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Critical Review

Mitochondrial Aβ: A Potential Cause of Metabolic Dysfunction in Alzheimer's Disease

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Summary

Deficits in mitochondrial function are a characteristic finding in Alzheimer's disease (AD), though the mechanism remains to be clarified. Recent studies revealed that amyloid β peptide (Aβ) gains access into mitochondrial matrix, which was much more pronounced in both AD brain and transgenic mutant APP mice than in normal controls. Aβ progressively accumulates in mitochondria and mediates mitochondrial toxicity. Interaction of mitochondrial Aβ with mitochondrial enzymes such as amyloid β binding alcohol dehydrogenase (ABAD) exaggerates mitochondrial stress by inhibiting the enzyme activity, releasing reactive oxygen species (ROS), and affecting glycolytic, Krebs cycle and/or the respiratory chain pathways through the accumulation of deleterious intermediate metabolites. The pathways proposed may play a key role in the pathogenesis of this devastating neurodegenerative disorder, Alzheimer's disease.

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Keywords Alzheimer's disease; amyloid β peptide; mitochondria; amyloid β binding alcohol dehydrogenase.

INTRODUCTION

Alzheimer's disease (AD) is the most common etiology of dementia in the elderly and causes gradual, relentless cognitive deterioration resulting in memory loss as well as other behavioral changes. The accumulation of amyloid-β peptide (Aβ) has been recognized to play an important role in causing this devastating disorder (*1*, *2*). Aβ is a 39 to 43 amino acid peptide cleaved from amyloid-β peptide precursor protein (APP), which is a 695 to 770 amino acid transmembrane protein encoded by the gene located at chromosome 21q (*3*, *4*). Three proteinases (α-secretase, β-secretase and γ-secretase) have been suggested to be involved in the post-translation processing of APP. Cleavage by α-secretase in the middle of the Aβ sequence precludes the production of Aβ (*5*). However, sequential cleavage of APP by β- and then γ-secretase produces Aβ peptide with a degenerated C-terminus (*6*–*8*). Extracellularly, Aβ can take various molecular conformations ranging from oligomer to highly aggregated amyloid fibers, a major component of amyloid plaques. Microscopic studies have demonstrated that, around the amyloid plaques, neurons undergo granulovacuolar degeneration, the formation of neurofibrillary tangles, and apoptosis (*9*, *10*). The affected neurons show a progressive degeneration of the dendritic arbor, a decrease in protein synthesis, and impaired axonal transport (*11*). Various mechanisms have been proposed to explain the relationship between amyloid accumulation and neuronal dysfunction, which include oxidative stress, perturbation of intracellular calcium homeostasis, and the activation of apoptotic pathways (*12*). Here we will summarize the data indicating that Aβ can progressively accumulate within mitochondria and lead to mitochondrial dysfunction through interfering with neuronal bioenergetics and propose that cerebral hypometabolism related to mitochondrial dysfunction might have an important implication in the pathogenesis of AD.

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CEREBRAL HYPOMETABOLISM IN AD

[^{18}F] 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET scan) has been widely used to measure the regional metabolic rate for glucose in the AD brain. As an indicator of glucose phosphorylation by hexokinase, the tracer accumulates in the areas with dense synaptic content. It is

believed that the observed hypometabolism in the pathological conditions may result from gross structural atrophy, loss of neurons, the simplification of synaptic architecture, or the inhibition of neuronal energy metabolism. Wolfe et al. (*13*) demonstrated that AD-related hypometabolism is usually most pronounced in the parietotemporal regions, followed later by a reduction in the frontal association areas. Typical PET scan abnormalities found in AD patients include either focal cortical hypometabolism in the parietal, temporal, and/or frontal lobes, or diffuse hypometabolism in associative cortex with relative sparing of sensorimotor cortex (*14*). In the early phases of the illness, parietotemporal hypometabolism may be asymmetrical, and at least one parietotemporal region is hypometabolic in about 92% of AD patients (*15*, *16*). Among carriers of the APOE4 allele, a common susceptibility gene for late-onset AD, the presence of temporoparietal hypometabolism on PET scans can predict which patients are at greatest risk for AD (*14*, *17*). Recent studies also demonstrated that cognitively normal, late-middle-aged carriers of the APOE4 allele have abnormally low rates of glucose metabolism (*18*, *19*), implying that carriers of a common Alzheimer's susceptibility gene have low glucose metabolic rate several decades before the onset of dementia (*2*). Pattern of with reduced metabolism can also predict cognitive decline in normal elderly subjects (*20–22*). Because the degree of hypometabolism correlates closely with the degree of clinical impairment, measurement of hypometabolism was used to follow the progression of the disease in some of studies. Although the sensitivity and specificity for diagnosis has not reached clinical requirements, the results obtained thus far indicate that regional glucose hypometabolism is a consistent feature of AD pathology.

