ANTIOXIDANTS & REDOX SIGNALING
Volume 16, Number 12, 2012

DOI: 10.1089/ars.2011.4277

FORUM REVIEW ARTICLE

Synaptic Mitochondrial Pathology in Alzheimer's Disease

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Abstract

Significance: Synaptic degeneration, an early pathological feature in Alzheimer's disease (AD), is closely correlated to impaired cognitive function and memory loss. Recent studies suggest that involvement of amyloid-beta peptide (Aβ) in synaptic mitochondrial alteration underlies these synaptic lesions. Thus, to understand the Aβ-associated synaptic mitochondrial perturbations would fortify our understanding of synaptic stress in the pathogenesis of AD. ***Recent Advances:*** Increasing evidence suggests that synaptic mitochondrial dysfunction is strongly associated with synaptic failure in many neurodegenerative diseases including AD. Based on recent findings in human AD subjects, AD animal models, and AD cellular models, synaptic mitochondria undergo multiple malfunctions including Aβ accumulation, increased oxidative stress, decreased respiration, and compromised calcium handling capacity, all of which occur earlier than changes seen in nonsynaptic mitochondria before predominant AD pathology. Of note, the impact of Aβ on mitochondrial motility and dynamics exacerbates synaptic mitochondrial alterations. ***Critical Issues:*** Synaptic mitochondria demonstrate early deficits in AD; in combination with the role that synaptic mitochondria play in sustaining synaptic functions, deficits in synaptic mitochondria may be a key factor involved in an early synaptic pathology in AD. ***Future Directions:*** The importance of synaptic mitochondria in supporting synapses and the high vulnerability of synaptic mitochondria to Aβ make them a promising target of new therapeutic strategy for AD. *Antioxid. Redox Signal*. 16, 1467–1475.

Introduction

NEURONS are distinct from many other eukaryotic cells by the unique architecture of the long processes stemming from the cell body. Synapses are the neuronal contact sites through which neurons receive and send information from/to each other (1, 16). Energy provision and calcium fluctuation in synapses are the prerequisite of inter-neuronal communication (73); to meet the high energy demands and to cope with constant calcium flux, mitochondria are enriched in synapses for on-site energy provision and calcium modulation (20, 55, 81). It follows then that deficits in mitochondrial function and amyloid-beta peptide (Aβ) accumulation in synapses lead to reduced synaptic activity and consequent neuronal perturbations. Such concurrent synaptic alteration and mitochondrial dysfunction have been observed in many neurodegenerative diseases including the Alzheimer's disease (AD).

AD characterized by progressive memory loss and cognitive impairment is the most common type of dementia in aged people. The cognitive impairments of patients with AD are strongly associated with synaptic deficits and synaptic loss (36, 84, 89). Studies of synaptic properties have shown that synaptic damage is an early event in the pathogenesis of AD and worsens with disease progression (44, 89). Although the precise etiology of synaptic failure in AD has not yet been elucidated, Aβ is considered to be an underlying pathogenic factor. Although the list of detrimental impact of Aβ accumulation on synapses/synaptic function is ever expanding, recent studies point to mitochondrial dysfunction as a major player in the synaptic alterations seen in AD (25). Notably, recent efforts to identify the changes in synaptic mitochondria in an Aβ-rich environment are significantly advancing our understanding of the mechanisms of synaptic degeneration in AD, especially in early stages before the presence of Aβ sets in motion the devastating cognitive impairments. In this article, we will focus on the subgroup of synaptic mitochondria and summarize the progress to date in research on synaptic mitochondrial alterations in AD.

Mitochondria at Synapses

Mitochondria are the energy warehouse of eukaryotic cells. In addition to their bioenergetics trait, mitochondria play a crucial role in maintenance of intracellular calcium homeostasis and induction of apoptosis, thus meaning that mitochondria are essential organelles in cell survival. Increasing evidence suggests that mitochondria in different types of cells

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and even in different subcompartments of one cell differ significantly in their function, morphology, and other properties; accordingly, mitochondria within one cell can be divided into multiple subgroups (43, 83). This recognition of mitochondrial heterogeneity facilitates our understanding of mitochondrial biology and even more so of mitochondrial pathology in many pathological scenarios.

