. Irrespective of the disease process of mitochondrial disorders, the ultimate problem of mitochondrial dysfunction is ROS production (6, 64, 77, 81). Therefore, therapeutic strategies need to decrease ROS production and to boost mitochondrial function. Strategies that may help to protect neurons from age-related mitochondrial toxicity and from mitochondrial dysfunction caused by Aβ in AD progression are: calorie restriction (CR) and the activation of SIRTUINS (longevity genes) and the targeting of mitochondria with antioxidants (Fig. 4).

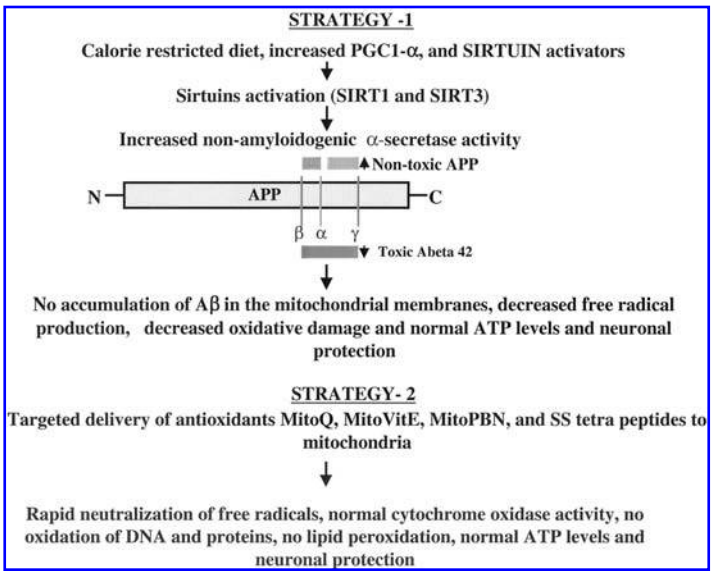

FIG. 4. Strategies of neuronal protection in Alzheimer's disease.

Calorie restriction and activation of SIRTUINS

Several recent studies have reported 4-kDa Aβ in mitochondrial membranes of AD neurons (12, 20, 22, 45, 76). Further, in brain specimens from AD patients, mitochondrial Aβ has been found to induce free radical production (12, 22), decrease cytochrome activity and ATP production (22, 49), and ultimately cause mitochondrial dysfunction (6, 64). If Aβ and aging are responsible for mitochondrial dysfunction, strategies that decrease toxicity caused by age-related mitochondrial Aβ may be useful to protect AD neurons form mitochondrial and Aβ toxicity. Recently, it has been proposed that CR may decrease Aβ production by the activation of SIRT1 (yeast Sir2 partner in mammals) and nonamyloidogenic α-secretase activity (88, 92). This possibility is supported by several recent AD transgenic mice studies (59, 62, 63, 91).

Wang *et al*. (91) investigated the connection between CR and amyloid pathology in APP transgenic mice. They found that this CR regimen diminished Aβ generation and Aβ plaque deposition (compared with that in control, well-fed mice), suggesting that CR may reduce Aβ production *via* activation of SIRT1 and α-secretase activity (91). In another study, Patel *et al*. (59) examined the effects of short-term CR in two AD-transgenic mice: APP(swe/ind) (J20) and APP(swe) + PS1(M146L) (APP + PS1). CR-restricted mouse in both lines were found to have a substantially decreased accumulation of Aβ-plaques [40% reduced in APP(swe/ind); CR, 6 weeks; and 55% in APP + PS1; CR, 14 weeks]. Both CR-restricted mouse lines also exhibited decreased astrocytic activation (GFAP immunoreactivity). The association of CR with AD transgenic mice is consistent with epidemiologic reports showing that high-caloric diets are associated with the risk of AD, (59) suggesting that dietary intervention in adult life might slow disease progression.

Qin *et al*. (63) investigated possible mechanistic links between CR and Aβ reduction in AD transgenic mice. They reported that the predicted attenuation of Aβ in the brains of these mice during CR was reproduced in mouse neurons *in vitro* by manipulating cellular SIRT1 expression/activity through mechanisms involving the regulation of the serine/threonine Rho kinase ROCK1, known in part for its role in inhibiting the nonamyloidogenic α-secretase processing of APP. However, they also found that the expression of constitutively active ROCK1 *in vitro* cultures significantly prevented a SIRT1-mediated response, suggesting that α-secretase activity is required for SIRT1-mediated prevention of Aβ neuropathology. Qin *et al*. (63) also found decreased ROCK1 expression and elevated α-secretase activity in transgenic mice expressing human SIRT1 gene. These findings suggest that SIRT1 activation may play a role in the influence of CR on AD amyloid neuropathology (63).