METABOLIC ENZYME DEFECTS IN AD

Correlating with the *in vivo* evidence of regional impairment of glucose metabolism in AD found with PET scanning, *in vitro* biochemical studies with brain homogenates have also demonstrated AD-associated enzymatic abnormality in several steps of the Krebs cycle. Assaying homogenates from the autopsied AD brain, Perry et al. (*23*) revealed a decrease of pyruvate dehydrogenase (PDH) activity in the frontal, temporal, and parietal cortex, which was confirmed by several other studies (*24–26*). Alpha-ketoglutarate dehydrogenase (KGDH) has been considered as a rate-limiting enzyme of the Krebs cycle and consists of 3 subunits, E1k, E2k and E3. Gibson et al. (*27*, *28*) found that KGDH activity was significantly reduced in the AD temporal and parietal cortex. Several studies have demonstrated that the diminished activity does not correlate with severity of pathology, indicating that the diminished KGDH activity precedes the development of pathology. The changes of immunoreactivity of the enzyme components do not correspond to the reduction in activity, suggesting that posttranslational modification or inhibition causes a decrease in KGDH activity (*29*). Brains from familial AD patients bearing the APP670/671 mutation also have reduced protein levels of E1k and E2k, but not E3, as determined by immunoreactivity (*30*). Thus, even in forms of AD where the primary deficit is in APP processing, changes in mitochondrial oxidative functions might also be an important component in the cascade leading to AD pathology.

Further assays for multiple Krebs cycle enzymes in autopsy dorsal lateral prefrontal cortex from AD brains by Bubber et al. (*31*) showed a significant decrease in the activities of PDH (−41%), isocitrate dehydrogenase (ICDH, −27%), and KGDH (−57%). The activities of succinate dehydrogenase (complex II) (+44%) and malate dehydrogenase (+54%) were increased, whereas the activities of citrate synthase, aconitase, succinate thiokinase, and fumarase were found to be unchanged. The decrease of PDH and KGDH activities is correlated with a deteriorated clinical dementia rating (CDR) score and the decrease of PDH activity is correlated with increased mean plaque count. PDH, ICDH and KGDH are the dehydrogenases in the first half of Krebs cycle and they are also decarboxylating enzymes. It is not clear whether this represents a coordinated regulation of metabolic pathways, or a specific vulnerability to AD pathology due to the shared enzymatic properties. Furthermore, it is unclear to what extent these marked energetic impairments of AD could be genetic or acquired. Thus far, the search for mutations associated with these defects has been largely inconclusive, suggesting an acquired mechanism.

RESPIRATORY CHAIN DYSFUNCTION IN AD

The mitochondrial respiratory chain is composed of five enzyme complexes embedded in the inner membrane of the mitochondria. The reduced equivalents of NADH+ and FADH derived from the oxidation of carbohydrates and fatty acids flow from complex I through complex IV via a series of oxidation-reduction events. The released energy during the process charges the inner mitochondrial membrane and drives ATPase (complex V) to synthesize ATP from ADP and inorganic phosphate.

In 1990, Parker et al. (*32*) assayed complex IV, cytochrome oxidase (COX), and other electron transport chain activities in platelet mitochondria isolated from patients with Alzheimer's disease. Five of the six patients had an over 50% reduction of platelet COX activity. Other electron transport chain catalytic activities were not significantly different from those of controls. Parker et al. (*33*) later demonstrated that, while concentrations of cytochromes *b*, *c1*, and *aa3* (a physical representation of COX) remain stable in AD, there is a general depression of respiratory chain enzyme activities with the most severe defect in COX activity. Purified COX from AD brains displayed anomalous kinetic behavior compared with control brain COX in that the low *K*m binding site was kinetically

unidentifiable, implying there is a structural abnormality with COX from AD brain (*34*).