A typical pattern of mitochondrial heterogeneity is seen in neurons. According to their physical position, neuronal mitochondria are categorized into synaptic mitochondria and nonsynaptic mitochondria (19, 25, 82). Although they share the same origin, synaptic mitochondria present in various sizes, trafficking patterns, function, lifespan, and other properties compared with their relatives residing in neuronal soma (4, 12, 46). Synaptic mitochondria are defined as those docked and aggregated in synapses; they play an important role in maintaining normal synaptic function through their ability to meet the high-energy demand of synapses while maintaining synaptic calcium. It is generally accepted that synaptic mitochondria are long lived but are more vulnerable to cumulative damage than nonsynaptic mitochondria (4). Several laboratories including ours have shown that synaptic mitochondria undergo increased oxidation during aging (2, 25, 54). In addition, synaptic mitochondria have higher levels of cyclophilin D (CypD), thus rendering them more susceptible to calcium insult (4, 25, 60). Our recent study demonstrated that synaptic mitochondria had higher levels of Aβ accumulation significantly before such accumulation in nonsynaptic mitochondria in a transgenic AD mouse model overexpressing Aβ (25). Thus, improved understanding of synaptic mitochondrial biology and pathology mechanisms is especially important as we attempt to further elucidate the etiology of synaptic degeneration in pathological scenarios such as aging and AD.

Synaptic mitochondria and synaptic neurotransmission

Neurons form a network to exchange information. The propagation of information is achieved by synaptic transmission, which entails presynaptic neurotransmitter release to synaptic cleft to stimulate postsynaptic neurons. ATP is essential to many steps of synaptic transmission such as the tethering, uncoating, and refilling of synaptic vesicles (50, 59, 81). It has been proposed that ATP *per se* is a neurotransmitter for the fast synaptic transmission (6). Although the glycolysis process contributes a modest level of ATP, neurons normally derive ATP from aerobic respiration *via* mitochondrial oxidative phosphorylation (5). However, in many pathological scenarios such as ischemia, deprivation of mitochondrial respiration leads to decreased ATP production and compromised synaptic transmission (18, 68). Further, the administration of glucose to enhance ATP production can efficiently attenuate protonophore-instigated synaptic depression (9, 61). These findings suggest the importance of mitochondrial ATP in supporting normal synaptic transmission.

Calcium is another essential player in neurotransmission and is also involved in neuronal plasticity. Synaptic membrane potential depolarization induces activation of voltage-dependent calcium channels, which consequently stimulates calcium entry into presynapses with rapidly increased calcium levels at intra and presynapse sites (38, 40). The rise in calcium levels is the initiating step for synaptic vesicle transport and membrane fusion release as well as for reuptake of neurotransmitters (15, 32, 47, 76); such transient increases in synaptic calcium levels are subsequently quenched to avoid injury due to long-lasting calcium stimulation (17, 20). Prevailing opinion supports the notion that mitochondria play a central role in regulating calcium ions in synapses after calcium influx (3, 66, 67). Although mitochondria and endoplasmic reticulum (ER) are major cellular structures with calcium buffering capacity, it has been shown that synaptic mitochondria have more rapid calcium uptake than ER and that mitochondria more quickly release calcium to sustain prolonged neurotransmitter exocytosis (64, 66, 67). The communication between ER and mitochondria is probably a part of an important mechanism for regulation of intra-synaptic calcium (56, 64). Therefore, synaptic transmission relies largely on mitochondria accumulation in synapses and mitochondrial ability to modulate calcium levels. The density of synaptic mitochondria and their role in energy provision and calcium modulation are key factors working to support synaptic transmissions. Deficits in synaptic mitochondria compromise synaptic activity.