Qin *et al*. (62) also tested possible benefits from CR on Aβ neuropathology, in squirrel monkeys (*Saimiri sciureus*). The monkeys were maintained on normal and CR diets throughout their life span until they died of natural causes. The researchers found reduced levels of Aβ1-40 and Aβ1-42 peptides in the temporal cortex of 30% of the CR monkeys, compared with the control (well-fed) monkeys. The decreased contents of the cortical Aβ peptide inversely correlated with SIRT1 protein concentrations in the same brain region; no detectable change in the total APP level was found. Most interestingly, Qin *et al*. (62) found a select elevation of α-, but not β- or γ-, secretase activity in 30% of the CR monkeys. The increase of α-secretase activity coincided with a decrease in ROCK1 proteins in the same brain region, compared with the control group. Collectively, these results suggest that CR may be an indirect approach to decrease Aβ pathology, by activating SIRT1 and nonamyloidogenic α-secretase activity.

It is well established that CR reduces the defects of electron transfer in ETC, decreases mitochondrial ROS, increases oxygen consumption, and maintains ATP production in brain neurons (2). If so, then it may be worthwhile to develop molecules that activate SIRTUINS, PGC1α, and activators of α-secretase activity to decrease Aβ toxicity and oxidative damage in AD patients. These molecules would activate nonamyloidogenic α-secretase activity, which would in turn ultimately decrease Aβ production in AD patients (see Fig. 4).

Currently, investigators are developing beta secretase and gamma secretase inhibitors. The long-term effects of beta secretase and gamma secretase inhibitors are clearly not understood. However, recent studies of beta secretase 1 (or BACE 1) knockout mice reported that, while excess BACE 1-cleaved Aβ is functionally pathologic, BACE 1 null mice exhibited spatial memory deficits (34, 39), suggesting that BACE 1 activity is critical for memory functions in the central nervous system.

Initial investigation of a γ-secretase inhibitor on Aβ-induced cognitive deficits in transgenic mice showed that modest Aβ reductions (15–30%) are sufficient to reverse Aβ-induced cognitive deficits in Tg2576 mice (4). However, γ-secretase inhibitors cause abnormalities in the gastrointestinal tract, thymus, and spleen in rodents. These changes likely result from the inhibition of the Notch cleavage, a transmembrane receptor involved in regulating cell-fate decisions (4).

These β- and γ-secretase inhibitors studies suggest that both β- and γ-secretase inhibitors have adverse effects in AD. Research is needed into developing molecules that activate SIRTUINS, PGC1α, and any other molecules that activate α-secretase activity that decrease Aβ production and toxicity, and also decrease mitochondrial toxicity (see Fig. 4).

Mitochondrially targeted antioxidants

One possible strategy to decrease mitochondrial toxicity and Aβ pathology in the brains of AD patients is to treat AD patients with mitochondrially targeted antioxidants. It is important to develop molecules that decrease oxidative damage in the brains of AD patients. In recent studies, AD transgenic mice were treated with antioxidants: a vitamin E–supplemented diet (16,80), melatonin dissolved in drinking water (47), and curcumin (93). The researchers reported decreased Aβ pathology and ameliorated cognitive deficits in AD transgenic mice (16, 47, 80, 93). However, the results were mixed for elderly individuals and AD patients. Several studies found a reduced risk of AD in elderly individuals who were treated with high doses of vitamins C and E (30, 50, 51, 52), but others did not (44). These conflicting findings suggest that currently available antioxidant approaches may not be effective for treating AD patients because (a) naturally occurring antioxidants, such as vitamins E and C, may not cross the blood–brain barrier and so cannot reach the relevant sites of free radical generation, especially if mitochondria are the primary source of ROS; and (b)

researchers may have been unable to increase sufficient levels of antioxidants in mitochondria in AD patients (67, 68). To overcome these problems, we need to deliver antioxidants effectively to the brain mitochondria of AD patients. This improved antioxidant delivery to the brain mitochondria may prevent oxidative damage and improve both neuronal survival and neurologic outcome in AD patients.

Further, recent cellular, molecular, and animal model studies of aging and AD revealed that mitochondrially generated ROS, particularly H_2O_2, is a critical factor in determining AD progression. If aging and Aβ are critical factors in generating H_2O_2 in aged and AD neurons, then mitochondrially targeted antioxidants may rapidly convert toxic H_2O_2 into H_2O and O_2. The continual conversion of H_2O_2 into H_2O and O_2 may reduce oxidative damage in aged neurons and may maintain mitochondrial function in the neurons of aged individuals. In the last decade, considerable progress has been made in developing mitochondrially targeted antioxidants. To increase the delivery of antioxidants into mitochondria, the following antioxidants have been developed: the triphenylphosphonium-based antioxidants MitoQ, MitoVitaE, and MitoPBN (54, 74), and the cell-permeable, tetrapeptide antioxidants SS-02 and SS-31 (87).

