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·Review·

# Mitochondrial dysfunction and cellular metabolic deficiency in Alzheimer's disease

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**Abstract**: Alzheimer's disease (AD) is an age-related neurodegenerative disorder. The pathology of AD includes amyloid-β (Aβ) deposits in neuritic plaques and neurofibrillary tangles composed of hyperphosphorylated tau, as well as neuronal loss in specific brain regions. Increasing epidemiological and functional neuroimaging evidence indicates that global and regional disruptions in brain metabolism are involved in the pathogenesis of this disease. Aβ precursor protein is cleaved to produce both extracellular and intracellular Aβ, accumulation of which might interfere with the homeostasis of cellular metabolism. Mitochondria are highly dynamic organelles that not only supply the main energy to the cell but also regulate apoptosis. Mitochondrial dysfunction might contribute to Aβ neurotoxicity. In this review, we summarize the pathways of Aβ generation and its potential neurotoxic effects on cellular metabolism and mitochondrial dysfunction.

**Keywords**: Alzheimer's disease; amyloid-β; metabolic deficiency; mitochondrial dysfunction

## 1 Introduction

Alzheimer's disease (AD) is one of the most common forms of neurodegeneration, characterized by extracellular accumulation of neurotoxic amyloid-β (Aβ) peptide, intracellular hyperphosphorylated tau, and loss of synapses and neurons. Aβ precursor protein (APP), conservatively expressed in many types of mammalian cells, is a type I transmembrane glycoprotein[1]. Both upregulated production and deficient removal result in Aβ accumulation. Aβ accumulation in the brain is a key event in the development of AD, resulting in cellular oxidative stress and tau hyperphosphorylation[2]. Therefore, Aβ is considered to be a central molecule and plays a key role in the development of AD. The pathological process of Aβ neurotoxicity, however, is not well known.

Increased protein oxidation and decreased cellular reduction are hallmarks of aging and age-related degenerative processes. Metabolic deficiency, especially in energy, as well as up-regulated oxidative stress, is critical to the development of AD pathology[3,4]. Increasing evidence shows decreased glucose absorption and abnormal glucose metabolism in the brains of AD patients[5,6]. In specific regions like the temporo-parietal and posterior cingulate cortex, an increased amyloid burden is coupled with decreased metabolism[7]. Generally, in the context of global cellular energy, the levels of glucose metabolism and ATP are remarkably decreased in AD patients[3,8,9]. A decrease of energy metabolism in the brain might contribute to the neuronal loss and cognitive decline in AD.

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The metabolic processing of glucose to ATP mainly involves glycolysis in the cytosol and the tricarboxylic acid (TCA) cycle as well as oxidative phosphorylation in the mitochondrial matrix. Glycolysis is the basis of aerobic glucose metabolism to generate cellular energy in the form of ATP. The metabolic pathways of the TCA cycle and oxidative phosphorylation are the center of aerobic glucose metabolism. Some key proteins involved in energy metabolism and ATP production, such as the respiratory chain complex and ATP synthase[9,10], might be expressed abnormally and alter enzymatic activity in the pathological process leading to AD. Oxidative modification of these proteins contributes to their decreased enzymatic activity. The oxidative modification and subsequent inactivation of glycolytic enzymes may result in a substantial decline in cellular metabolism, further inducing mitochondrial dysfunction, and resulting in the release of key factors leading to mitochondrial damage-related apoptosis. Increasing evidence indicates that AD pathology is correlated with mitochondrial dysfunction, including autophagy, fission–fusion dynamics, and biogenesis[11,12]. In this review, we summarize the pathways of Aβ generation and its potential neurotoxic effects causing cellular metabolic deficiency and mitochondrial dysfunction.