Synaptic mitochondrial generation and trafficking

Mitochondria are membrane-bound mobile organelles that undergo constant movement in neurons and accumulate in synapses to meet synaptic energy demands. Although there are several copies of DNA in mitochondrion, mitochondrial DNA only encodes 13 essential mitochondrial proteins (less than 5% of all mitochondrial proteins). In fact, most essential mitochondrial proteins are encoded by nucleic DNA and then imported into mitochondria. Mitochondrial synthesizing and packaging machineries are located in the perinuclear region of neuronal cytoplasm and are extremely deficient in dendrites and axons (13, 39). Therefore, mitochondria are generated in neuronal soma and transported to synapses *via* mitochondrial transport systems to achieve their synaptic support function. Based on studies to date, kinesin is responsible for mitochondrial anterograde transport that carries mitochondria from soma to the distal axon tip (35, 63); and dynein is important for mitochondrial retrograde transport that inversely sends mitochondria toward the proximate axon end (63). Adaptor proteins play an important role in binding mitochondria to motor proteins (kinesin and dynein). A variety of adaptor proteins have been identified to connect mitochondria to kinesin, that is, Miro (70), Milton (57) and syntabulin (77). These adaptor proteins play a dual role in mitochondrial trafficking—they tie mitochondria to kinesin, thus enabling mitochondrial transport from soma to synapses; on the other side, these adaptor proteins dissociate from kinesin to enable mitochondrial docking around synapses. For example, Miro, a calcium sensor protein, recognizes a high level of calcium and then discharges mitochondria from kinesin (7, 48). Mitochondrial transport is also regulated by multiple intracellular signaling pathways such as protein kinase A (PKA) (69), glycogen synthase kinase 3β (GSK 3β) (21, 69), and mitogen-activated protein kinase (MAPK) (75) that control mitochondrial undocking from motor proteins. The finely controlled mitochondrial trafficking and docking processes enable mitochondria to be physically adjacent to synapses to modulate synaptic function.

Alterations of Synaptic Mitochondria in AD

Mitochondrial dysfunction is recognized as a predominant AD pathological change that occurs concurrently with synaptic alterations and exacerbates disease progression. Based on the critical role of synaptic mitochondria in sustaining synaptic activity, recent efforts have focused on unraveling the mechanisms driving synaptic mitochondrial dysfunction as a potential player in synaptic failure in AD.

Deficits in synaptic mitochondrial function in AD

Investigations into the pathogenesis of AD in the past century have yielded a large body of evidence showing that Aβ and Aβ-associated cellular changes are important causative factors underlying neuronal perturbation and synaptic distress in AD. Aβ is a small molecule cleaved from amyloid-beta precursor protein (APP) by the proteolysis of β- and γ-secretases. Aβ plaques and intra-cellular, particularly intra-mitochondrial Aβ, are pathological features in AD. Notably, recent studies revealed that Aβ accumulates inside AD brain mitochondria including synaptic mitochondria (Fig. 1) (11, 22–26, 30, 37, 49, 51, 62, 79, 80, 92, 93) and that the levels of mitochondrial Aβ are associated with abnormalities of mitochondrial structure and function. Indeed, mitochondrial malfunction has been documented in the studies on human AD and AD animal models as well as Aβ-overexpressing cell models, thus suggesting that deficits in mitochondrial function occur in an Aβ-rich environment. The most recognized forms of mitochondrial dysfunction in AD include Aβ accumulation in brain mitochondria, decreased mitochondrial ATP provision, elevated mitochondria-associated oxidative stress, increased mitochondrial permeability transition, reduced mitochondrial calcium modulating capacity, impaired respiratory function, and release of pro-apoptogenic factors from mitochondria (10, 24–26, 42, 49, 62, 65, 71, 79, 80, 92). Synaptic mitochondria are an early target of Aβ, thus demonstrating early pathological changes before observed global brain mitochondrial damage.