MitoQ. MitoQ is a promising therapeutic antioxidant that has been successfully targeted to mitochondria (54). MitoQ consists of two redox forms of mitochondrially targeted ubiquinone derivatives: reduced mitoquinol and oxidized mitoquinone (54). MitoQ accepts two electrons from complexes I and II in the inner mitochondrial membrane, to form ubiquinol, a reduction product that donates electrons to complex III. Ubiquinone *in vivo* exists largely in a reduced form, acting as an antioxidant and a mobile electron transfer. Ubiquinol has been reported to function as an antioxidant by donating a hydrogen atom from one of its hydroxyl groups to a lipid peroxyl radical, thereby decreasing lipid peroxidation within the mitochondrial inner membrane (68). The semiubiquinone radical formed during this process may then disproportionate into ubiquinone and ubiquinol. The respiratory chain may subsequently recycle ubiquinone back to ubiquinol, restoring an antioxidant function. MitoQ may excessively accumulate in the mitochondria and convert H_2O_2 to H_2O and O_2 and reduce toxic insults from free radicals in the mitochondria. This reduction may ultimately lead to the protection of neurons from age-related and AD-related mitochondrial insults. MitoQ is in the early stages of being administered to animal models of mitochondrial diseases (54), and further research is required to explore MitoQ applications to human mitochondrial diseases, including AD.

MitoVitE. MitoVitE, an antioxidant, is a derivative of vitamin E that was developed to study mitochondrial oxidative damage. MitoVitE is rapidly taken up by mitochondria. Accumulation ratios of 5,000–6,000 units have been achieved after incubating mitochondria with 1–20 μM MitoVitE (74). MitoVitE is cytotoxic at 50 μM. The effects of MitoVitE have been tested in Jurkat cells. MitoVitE was found to reduce H_2O_2-induced caspase activity and to prevent cell death induced by oxidative stress, in cultured fibroblasts from Friedreich ataxia patients. At 1 μM, MitoVitE was found to inhibit cytochrome *c* release and caspase-3 activation, to inactivate complex 1, and to restore mitochondrial membrane potential and proteosomal activity in bovine aortic epithelial cells (23).

MitoPBN. MitoPBN is an antioxidant that has been reported to block the activation of uncoupled proteins. MitoPBN was prepared in a mitochondrially targeted analogue form to determine the effect of ROS in mitochondria (53). Similar to MitoQ and MitoVitE, MitoPBN was rapidly taken up by mitochondria, with a resulting concentration ranging from 2.2 to 4.0 m*M*. Further research is required to explore MitoPBN applications to AD mice, elderly humans, and AD patients.

Cell-permeable SS tetra peptides. Recently, Szeto and Schiller (86, 87) developed a series of four small, cell-permeable SS peptides (Szeto-Schiller or SS peptides). These peptides are known to protect mitochondria from oxidative damage (84, 86, 87, 95–97), so may serve, in their own right, as a drug for mitochondrial diseases, including AD. SS peptides also are known to target mitochondria (86, 87). The structural motif of these SS peptides centers on alternating aromatic residues and basic amino acids (aromatic-cationic peptides). They scavenge H_2O_2 and $ONOO^-$, and inhibit lipid peroxidation. Their antioxidant action can be attributed to the tyrosine, or dimethyltyrosine (Dmt), residue. Tyrosine scavenges oxyradicals and forms relatively unreactive tyrosyl radicals, followed by radical–radical coupling to give rise to dityrosine or to react with superoxide, to form tyrosine hydroperoxide (92). Dimethyltyrosine is more effective than tyrosine in scavenging ROS. The specific location of the tyrosine or dimethyltyrosine residue does not appear to be significant, as SS-31 was found to be as effective as SS-02 in scavenging H_2O_2 and inhibiting LDL oxidation (86, 87).

The SS peptide SS-02 contains an amino acid sequence, allowing SS-02 to penetrate cells freely, even though they carry a 3+ net charge at physiologic pH (96). These aromatic-cationic peptides are taken up into cells in an energy-independent, nonsaturable manner. Uptake studies with [^{3}H]SS-02 showed rapid uptake with steady state achieved in $<$30 min (97). This finding suggests that these peptides freely pass through the plasma membrane in both directions. Unlike the larger cationic peptides, such as the *Tat* peptide (21, 24), no evidence was found of vesicular localization that would result from endocytosis. Incubation of isolated mitochondria with [^{3}H]SS-02 confirmed that it is taken up and concentrated $>$1,000-fold in mitochondria (97).