Kish et al. (*35*) measured the COX activity in homogenates of autopsied brain regions from 19 AD patients and 30 controls. The mean enzyme activity in the average AD brain was reduced in the frontal (−26%), temporal (−17%), and parietal (−16%) cortices. In the occipital cortex and putamen, COX activity was normal, whereas in the hippocampus, COX activity, on average, was elevated (20%). Histochemical assay of the autopsy brain tissues by Valla et al. (*36*) demonstrated that there is a decline in COX activity in AD patients, the most significant decline occurred in the posterior cingulated cortex and most severe in the superficial, synapse-rich molecular layer of cortex.

Various studies have demonstrated impairments of all five complexes in multiple zones of the AD brain (*37–40*). Complex I protein levels were significantly reduced in the temporal, parietal, and occipital cortex from AD brains compared to age-matched controls; complex III protein levels were significantly reduced in the temporal cortex; and complex V proteins were significantly reduced in the hippocampus. Kim et al. (*38*) demonstrated lowered biosynthesis of one subunit of complex I in the temporal and occipital cortices, and of a different complex I subunit in the parietal cortex.

MITOCHONDRIAL TRAFFICKING OF AB

Several studies indicate that addition of Aβ, at micromolar concentrations, can directly damage the neuronal cells by inhibiting mitochondrial respiration and key enzyme activities, including KGDH, PDH, and complex IV activities (*41*, *42*). One of the most consistent findings is diminished complex IV activity of mitochondria in an Aβ-rich environment. Rat brain mitochondria incubated with Aβ showed a decreased stage III and IV in mitochondrial respiration. COX, KGDH, and PDH activities were also diminished in mitochondria incubated with Aβ (*33*, *35*, *40*, *43*, *44*). *In vitro* studies have demonstrated that nanomolar concentrations of Aβ can impair a general measure of cellular dehydrogenase activity (*45*).

Direct physical association between mitochondria and Aβ, as well as its precursor APP, has been demonstrated by several recent studies. The presence of APP in the mitochondrial membrane fraction in the AD brain was initially observed by Yamaguchi et al. (*46*), though the nature of this association and the role of APP in mitochondrial functions was not investigated. Anandatheerthavarada et al. (*47*) further demonstrated that three positively charged residues (Arginine40, Histidine44 and Lysine55) in the N-terminal of APP were essential for mitochondrial targeting. The orientation of APP in mitochondria, based on crosslinking studies, seemed to be embedded in the inner mitochondrial membrane in close association with mitochondrial translocase proteins and with its N-terminus facing the mitochondrial matrix. The C-terminus (about 73 kD) was exposed in the cytosol, and because of an acidic domain in APP (residues 220 to 290), the molecule is trapped in the mitochondrial membrane due to translocation arrest. Thus, APP accumulates in the mitochondrial membrane, and this appears to interfere with mitochondrial functions, including reducing COX activity, diminishing levels of cellular ATP, and decreasing mitochondrial transmembrane potential based on *in vitro* studies. Because APP was trapped in the inner mitochondrial membrane with the C-terminal as well as the Aβ sequence still exposed outside of the inner membrane, this orientation precludes the possibility of producing intra-mitochondrial Aβ through *in situ* cleavage.

Using mitochondria purified from cerebral cortices of transgenic (Tg) mAPP mice (J-20) (*48*), our group demonstrated that Aβ can progressively accumulate in the mitochondria and is associated with diminished enzymatic activity of respiratory chain complexes III and IV, as well as a reduction in the rate of oxygen consumption. The time course of accumulation of Aβ in the mitochondria from the brains of Tg mAPP mice was assessed in animals in 4–24 months of age. The most rapid phase of Aβ accumulation appeared to be at 8–12 months of age, for both Aβ42 and Aβ40. However, levels of Aβ42 were considerably higher than Aβ40, as is true for intracellular Aβ in other compartments. Mitochondrial Aβ was first detectable at 4 months of age, before significant extracellular deposition of Aβ in this animal model. Protease sensitivity assays further showed that a certain amount of Aβ peptide is also protected within the inner membrane compartment, suggesting the Aβ gains access into the mitochondrial matrix rather simply by being absorbed to the external mitochondrial surface (*49*). It is well known that intracellular Aβ is generated in the ER/Golgi compartment, multivesicular bodies, and the endosomal/lysosomal system as well as the cell surface (*50–60*), we hypothesize that Aβ might gain access into the mitochondrial matrix by an intracellular trafficking mechanism instead of through *in situ* processing within the mitochondria. Morphologic studies provide further evidence of the presence of Aβ in mitochondria.