Synaptosomes are membrane-sealed neuronal terminals containing synaptic mitochondria and other synapse-related structures such as synaptic vesicles and lysosomes (29, 72). In a Mungarro-Menchaca *et al*. study, incubation of synaptosomes from Wistar rats with Aβ25–35 (58) altered ultrastructure of synaptosomes with swollen synaptic mitochondria and significantly reduced the number of synaptic vesicles. The combination of Aβ with Ryanodine, an agonist of Ryanodine receptor, exacerbated the aforementioned ultrastructural changes of synaptic mitochondria and synaptic vesicles, thus suggesting that Aβ toxicity is more predominant in calcium-stressed synaptosomes (58). Additionally, an independent *in vitro* experiment using Aβ1–40 to treat synaptosomes isolated from C57B mice demonstrated remarkable synaptic mitochondrial changes, including membrane potential collapse, mitochondrial calcium accumulation, and increased free radical production (41); these studies raise the possibility of the potential impact of Aβ on synaptic activity and synaptic mitochondrial properties. Lastly, an *in vivo* study in human patients with AD and an AD mouse model (Tg2576 mice) provided direct evidence of the existence of Aβ and Tau pathology in synaptosomes (33, 34).

Since synaptic mitochondria are more vulnerable to cumulative damage induced by deleterious factors such as Aβ, it is possible that synaptic mitochondria undergo earlier changes than detectable alterations in global brain mitochondria. An AD mouse model (Tg mAPP mice) demonstrates age-dependent brain Aβ accumulation starting in 4–5-month-old mice and exacerbating with age, thus mimicking the process of Aβ pathology in human AD (25). Tg mAPP synaptic mitochondria from young mice in which no brain Aβ plaques

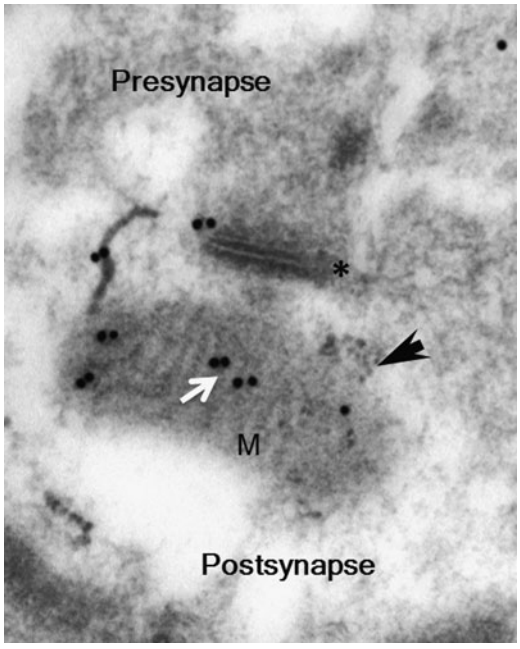

FIG. 1. Accumulation of Aβ in synaptic mitochondria. Immunogold electron microscopy images with a specific Aβ1–42 antibody followed by gold-conjugated antibody (18 nm) to show the presence of intra-mitochondrial Aβ accumulation (*white arrow*) in 12-month-old Tg mAPP. The *black arrow* denotes mitochondria. The asterisk (*) denotes a synapse. M indicated mitochondria. Aβ, amyloid-beta peptide; APP, amyloid-beta precursor protein.

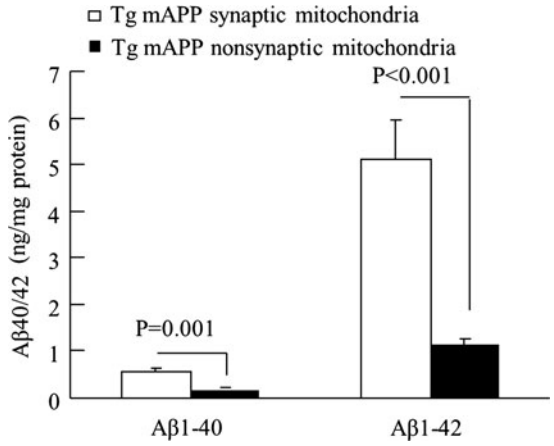

FIG. 2. Synaptic mitochondria are more vulnerable to Aβ accumulation. Synaptic mitochondria and nonsynaptic mitochondria were prepared from Tg mAPP mice at age of 4 months and subjected to measure the levels of Aβ1–40 and Aβ1–42. The data showed that levels of both Aβ species were significantly increased in synaptic mitochondria.

were found showed significant accumulation of Aβ; in contrast, the Aβ levels in the same preparations of Tg mAPP nonsynaptic mitochondria were significantly lower (Fig. 2). Both Tg mAPP mouse synaptic and nonsynaptic mitochondria demonstrated elevated Aβ levels with age, but Tg mAPP synaptic mitochondria had a more prominent increase in Aβ levels than nonsynaptic mitochondria in Tg mAPP mice at the same age. These results provide evidence that synaptic mitochondria are more vulnerable to Aβ accumulation than nonsynaptic mitochondria and that synaptic mitochondrial Aβ aggregation is an early mitochondrial pathological process relevant to the Aβ pathology.