## 2 Aβ production and molecular interactions

**2.1 Profiles of APP cleavage** Aβ is considered to play a central and key role in the development of AD. Aβ aggregation in neuritic plaques incurs oxidative neuronal damage, neurofibrillary tangles, and loss of hippocampal neurites and synapses[2]. APP belongs to the type I transmembrane protein family. In humans, the AβPP gene contains 18 exons, of which exons 7, 8 and 15 are alternatively spliced to produce at least 8 splice variants of AβPP mRNA. APP695, APP751 and APP770 are the predominant transcript proteins[1]. APP is known to modulate neuronal responses, such as neuritic growth and synaptic generation and plasticity. Aβ production from APP is a key event for the physiological function of APP and the pathological process underlying AD. Full-length APP770 is cut by α-secretase between amino-acids 687 and 688 in the α-cleavage pathway; the P3 fragment, not Aβ, is derived from APP when γ-secretase cleaves the remaining C83 fragment. However, APP is cut by β-secretase between amino-acids 671 and 672 and by γ-secretase in the transmembrane domain in the Aβ pathway; Aβ peptides of different lengths (39–43 amino-acids) are generated, depending on the site of cleavage by γ-secretase (Fig. 1A). In terms of subcellular structure, however, a question remains over where Aβ is generated. There are three potential means of Aβ production (Fig. 1B). First, Aβ is thought to be shed from the cell surface, based on the facts that APP is an integral membrane protein and that Aβ-rich senile plaques are deposited extracellularly. Second, Aβ is considered to be generated in an endosomal/lysosomal pathway[13-16]. Third, Aβ is suggested to be produced in the endoplasmic reticulum (ER) and Golgi apparatus/trans-Golgi network[17-19], but this needs to be confirmed.

**2.2 Cell surface proteins binding to Aβ** The extracellular accumulation of Aβ in neuritic plaques is one of the characteristics of AD. Therefore, the increased extracellular Aβ is thought to be a key factor in the induction of cell damage, and numerous AD models are based on the exposure of cultured cells to elevated exogenous Aβ. However, the subsequent cell signaling is not well known. By virtue of its structure, Aβ can bind to a variety of molecules, including lipids, proteins and proteoglycans. Binding of the soluble or fibrillar form of Aβ to plasma membrane proteins is regarded as causing the direct toxicity of Aβ to neurons. These membrane proteins include not only the loading and proteolytic proteins but also the receptors on neurons and glia; the former clear the accumulated Aβ, while the latter mediate neuronal signals. Some membrane receptors have been suggested to bind to the monomeric, oligomeric or fibrillary form of Aβ, such as receptor for advanced glycation end-products (RAGE), α7-nicotinic acetylcholine receptor, α-5-β-1 integrins, serpin enzyme complex receptor and neurotrophin receptor (p75NTR), tumor necrosis factor receptor α, the scavenger receptors A and B1 (SR-A, SR-B1), CD36, CD47[20], and other integrins[21]. However, the specific receptors binding to Aβ are still under investigation. The binding of Aβ to receptors may induce