Under confocal microscopy, Aβ42 was shown to co-localize with HSP60, a marker of the mitochondrial matrix. Neurons in the cortex and hippocampus of Tg mAPP mice displayed an overlapping distribution of Aβ42 and HSP60 antigens. About 40% and 20% of mitochondria were stained with Aβ42 in the cerebral cortex and hippocampus, respectively. In contrast, non-Tg littermates showed undetectable Aβ42 antigen (*49*).

After demonstrating intra-mitochondrial accumulation of Aβ, we further determined functional abnormalities in the Aβ-laden mitochondria by using purified mitochondria and measuring the respiratory control ratio (the ratio of oxygen consumption in state III/state IV). Although oxygen consumption was comparable at age 4 months in Tg mAPP mice and non-Tg littermates, by age 8 months there was a trend towards lower levels in Tg mAPP mice that achieved statistical significance by 12 months. Since changes in oxygen consumption could result from multiple defects in mitochondrial

properties, we assessed the activity of key enzymes in respiratory chain complexes to localize possible sites of dysfunction. There were no significant differences in enzymatic activities representative of complex I, II, III, and IV from mitochondria harvested from Tg mAPP mice or non-Tg littermates at 8 months of the age. However, there was a significant decrease in the activity of succinate-cytochrome *c* reductase (complex III) and COX activity (complex IV) by the 10-month time point. These data indicate that the accumulation of Aβ within the mitochondria correlates temporally with changes in mitochondrial function at the level of oxygen consumption and activity of key enzymes in complex III and IV of the respiratory chain (*49*). Using another line of Tg mAPP mice (Tg2576), Manczak et al. also reported the presence of both Aβ40 and Aβ42 inside of mitochondria, which is associated with an increase in hydrogen peroxide level and a decrease in COX activity in the brain (*61*).

The association between mitochondrial Aβ and AD was further supported by the data derived from postmortem AD samples and non-demented (ND) control brains which were harvested with a time delay of less than 3.5 hours. With immunogold staining, we demonstrated the presence of intramitochondrial Aβ in the mitochondria purified from AD brains, but to a much lesser extent in ND control. Confocal microscopic study of double immunofluorescence staining demonstrated that 40% (temporal lobe tissues) and 70% (hippocampus) of the mitochondria from AD brain were costained with an antibody to Aβ versus 5% (temporal lobe) and 14% (hippocampus) from ND control, in the temporal lobe and hippocampus, respectively (Fig. 1) (*49*).

The presence of Aβ in mitochondria suggests that Aβ might target vulnerable mitochondrial structures thereby impair overall properties of the organelle and interfere with its functions. In view of the known effect of Aβ to destabilize membranes, especially at higher concentrations, it is certainly possible that nonspecific mechanisms are responsible for Aβ-induced mitochondrial dysfunction (*62–64*). Through interaction with lipid membranes (*65*), Aβ might have the following consequences: (i) inducing permeability transition pore (PTP) in the inner mitochondrial membrane that would dissipate the proton motive force which drives ATP production (*66*), and (ii) facilitating the release of reactive oxidative species (ROS). Other studies have examined the triggering of apoptotic cascades and organelle swelling following exposure of the mitochondria to Aβ (*67*). The relevance of these results, in which isolated mitochondria were exposed to high concentrations of synthetic Aβ, to the *in vivo* environment is not clear.