As a result, Aβ-insulted synaptic mitochondria from young Tg mAPP mice undergo significant decline in respiratory function and cytochrome c oxidase activity, increased oxidative stress, and enhanced probability of mitochondrial permeability transition pore processes (25). Further, Aβ-insulted synaptic mitochondria also showed increased expression of CypD and Aβ-binding alcohol dehydrogenase (ABAD). Both mitochondrial proteins (CypD and ABAD) have been shown to interact with Aβ, thereby accelerating and exacerbating mitochondrial stress in an Aβ-rich environment (24, 26, 27, 49, 60, 80, 91). In contrast, nonsynaptic mitochondria isolated from young Tg mAPP mice demonstrated preserved function comparable to those in age-matched wild type mice. However, both synaptic and nonsynaptic mitochondria from aged Tg mAPP mice presented compromised function, but changes in synaptic mitochondria were more profound. These findings suggest that synaptic mitochondria are an early victim of Aβ and undergo pathological changes before nonsynaptic mitochondria. Consistent with our observation, Gillardon's study reported detectable Aβ accumulation in synaptosomal fractions from young Tg2576 mice (another AD mouse model) before detectable brain Aβ plaques; accordingly, synaptic mitochondria were functionally compromised in these young Tg2576 mice (34). Taken together, these data indicate that synaptic mitochondrial functional disturbances are early deficits in the progress of AD and synaptic mitochondrial dysfunction is a key player in Aβ-mediated mitochondrial and neuronal toxicity.

Synaptic mitochondrial transport and dynamics change in AD

Mitochondria are mobile and dynamic organelles. The accumulation of mitochondria in synapses depends on mitochondrial transport to neuronal terminals. The constant mitochondrial fusion and fission regulates mitochondrial density and morphology and is closely related to mitochondrial function. Indeed, concomitant mitochondrial dysfunction and motility change has been observed in patients with AD and Aβ overexpression cell lines as well as in AD animal models. As a major causative factor of AD, Aβ disrupts mitochondrial motility and dynamics in neurites, thus resulting in disorganized synaptic mitochondrial distribution. Rui *et al.* showed that acute treatment with 20 μM Aβ25–35 on cultured cortical neurons caused a significant decrease in neuronal mitochondrial movement (69). Several other laboratories have obtained similar results regarding the impact of Aβ on neuritic mitochondrial movement including axonal mitochondrial transport (8, 21, 25, 85). Two recent studies using chronic treatment of low concentration, for example, 200 nM, oligomeric Aβ on neurons, which mimics the Aβ toxicity in AD brains, reported significant alterations in axonal mitochondrial transport (21, 25). Impairment on anterograde movement of Aβ–superimposed axonal mitochondria is more pronounced than on retrograde movement (8, 25) as shown by decreased percentage of anterograde mitochondria and reduced mobility of anterograde speed. In contrast, the retrograde speed is not significantly decreased after treatment with 200 nM oligomeric Aβ for 24 h (Fig. 3) (25). The precise mechanism of this discrepancy in impairment on mitochondrial anterograde and retrograde movement remains unknown. Given that PKA and GSK 3β signaling cascades are implicated in Aβ-induced mitochondrial trafficking impairments (21, 69) and that activation of PKA or suppression of GSK 3β rescues Aβ-injured mitochondrial motility (21, 69), interference with the mitochondria-dependent signal transduction pathway might be a key factor involved in synaptic mitochondrial transport and trafficking such as Aβ-mediated injury.