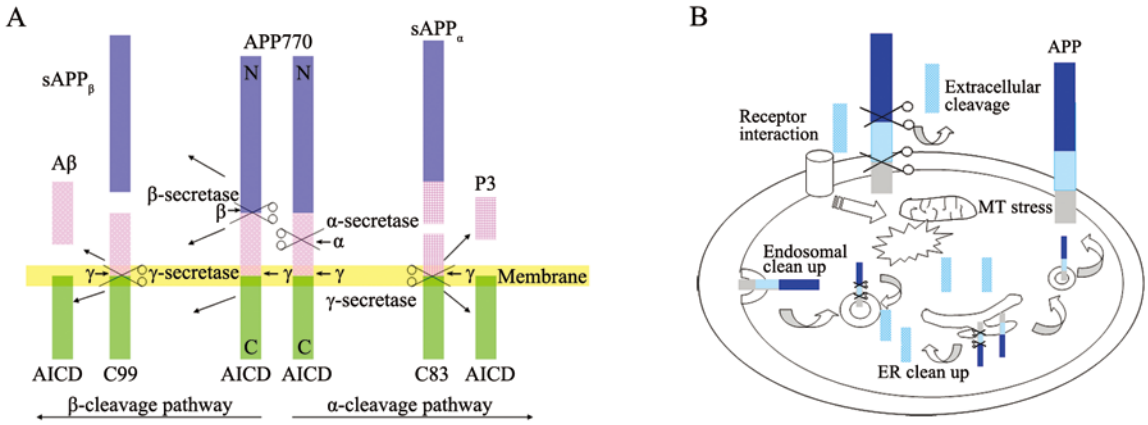


**Fig. 1. APP processing and cleavage pathways. A: Two pathways of APP processing. In the β-cleavage pathway, APP is cleaved into sAPP$_\beta$ (a secretory ectodomain) and C99 (a membrane-bound fragment). The C99 fragment is subsequently cleaved by γ-secretase to generate an intracellular domain of APP (AICD) and Aβ. In the α-cleavage pathway, APP is cleaved into sAPP$_\alpha$ (a secretory ectodomain) and C83 (a membrane-bound fragment). The C83 fragment is subsequently cleaved by γ-secretase to yield a 3-kDa fragment (P3) and AICD[1]. Cited from Huang *et al.* 2011, J Alzheimers Dis[1]. B: Newly-translated APP matures on the endoplasmic reticulum (ER) and Golgi apparatus. On one hand, mature APP is inserted into the cell surface by the delivery of secretory vesicles. On the other hand, either immature or mature APP might be cleaved at the ER and Golgi apparatus/trans-Golgi network. Cell surface APP is not only cleaved to generate Aβ on the cell surface, shedding Aβ into extracellular space, but is also endocytosed by the endosomal/lysosomal pathway and Aβ is shed into intracellular space. Both extracellular and intracellular Aβ might induce mitochondrial (MT) stress.**

trafficking, endocytosis, or phosphorylation of the intracellular domain of receptors, resulting in a subset of cell signals in response to oxidative stress and cellular metabolism.

**2.3 Intracellular Aβ accumulation** Intracellular Aβ has been found in transgenic mice overexpressing mutant human APP and in brains from patients with AD and Down's syndrome[22-24]. Intracellular Aβ is increasingly suggested to participate in pathological processes leading to AD. It is present in AD-affected areas of the brain and seems to appear prior to neurofibrillary tangles and senile plaques[25]. Both intracellular cleavage of APP and Aβ internalization from the extracellular milieu result in its intracellular accumulation[26]. Synaptic loss is a pathological correlate of the cognitive impairment in AD and synaptic dysfunction is considered to be the earliest event in the development of AD. Recently, it was suggested that intracellular Aβ is linked to synaptic activity, and that synaptic activity responds to the intracellular Aβ product[27]. On one hand, synaptic activity is suggested to decrease intracellular secretion of Aβ, which protects synapses[28]. On the other hand, intracellular Aβ accumulation results in a deficit in long-term synaptic plasticity[29,30].

Accumulation of Aβ in intracellular compartments has been demonstrated in the ER, Golgi apparatus, and mitochondria[31,32]. Mitochondria, the organelles that generate energy for the cell, play important roles not only in regulating energy metabolism but also in signaling, including cellular differentiation and apoptosis-programmed cell death. Increasing evidence supports the concept that mitochondrial dysfunction is involved in the ageing process and the pathology of AD and mitochondrial dysfunction occurs early in AD[33].

**2.4 Aβ and mitochondrial Aβ-binding alcohol dehydrogenase (ABAD)** ABAD, first identified in 1997 by Yan *et al.* using a yeast two-hybrid screen[34], is the best characterized intracellular Aβ-binding protein. It is a type-10 member of the protein family known as the 17β-hydroxysteroid dehydrogenases. ABAD was first found in the ER and so was termed ER-associated amyloid-binding protein. Later, it was found to also reside in mitochondria[35]. The traffic of ABAD between the ER and mitochondria may be important for cell survival. ABAD might play important

roles in cellular metabolic homeostasis and in response to mitochondrial stress[36]. Recent studies indicate that Aβ and ABAD are co-localized to mitochondria as visualized by electron microscopy and they co-immunoprecipitate from a mitochondrial preparation. Aβ may interact directly with the mitochondrial enzyme ABAD[37]. Binding of Aβ to ABAD distorts the structure of the enzyme. The structural relationships of Aβ and ABAD show that Aβ binds to ABAD in such a way as to exclude $NAD^+$ binding, which is needed in its enzymatic action[37]. The Aβ-ABAD interaction inactivates the metabolic properties of the enzyme and promotes the mitochondrial generation of free radicals. In APP/Presenilin double-transgenic mice, the level of ABAD is increased in an Aβ-rich environment and the mice demonstrate accelerated formation of senile plaques and a decline in spatial learning/memory[36]. Inhibition of the Aβ-ABAD interaction, however, reduces mitochondrial Aβ accumulation and improves mitochondrial function[38]. Therefore, intracellularly accumulated Aβ may be a factor in the metabolic deficit and in the generation of mitochondrial reactive oxygen species, leading to oxidative cellular damage.