ABAD AS AN INTRA-MITOCHONDRIAL TARGET

Using the yeast two-hybrid system, our group identified a specific Aβ binding alcohol dehydrogenase (ABAD) in the mitochondrial matrix [Note: we initially termed this Aß binding polypeptide as ERAB and later have changed its name to ABAD in view of its functional properties (*7*, *68*, *69*)]. ABAD is a 261 amino acid mitochondrial enzyme encoded by HADH2 (MIM: 300256; GeneID: 3028) gene located at chromosome Xp11.2. Due to its functional multiplicity in metabolic homeostasis, various names, such as ABAD, HCD2, MHBD, SCHAD, HSD17B10, 17b-HSD10, have been used in the literature to designate the same enzyme (*68*, *70*, *71*). The name, ABAD, is used in this review to reflect its initial identification through its Aβ binding property and its potential role in mediating Aβ toxicity. In human, point mutations in ABAD have been linked to 2-methyl-3-hydroxybutyryl-CoA dehydrogenase (MHBD) deficiency affecting isoleucine metabolism. Individuals affected by MHBD deficiency characteristically present a progressive loss of mental and motor function starting within the first year of life (*72–75*). Biochemically, MHBD-deficient patients suffer from lactic acidosis accompanied by increased urinary excretion of 2-methyl-3-hydrobutyrate (MHB) and tiglylglycine (TG). A reduction of respiratory chain complex I and IV activities has been demonstrated in the skeletal muscle samples derived from patients with MHBD deficiency (*73*, *76*, *77*). *In vitro*, studies with rat cerebral cortex tissue have shown that MHB at 0.01 mmol/L and higher concentrations inhibits CO_2 production from glucose, acetate and citrate, indicating inhibitory effects on the Krebs cycle, and also shows specific inhibition on respiratory chain complex IV activity (*16*).

In vitro binding studies demonstrated that Aβ42, Aβ40, and Aβ (1–20) each display dose-dependent saturable binding to ABAD. In contrast, the C-terminal portion of Aβ (25–35) does not bind to ABAD, indicating that ABAD-Aβ interaction was not due to nonspecific interaction with aggregated or fibrillar material. This observation also suggested the possibility that Aβ might bind to ABAD via its N-terminus and thereby leaving the C-terminus free, allowing it to multimerize with additional Aβ. Our studies have further proved that Aβ and ABAD form a complex in the mitochondrial matrix. Immunoprecipitation studies of the AD brain demonstrated a complex formation between ABAD and Aβ in brain and mitochondrial extracts (*70*).

The Aβ-ABAD complex has also been studied by high resolution crystallography which demonstrated considerable distortion of ABAD structure in the presence of Aβ (*70*). Specifically, the NAD cofactor was excluded from the structure due to Aβ binding. Aβ binding induced multiple structural changes in the loops of ABAD (L_D, L_E, L_F) whose orientation is important for ABAD activity. Particularly relevant is the observation that the disordered structure of L_D loop was observed only in the Aβ-ABAD complex, but not in crystals of NAD-ABAD. Comparison of the L_D loop of ABAD to other enzymes within this family showed an 11 amino acid insertion, which is unique to ABAD, suggesting the possibility that this might be a site mediating the binding to Aβ. To determine whether the L_D loop is sufficient for Aβ interaction, a peptide encompassing this region