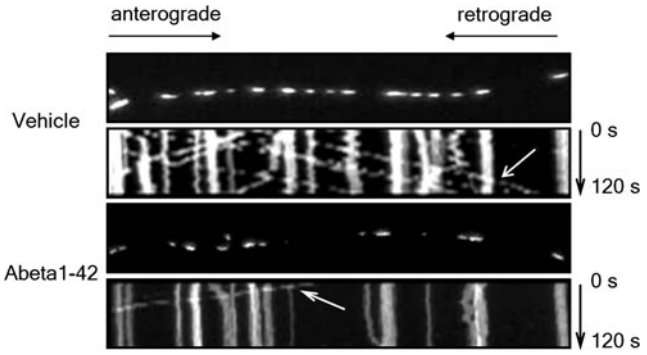

FIG. 3. Aβ affects axonal mitochondrial movement. Representative kymograph images of the vehicle and Aβ1–42-treated axonal mitochondrial movement showing injured axonal mitochondrial movement. The *arrows* denote the traces of mitochondrial movement.

In addition to changes in mitochondrial movement, Aβ also is an instigating factor in abnormal mitochondrial dynamics, thus leading to defects in mitochondrial fusion and fission. A series of studies from the Zhu's laboratory demonstrated the altered expression levels of mitochondrial fusion- and fission-related proteins that are thought to be associated with increased mitochondrial fission and lowered mitochondrial fusion in an Aβ-rich environment (86–88). This imbalance in mitochondrial dynamics resulted in increased mitochondrial fragmentation, decreased neuritic mitochondrial density, and altered synaptic mitochondrial distribution. Similar changes have been further observed in patients with AD, APP overexpressing cell lines, and Aβ-treated primary cultured neurons in several studies (8, 25, 52, 87, 88) including ours (Fig. 4). Among many changes in mitochondrial fusion and fission proteins in AD, dynamin-like protein 1 (Dlp1) has been intensively studied—reports showed changes in Dlp1 expression levels (87), increased Drp1 S-nitrosylation (14), and Drp1 interaction with Aβ (52), thus implicating the role of Dlp1 in neuronal mitochondrial dynamics changes seen in AD.

Changes in Aβ-related neuronal/synaptic mitochondrial motility and dynamics are closely related to synaptic mitochondrial malfunction as well as consequent impaired synaptic function. Therefore, although the studies on mitochondrial

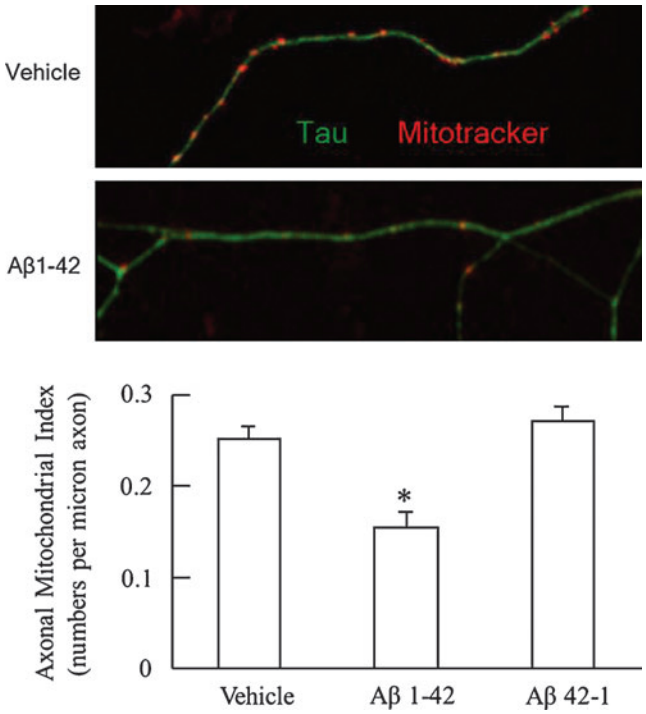

FIG. 4. Aβ alters axonal mitochondrial distribution. The axonal mitochondrial density is decreased after Aβ1–42 (200 n*M*) treatment for 24 h on cultured hippocampal neurons (*Lower panel*). *$p < 0.05$ vs. cells treated with vehicle or reversed Aβ42-1. The *upper panel* shows representative images for vehicle- or Aβ-treated axonal mitochondrial distribution. Double immunostaining with Mitotracker (red, mitochondrial marker) and Tau (green, axonal marker) was performed. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