## 3 Oxidative stress and mitochondrial dysfunction

Increasing evidence has supported the concept that accumulated Aβ induces wide oxidative cellular damage, including modified products of nucleic acids[39,40] (e.g., 8-hydroxydeoxyguanosine and 8-hydroxyguanosine) and proteins (e.g., 3-nitrotyrosine and protein carbonyls), as well as products of lipid peroxidation[41] [e.g., 4-hydroxynonenal (HNE), F2-isoprostane and malondialdehyde], protein oxidation[42] and glycoxidation[43] (e.g., carboxymethyllysine and pentosidine). The level of oxidative stress is elevated in cells cultured with Aβ *in vitro* and in the brains of transgenic APP animals and AD patients.

**3.1 Oxidation of lipids, proteins and DNA** Lipid peroxidation is considered to occur early in the pathogenesis of AD and it has two outcomes: structural damage of membrane integrity and the generation of α,β-unsaturated aldehydic by-products including HNE and acrolein. Both HNE and acrolein are elevated in vulnerable brain regions of subjects with mild cognitive impairment[44], preclinical AD[45], and late-stage AD[46,47]. The lipid oxidation by-product HNE may cause protein oxidation and form HNE-protein adducts; therefore the activity of enzymes involved in energy metabolism, such as glucose transporters and ATP synthase, would decrease[48,49]. However, HNE modification of nicastrin, a key subunit of γ-secretase, is suggested to enhance binding to its substrate and to increase γ-secretase activity[50]. Acrolein not only interacts with $NAD^+$ to decrease the production of NADH, but also inhibits the enzymatic activity of NADH-linked mitochondrial pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase, resulting in down-regulation of energy metabolism in the TCA cycle[51].

Increasing and considerable evidence suggests that oxidative damage to DNA begins with mild cognitive impairment and is associated with AD[52]. However, the ability to repair DNA is deficient in neurodegenerative conditions, including AD[53]. The levels of the DNA repair-related proteins Rad50, Mre11 and Nbs1 in the Mre 11 DNA-repair complex are significantly decreased in AD neocortex compared to age-matched controls[53]. Attack by free radicals can lead to strand breaks, DNA–DNA and DNA–protein cross-interactions, and the formation of base adducts. The α,β-unsaturated aldehydic by-products of lipid peroxidation, including HNE and acrolein, can interact with DNA bases leading to the formation of bulky exocyclic adducts. Oxidative damage of mitochondrial DNA (mtDNA) is dramatically increased in AD brains[54].

**3.2 Mitochondrial damage and apoptosis** Morphological changes have been described in brain samples from AD patients. Both mitochondrial profiles (shape and size) and the organization of cristae (fragmentation) are substantially changed in AD[55]. Unlike nuclear DNA, mtDNA is sensitive to oxidative damage due to failure of protection by histones or DNA-binding proteins and in the repair of mtDNA in the central nervous system. In specimens from autopsied AD patients, mitochondrial mass including mtDNA is reduced while mtDNA fragmentation is increased[56]. This damage is correlated with oxidative mitochondrial damage.

Mitochondrial abnormality is a key factor in apoptosis[57-59]. Increasing evidence has indicated that Aβ induces mitochondria-related programmed cell death. In cultured rat cortical neurons and human neuroblastoma cells, exogenous or over-expressed Aβ triggers mitochondrial apoptosis signaling. Under Aβ stimulation, the mitochondrial permeability transition pore tends to open and the mitochondrial membrane potential is depolarized. Bcl-2–associated X protein translocates from the cytosol into the outer mitochondrial membrane and forms mitochondrial apoptosis-induced channels, an early marker of the onset of apoptosis. The release of cytochrome *c* from mitochondria into the cytosol activates cysteine-dependent aspartate-directed proteases (caspases), resulting in the caspase cascade and further apoptosis.

## 4 Cellular metabolic deficiencies

**4.1 Cellular metabolic dyshomeostasis** An extensive imbalance of cellular metabolism is implicated in AD pathology. Based on the assessment of regional hypometabolism by imaging studies using positron emission tomography with $^{18}$F-fluorodeoxyglucose, a pattern of bilateral temporo-parietal hypometabolism, especially associated with dementia, is considered to be a characteristic of AD[60]. Further, based on the results of $^{1}$H NMR spectroscopy, there is a decrease in N-acetyl-*L*-aspartate, glutamate, glutamine, taurine (except in the hippocampus), γ-amino butyric acid (except in the frontal cortex), choline and phosphocholine, creatine and phosphocreatine, and succinate in the hippocampus, cortex, frontal cortex, and midbrain of transgenic AD mice. However, the concentrations of lactate, aspartate, glycine (except in the midbrain), alanine (except in the frontal cortex), leucine, iso-leucine, valine and water-soluble free fatty-acids are increased[61]. In the frontal cortex of postmortem AD brains, the concentration of lactate is also increased but the pH and activity of pyruvate dehydrogenase are suggested to decrease[62]. In the cerebrospinal fluid of AD patients, lactate is also increased, but succinate, fumarate, and glutamine are decreased[63]. These findings indicate that cellular metabolism is disturbed in AD.