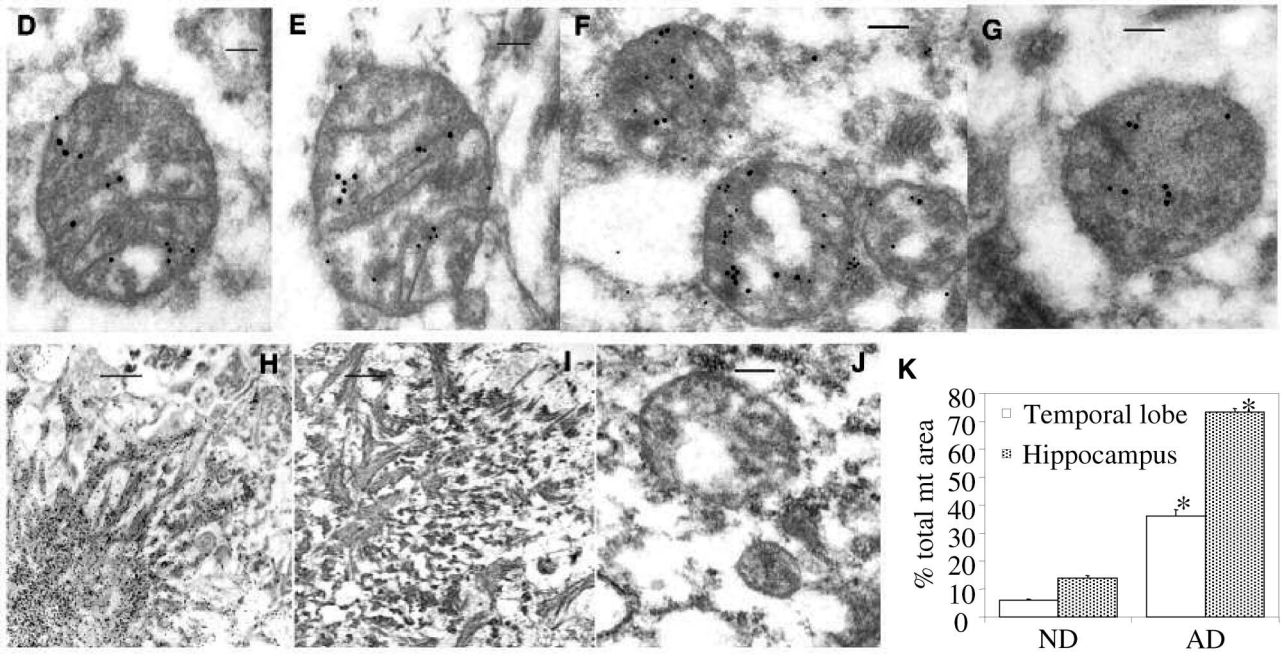

Figure 1. Mitochondrial Aβ is more abundant in AD brains than in non-demented (ND) controls. Mitochondrial Aβ detected with immunogold staining with anti-Aβ42 IgG and electron microscopy in AD brains (D – F) and nondemented brain (G). The positive control is the immunogold staining of plague from brain of Tg mAPP mouse at the age of 8 months (H); the staining is prevented by pre-absorption with Aβ peptide in amyloid plague (I) and mitochondria of human AD brain (J). Panel K is the confocal microscopic result showing the proportion of anti-Aβ42 IgG stained mitochondrial (mt) area in AD brains versus ND controls in both temporal lobe tissue (blank box) and hippocampus (stippled box).