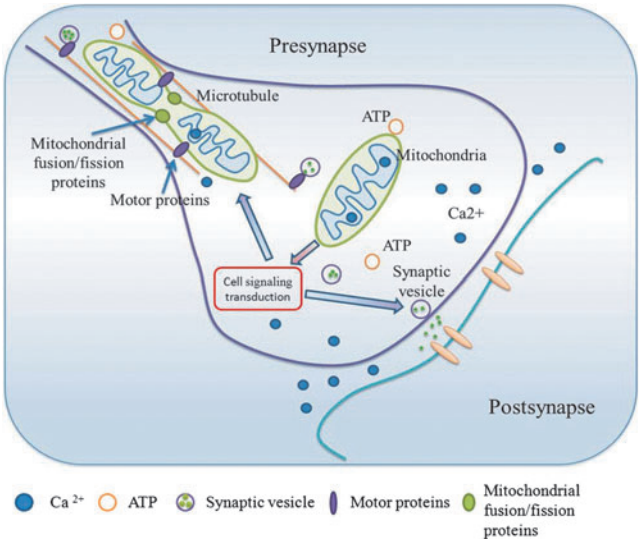

FIG. 5. Schematic figure to show the role of synaptic mitochondria in supporting synaptic activity. Synaptic mitochondria are generated in neuronal soma and further transported to synapses. Normal synaptic mitochondrial movement, docking, and dynamics are crucial features for mitochondria to exert their function on ATP production, calcium modulation, and regulation of cell signaling cascades, consequently maintaining synaptic plasticity and transmission. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

motility and dynamics change in AD are still at an early stage, elucidation of the detailed mechanisms will be likely to fully depict the role of synaptic mitochondrial morphological and transport changes in mitochondrial and neuronal injury in AD.

Summary and Perspectives

Increasing evidence suggests the close correlation of brain mitochondrial dysfunction with synaptic degeneration, both of which are early lesions in AD. Here, we focused on changes in synaptic mitochondria in AD, particularly on the exposure to Aβ and summarized recent progress in the study of Aβ-related synaptic mitochondrial pathology. Due to their physical proximity to synapses, synaptic mitochondria demonstrate a critical role in directly supporting synaptic activity; in addition, synaptic mitochondria undergo constant activation to meet energy demands and control calcium modulation in synapses. Correspondingly, in comparison to somatic mitochondria, synaptic mitochondria are more vulnerable to cumulative damages due to Aβ insult (4, 25, 60). Synaptic mitochondria demonstrate early Aβ accumulation, impaired respiration, lowered calcium handling capacity, and enhanced oxidative stress (25). Importantly, synaptic mitochondria undergo pathological changes before nonsynaptic mitochondria in presymptomatic AD animal models even in conditions of

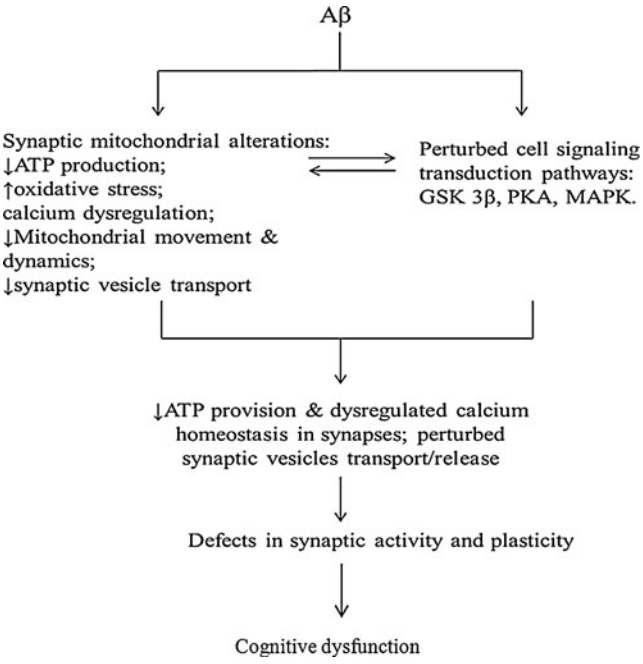

FIG. 6. Working hypothesis. In the presence of Aβ, mitochondrial transport and dynamics are injured with compromised synaptic mitochondrial structure and function, thus leading to decreased energy metabolism, dysregulated calcium homeostasis, and perturbed cell signaling cascades, eventually leading to synaptic injury and cognitive dysfunction.