**4.2 Energy metabolism** In terms of global cellular energy, the levels of glucose metabolism and ATP are remarkably decreased in AD patients[3,8]. The metabolic processing of glucose to ATP involves glycolysis in the cytosol and the TCA cycle as well as oxidative phosphorylation in the mitochondrial matrix. Both oxidized and reducing nicotinamide adenine dinucleotide ($NAD^+$/NADH) play crucial roles in many cellular processes as not only a coenzyme for redox reactions and but also a substrate to donate ADP-ribose units. The levels of both are important for the maintenance of normal cellular energy metabolism.

**4.2.1 $NAD^+$/NADH** $NAD^+$ and NADH are involved in glycolysis, the TCA cycle, and oxidative phosphorylation. Under physiological conditions, the ratio of free $NAD^+$/NADH in the cytosol is about 700 to 1[64,65] and they regulate glycolysis by acting as cofactors for the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH). While the ratio of mitochondrial free $NAD^+$/NADH is about 7 to 1[64], $NAD^+$ and NADH are also key mediators of the mitochondrial TCA cycle and oxidative phosphorylation. $NAD^+$ is involved in the conversion of pyruvate to acetyl-CoA by enzymatic processing in the pyruvate dehydrogenase complex, generating reducing NADH. Acetyl-CoA enters the TCA cycle and initiates the oxidation of citric acid. After one TCA cycle, there are three NADH generations, that is, three $NAD^+$ are consumed in the three oxidative processes: (1) isocitrate is oxidized to oxalosuccinate by isocitrate dehydrogenase; (2) α-ketoglutarate is converted into succinyl-CoA α-ketoglutarate dehydrogenase; and (3) *L*-malate is converted into oxaloacetate by malate dehydrogenase. In oxidative phosphorylation, NADH is used to transport electrons for the generation of ATP.

Cytosolic $NAD^+$/NADH cannot move freely through the mitochondrial inner membrane. The reducing cytosolic NADH is shuttled into the mitochondrial matrix *via* the malate-aspartate shuttle and/or the glycerol 3-phosphate shuttle. The malate-aspartate shuttle is considered to be predominant in neurons[66]. Through the cycling of the NADH shuttle, $NAD^+$ in the cytosol is reduced to NADH again by another round of glycolysis, and NADH/$FADH_2$ in the mitochondrial matrix can be used to transfer elec-

trons to the electron transport chain so that ATP can be synthesized. In anaerobic respiration, mitochondrial ATP generation *via* oxidative phosphorylation is deficient; therefore, glycolytic pyruvate is further reduced to lactate in the cytosol by lactate dehydrogenase as well as generating $NAD^+$ for use in cytosolic glycolysis to generate ATP. In cultured human neuroblastoma SH-SY5Y cells, we demonstrated that both reducing NADH and ATP per unit protein in Aβ-treated cells are decreased dramatically, implying that Aβ suppresses cellular energy metabolism[67].

**4.2.2 Lactate** Imbalance of lactate is implicated in AD pathology through the regulation of APP processing. The enzymatic activity of β-amyloid-cleaving enzyme (BACE1, or β-secretase) is strongly dependent on pH with an optimum well below 6.0. The evaluated lactate results in the decrease of cellular pH. Sustained elevation of lactic acid could be a risk factor for amyloidogenesis-related AD through aberrant APP processing, leading to increased Aβ production. Furthermore, glucose-regulated protein 78 (Grp78), an ER chaperone protein, has been demonstrated to bind APP[68]. ER stress could alter the localization of APP from late to early compartments of the secretory pathway and decrease Aβ production[69]. Lactic acidosis is implicated in ER stress responses. Therefore, lactate is suggested to enhance APP interaction with Grp78, leading to aberrant APP processing with increased generation of Aβ[63].