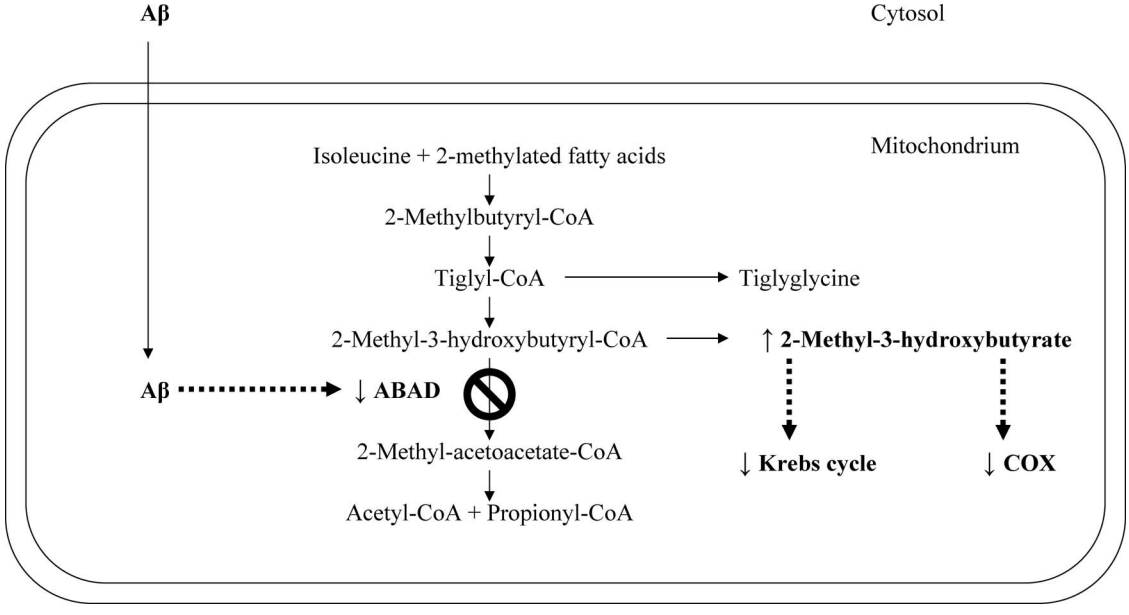

Figure 2. Schematic diagram of Aβ-ABAD interaction in the mitochondrial matrix. Aβ gains access into the mitochondrial matrix via intracellular trafficking and binds to ABAD. Inhibition of ABAD activity due to Aβ binding causes the accumulation of 2-methyl-3-hydroxybutyrate (MHB), which can inhibit the Krebs cycle enzymes and cytochrome *c* oxidase (COX) and leads to mitochondrial dysfunction. Aβ: amyloid β peptide; ABAD: amyloid β peptide binding alcohol dehydrogenase. ↑ denotes increase in activity and ↓ denotes decrease in activity.

(residues 92–120) of human ABAD [termed ABAD decoy peptide (ABAD-DP)] was tested by surface plasmon resonance for its ability to inhibit the interaction of the intact ABAD with Aβ. ABAD-DP inhibited the binding of Aβ40 and Aβ42 to immobilized intact ABAD with inhibitory constants of 4.9 and 1.7 μM respectively, whereas a peptide with the same amino acids, but reversed sequence [term ABAD (120–92) or ABAD reversed peptide or RP] was inactive. These data indicate that the L_D loop of ABAD is critical for Aβ binding to ABAD (*70*).

Initial immunoblot study of temporal lobe homogenates from the AD brain showed increased ABAD immunoreactivity as compared to age-matched normal controls (*69*). The expression of ABAD in the hippocampus can be further induced by overexpression of APP in the transgenic mouse model (*78*, *79*). *In vitro* study revealed that ABAD is an enzyme with broad substrate specificity. As a member of the short-chain alcohol dehydrogenases, ABAD catalyses the reversible NAD/NADH-dependent oxidation/reduction of a range of substrates, including linear alcohols, steroid substrates (such as 17β-estradiol), S-acetoacetyl-CoA and β-hydroxybutyrate using the same catalytic mechanism (*7*, *80*, *81*). Our *in vitro* study demonstrated that the addition of micromolar levels of synthetic Aβ40 to purified ABAD can inhibit its enzymatic activities in reduction of S-acetoacetyl-CoA ($Ki \approx 1.6$ μM), as well as oxidation of 17β-estradiol ($Ki \approx 3.2$ μM) and (-)- 2-octanol ($Ki \approx 2.6$ μM) (*7*).

The relevance of ABAD for promoting Aβ-induced cell stress was demonstrated in studies with transgenic mice overexpressing APP and ABAD in their neurons. These double transgenic mice displayed increased generation of ROS in the brain, by electron paramagnetic resonance spectroscopy, accelerated impairment of energy metabolism as shown by reduction of ATP generation and glucose utilization, and exaggerated spatial learning/memory deficit and neuropathological changes. Cultured neurons from these double transgenic mice showed spontaneous release of ROS (the defect resulting in oxygen free radical production appears to occur at complex III) and cytochrome *c* from their mitochondria. Furthermore, neurons from these double transgenic mice also displayed spontaneous apoptosis (*82*).

CONCLUSION

Both the *in vivo* PET scan data and the *in vitro* biochemical data have implicated that mitochondrial metabolic failure plays a pivotal role in AD pathogenesis. However, the mechanisms involved thus far remain to be elucidated. Based on the recent demonstration of intra-mitochondrial Aβ and the specific interaction of Aβ with a mitochondrial matrix enzyme ABAD, we propose that the inhibitory effect of mitochondrial Aβ on ABAD enzymatic activity intervene in the glycolytic, Krebs cycle and/or the respiratory chain pathways through the accumulation of deleterious intermediate metabolites, such as MHB (Fig. 2). Blockade of accumulation of Aβ in mitochondria and interception of Aβ-ABAD interaction may be an important therapeutic approach for Alzheimer's disease.

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