low or undetectable levels of Aβ in nonsynaptic mitochondria. In scenarios with substantial Aβ pathology, synaptic mitochondrial injury is still more predominant than nonsynaptic mitochondrial damage. Moreover, the negative effect of Aβ on synaptic mitochondrial motility and dynamics significantly and adversely impacts normal synaptic distribution, density, and morphology, which, in turn, substantially compromises effects of synaptic mitochondria on synaptic function (Figs. 5 and 6). Thus, although alterations of synaptic mitochondria in AD are a nascent target of AD pathogenesis, the resultant early deficits and high vulnerability of synaptic mitochondria in response to Aβ toxicity have attracted intensive research efforts. A more complete understanding of synaptic mitochondrial dysfunction in AD will also broaden our knowledge regarding the pathogenesis of this neurodegenerative disease. Current study in this field is just beginning, and more detailed mechanisms of synaptic mitochondrial pathology in AD should be elucidated to address the following questions: (i) what are the reasons/mechanisms of early Aβ deposition in synaptic mitochondria; (ii) what are the precise mechanisms controlling synaptic mitochondrial motility and dynamics in "normal" and Aβ-related scenarios; and (iii) what is the impact of early synaptic mitochondrial dysfunction on synapses. We believe that the answers to these questions will provide new insights into synaptic mitochondrial structure/properties relevant to AD pathogenesis and, in particular, Aβ-mediated synaptic pathology.

Early changes in synaptic mitochondria before devastating Aβ pathology in AD and the importance of synaptic mitochondria for normal synaptic activity make synaptic mitochondria a preferential target for the treatment of AD. Previous studies have provided evidence for the protection of mitochondrial function in ameliorating synaptic changes and the consequent cognitive impairments in AD animal models. A representative example of the many mitochondria-protecting approaches is the application of antioxidants to human AD, AD animal and cell models, which demonstrates significant amelioration of mitochondrial/neuronal dysfunction against Aβ toxicity (28, 31, 74, 90). More recent studies suggested the striking efficacy of mitochondria-targeting antioxidants including MitoQ, SS peptides, and MitoE in strengthening mitochondria in their respiration, membrane potential, and calcium-handling capacity from toxic insults including the Aβ (45, 53, 78). It is noted that MitoQ and SS31 significantly reversed Aβ-induced CypD elevation, mitochondrial fusion/fission proteins imbalance, and neurite growth in AD cell models, thus suggesting the close relationship between neuronal mitochondrial dysfunction and neuronal/synaptic perturbation and the value of eliminating neuronal mitochondrial oxidative stress in the treatment of neuronal/synaptic alterations in AD (53). Thereby, interventions affecting mitochondrial activity are likely promising therapeutic strategies for halting and treating AD. Rescuing and protecting synaptic mitochondria in presymptomatic subjects or in patients suffering from AD with mild cognitive impairments may be appropriate targets for amelioration of synaptic alterations at the early stage of AD.

Acknowledgments

This work was supported by the National Institute on Aging (NIH/NIA PO1AG017490, R37AG037319, R21AG040011, and K99AG037716) and the Alzheimer's Association.

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Date of first submission to ARS Central, September 13, 2011; date of acceptance, September 25, 2011.

Abbreviations Used

Aβ = amyloid-beta peptide
ABAD = amyloid beta-peptide binding alcohol dehydrogenase
AD = Alzheimer's disease
APP = amyloid-beta precursor protein
CypD = cyclophilin D
Dlp1 = dynamin-like protein 1
ER = endoplasmic reticulum
GSK 3β = glycogen synthase kinase 3β
MAPK = mitogen-activated protein kinase
PKA = protein kinase A