Calcium overload can also lead to an increase in mitochondrial ROS and an opening of the MPT pore (68). By reducing mitochondrial ROS, SS peptides (SS-02 and SS-31) were able to inhibit MPT, prevent mitochondrial swelling, and reduce cytochrome *c* release in response to Ca^{2+} overload (86). SS-02 was found to prevent MPT, leading to a minimization of MPT-induced ROS accumulation and, further, a reduction in oxidative damage, in mitochondria (5). It appears that both SS-02 and SS-31 may have potential in reducing mitochondrially generated free radicals and decreasing mitochondrial oxidative damage (5, 60) because the SS small peptides are highly "druggable" and have excellent pharmacokinetic profiles (86, 87). They are small and easy to synthesize (87), readily soluble in water, and resistant to peptidase degra-

dation. The presence of a *D*-amino acid in either the first or the second position minimizes aminopeptidase degradation, and amidation of the C-terminus reduces hydrolysis from the C-terminus. The ability of SS-02 to penetrate the blood–brain barrier is also supported by the observation that SS-02, which also possesses high affinity for the μ-opioid receptor, is a very potent analgesic after subcutaneous administration in mice (95). The duration of analgesia achieved with a single subcutaneous dose of SS-02 was 4 times longer than the duration of analgesia with an equipotent dose of morphine (85). However, the efficacies of SS-02 and SS-31 peptides have not been tested in AD neurons.

Overall, preliminary investigations of these mitochondrially targeted antioxidants are promising to treat mitochondrial diseases, including AD. These mitochondrially targeted antioxidants preferentially enter the mitochondria, where they neutralize free radicals, decrease oxidation, and may protect neurons. However, further research is needed to determine whether these mitochondrially targeted molecules can be used in mouse models of aging and AD before they can go for clinical trials in AD patients.

CONCLUSIONS

Increasing evidence suggests that mitochondria play a significant role in aging and age-related neurologic diseases. Mitochondria are the major source of energy for eukaryotic brain cells to function normally. Dysfunction of mitochondria has been found to lead to the generation of ROS, impaired intracellular calcium levels, and reduced mitochondrial ATP production. Increased production of ROS has been found to damage neurons in neurodegenerative diseases. In recent studies of neurons from postmortem AD brain specimens, transgenic AD mice revealed that oxidative damage induces soluble Aβ, which enters mitochondria early in the disease process and disrupts the ETC, generates reactive oxygen species, and inhibits the production of cellular ATP, which prevents neurons from functioning normally. Further, the accumulation of mtDNA changes may contribute to mitochondrial dysfunction in an age-dependent manner, suggesting that involvement of mitochondrial dysfunction plays a large role in AD progression.

Recently, AD researchers have been studying Aβ toxicity and trying to develop strategies to reduce it. By using anti-amyloid approaches, they are trying to eliminate or to decrease Aβ production and Aβ deposits. However, given the limited success of such approaches, it is high time to develop alternate strategies, such as (a) develop molecules that activate SIRTUINS (calorie restricted diet) and nonamyloidogenic α-secretase activity, and (b) develop mitochondrially targeted antioxidants. Preliminary studies of SIRTUIN activators, such as CR in AD transgenic mice, are promising in decreasing Aβ pathology and ameliorating cognitive deficits. Further investigation of these molecules is urgently needed. It is equally important to test mitochondrially targeted antioxidants for treating elderly individuals and even AD patients. These approaches have thus far shown no adverse effects and may be promising strategies to treat AD patients.

ABBREVIATIONS

Aβ, Amyloid beta; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; ATP, adenosine triphosphate; BACE1, beta-site amyloid precursor protein cleaving enzyme 1; COX, cytochrome oxidase; CR, caloric restriction; ETC, electron-transport chain; FRDA, Friedreich ataxia; H_2O_2, hydrogen peroxide; HD, Huntington disease; IMM, inner mitochondrial membrane; MPT, mitochondrial permeability transition; mtDNA, mitochondrial DNA; $O_2^{\bullet -}$, superoxide radical; OMM, outer mitochondrial membrane; OXPHOS, oxidative phosphorylation; PD, Parkinson disease; ROS, reactive oxygen species; SS peptide, Szeto-Schiller peptide; TCA, tricarboxylic acid.

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Address reprint requests to:
P. Hemachandra Reddy, Ph.D.
Neurogenetics Laboratory
Neurological Sciences Institute
Oregon Health & Science University
505 NW 185th Avenue
Beaverton, OR 97006

E-mail: reddyh@ohsu.edu

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