**4.2.3 GAPDH** GAPDH (Enzyme Commission number 1.2.1.12), known for its role in glycolytic metabolism, is one of the abundantly expressed oxidoreductases and comprises 10%–20% of total cellular protein[70]. Besides glucose metabolism, GAPDH participates in several non-metabolic processes, including transcription activation[71], initiation of apoptosis[72], and ER-to-Golgi vesicle shuttling[73]. Glycolytic GAPDH is a homologous tetramer (150 kD). Each monomer contains two binding domains: an N-terminal coenzyme domain-binding domain ($NAD^+$-binding domain) and a C-terminal catalytic binding domain [glyceraldehyde-3-phosphate (G3P)-binding domain]. In glycolysis, this enzyme catalyzes the reversible phosphorylation of G3P to 1,3-bisphosphoglycerate. Under oxidative stress, GAPDH undergoes oxidative modifications, which may influence its structure and enzymatic activity[74]. Since oxidative stress and damage are major features of AD pathology, decreased activity may contribute to the hypometabolism in AD etiology. Decreased dehydrogenase activity of cerebral GAPDH has been reported in both transgenic mice (Tg2576) and in animal models receiving hippocampal injections of Aβ[75]. Increased disulfide-linked GAPDH has been reported in AD brains and aged transgenic AD mice[76], and detergent-insoluble GAPDH is further found to co-localize with neurofibrillary tangles in the AD brain[77]. The cytoplasmic domain of APP is suggested to interact with GAPDH and regulate cellular energy metabolism[78]. However, non-glycolysis-related forms of GAPDH are suggested to bind Aβ. Native tetrameric GAPDH does not interact with soluble Aβ, but non-native forms, including that induced by cold denaturation, unfolding in guanidine hydrochloride, and modification by oxidation, bind to soluble but not aggregated Aβ[79].

**4.2.4 Mitochondrial biogenesis** Mitochondria respond to the need for cellular energy. The electron-transport chain couples electron transfer between the electron donors NADH and $FADH_2$ and the electron acceptor $O_2$ with the transfer of protons across the inner mitochondrial membrane. Driven by this proton gradient, the $F_0F_1$ ATP synthase complex generates ATP *via* oxidative phosphorylation. Abnormal changes in electron-transport chain complexes and ATP synthase have been reported in AD. In autopsied brains from AD patients, mitochondria demonstrated a general depression of activity of all electron-transport chain complexes and oxidative phosphorylation, especially NADH dehydrogenase (Complex I), cytochrome *c* oxidase (COX) (Complex IV) and ATP synthase activity[10,80,81]. At the mRNA level, the transcription of mitochondrial genes encoding cytochrome *b* (a component of complex III), COX subunit 1 (complex IV) and the ATPase δ-subunit is increased in brain sections from AD patients compared with control subjects; transcription of the mitochondrial gene encoding the NADH 15-kDa subunit (complex I), however, is decreased[82]. Over-expression of these mitochondrial genes might be a result of functional compensation for the depression of enzymatic activity.

The generation of free radicals is sensitive to the electron-transport chain; abnormal changes in the electron-transport chain, in turn, contribute to the deficit in cellular energy generation and oxidative damage.

Furthermore, mitochondrial biogenesis is regulated by the pathway of peroxisome proliferator activator receptor γ-coactivator 1α (PGC-1α)–nuclear respiratory factor (NRF)–mitochondrial transcription factor A. In hippocampal tissues from AD patients and APPswe M17 cells, the levels of PGC-1α, NRF 1, NRF 2, and mitochondrial transcription factor A are significantly decreased compared with controls[12]. This finding also suggests reduced mitochondrial biogenesis in AD. Activation of the PKA/CREB pathway is suggested to rescue the deficiency in mitochondrial biogenesis[12].

## 5 Conclusion and perspective

In conclusion, increasing evidence suggests that glucose absorption is reduced and glucose metabolism is abnormal in the brains of AD patients. Accumulated extracellular and intracellular Aβ might both induce dyshomeostasis of cellular metabolism including ATP and other metabolic biomarkers. Mitochondria not only supply the main cellular energy as ATP but also regulate apoptosis; Aβ might induce defective mitochondrial energy metabolism by disturbing the TCA cycle and oxidative phosphorylation. Dysfunctional mitochondria promote cellular oxidative stress and initiate the mitochondrial damage-related cascade of apoptosis. Substances that prevent the Aβ-induced cellular metabolism deficit, especially mitochondrial dysfunction, may be beneficial for AD treatment.

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