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REVIEW ARTICLE

Mitochondria as a therapeutic target in Alzheimer's disease

Jian Wang, Guo-Jun Chen*

Department of Neurology, The First Affiliated Hospital of Chongqing Medical University, Chongqing Key Laboratory of Neurology, 1 Youyi Road, Chongqing 400016, China

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Abstract Alzheimer's disease (AD) remains the most common neurodegenerative disease characterized by β-amyloid protein (Aβ) deposition and memory loss. Studies have shown that mitochondrial dysfunction plays a crucial role in AD, which involves oxidative stress-induced respiratory chain dysfunction, loss of mitochondrial biogenesis, defects of mitochondrial dynamics and mtDNA mutations. Thus mitochondria might serve as drug therapy target for AD. In this article, we first briefly discussed mitochondrial theory in the development of AD, and then we summarized recent advances of mitochondrial abnormalities in AD pathology and introduced a series of drugs and techniques targeting mitochondria. We think that maintaining mitochondrial function may provide a new way of thinking in the treatment of AD.

Introduction

Alzheimer's disease (AD) is the most common form of neurodegenerative disease. Patients with AD exhibit memory loss, declines of problem-solving skills and personality changes, which not only affect the normal life but often has fatal prognosis.[1] It is estimated that by 2010, approximately 24 million people worldwide will suffer from dementia, most of which are AD. By 2020 there will be 42.3 million people living with AD and other forms of dementia, and this figure will rise to 81.1 million by 2040.[2] AD causes a huge burden on individuals, families and society, which would finally translate into extremely high health care costs. With the increase in life expectancy, AD is becoming an intractable health problem in aging society.

The pathophysiology of AD is featured by progressive loss of neurons and synapses, accumulation of amyloid β peptide (Aβ) deposits and intracellular neurofibrillary tangles (NFTs). Despite the large number of existing research, the pathogenesis of AD remains to be clarified. The amyloid cascade hypothesis proposed by Hardy and Allsop[3] in 1991 stated that APP mis-metabolism and beta-amyloid deposition were the

* Corresponding author.
E-mail address: woodchen2015@163.com (G.-J. Chen).
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primary events in the disease process, yet this hypothesis still cannot fully explain all the results convincingly. Recent studies have found amyloid may also present in the brain that has no clinical manifestations and elevated levels of Aβ is not consistent with the clinical severity of dementia.[4] Further, anti-amyloid drugs in clinical trials do not always benefit significantly.[5] Thus it is still a debate whether amyloidosis in sporadic Alzheimer's disease is the primary cause or secondary to other pathological processes.

Mitochondria exist in most eukaryotic cells, known as the power plants. In 2004, Swerdlow and Khan proposed mitochondrial cascade hypothesis, emphasized the importance of mitochondrial dysfunction caused by oxidative stress in the pathogenesis of sporadic AD.[6] Mitochondrial cascade hypothesis believes that each individual has inherited a certain baseline level of mitochondrial function and mitochondrial durability. Baseline represents the total capacity of mitochondrial bioenergetics, while durability determines the rate of the occurrence of age-related mitochondrial dysfunction.[7] When mitochondrial declines exceed the threshold, the AD-related pathological changes such as Aβ deposition and NFTs occur. Aβ is thus an epiphenomenon of pathological development of AD rather than the cause of the disease. This is consistent with the finding that early mitochondrial dysfunction can lead to increased production and aggregation of Aβ.[8] If mitochondrial durability and functional decay rates are constant, the time for the occurrence of the disease is determined by the baseline levels of mitochondrial function. On the other hand, when mitochondria have a certain baseline level, the longer mitochondrial function sustain, the slower the occurrence of age-related decay rates would be.[7] These studies suggest that mitochondria might be a very promising therapeutic target for AD.

Current treatments for AD are not directly targeted to mitochondria. Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and N-methyl-D-aspartate receptor antagonist memantine are the only two kinds of drugs approved by the FDA for AD treatment,[9] which show only modest clinical symptom improvement. Phase I clinical trials of anti-amyloid vaccine immunotherapy have been failed due to a variety of serious adverse drug reactions.[10] Over the past few years, the development of β- and γ-secretase inhibitors[11] and new vaccines[12] has achieved some encouraging results. However, effective therapy to slow or halt the progression of AD is still lacking.

Given the importance of mitochondrial dysfunction in the pathogenesis of AD, new treatment strategies have been proposed to improve or ameliorate mitochondrial function. The most challenging problem in the treatment of mitochondrial dysfunction is not the development of drug itself, but the lack of a specific targeting medium that transports drugs to mitochondria and improves their distribution in mitochondria. In this article, we mainly elaborate that mitochondrion is a potential therapeutic target for AD, and systematically introduce mitochondria-targeting drugs and related technologies.

Mitochondria and oxidative stress

Reactive oxygen species (ROS) including the superoxide radical (•O2−), hydrogen peroxide (H_2O_2) and hydroxyl radical (•OH) are mainly produced in the mitochondria. In physiological conditions, the concentration of ROS is strictly controlled by endogenous antioxidant defense mechanisms, such as superoxide dismutase, catalase and glutathione reductase. Excessive intracellular ROS may lead to oxidative stress and consequent cellular abnormalities.

Most antioxidants protect cells from oxidative damage, and enhance the efficiency of aerobic metabolism. Drugs such as coenzyme Q and glutathione can limit the mitochondrial ROS production, oxidative stress and reduce inflammation. While others such as creatine, pyruvic acid may increase mitochondrial biogenesis. Coenzyme Q10 regulates electron transfer from the complex I & II to complex III and exhibits some antioxidant effects. Idebenone, a synthetic analogue of coenzyme Q10, can effectively penetrate the blood-brain barrier; but it fails to slow cognitive decline in AD patients in clinical trials.[13] Exogenous creatine has been shown to be neuroprotective in vitro and in vivo experiments since creatine/phosphocreatine system controlled by mitochondrial creatine kinase plays an important role in maintaining energy balance in the brain. Lipoic Acid (LA), a coenzyme of mitochondrial pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, is also a powerful antioxidant that can recycle other antioxidants such as vitamin C and E, glutathione GSH. Study has shown that long-term dietary LA supplement can ameliorate learning and memory deficits in Tg2576 mice,[14] probably by improving the recovery of mitochondrial integrity and functionality and by reducing the number of severely damaged mitochondria.[15] In a study on 43 AD patients LA effectively slowed the decline of cognitive processes.[16] Another recent study of 39 AD patients taking ω-3 fatty acids and LA also reveals consistent results.[17]

However, it is difficult for the traditional antioxidants such as coenzyme Q and vitamin E to achieve the desired effect because of their limited distribution in mitochondria. Efforts have been made to increase the efficacy of drug targeting, to reduce drug dosage and metabolism outside mitochondria and the side effects. The most common way to achieve mitochondrial targeting is to attach these antioxidants to a lipophilic and cationic triphenylphosphine (TPP+). In the presence of the lipid-soluble cationic phenyl group (positively charged) that can bind to mitochondrial membrane (negatively charged), antioxidants gathered in the mitochondrial matrix may increase by 100—1000 times. However, excessive intake of lipophilic cations may lead to mitochondrial membrane potential depolarization, thus this strategy still requires further study.

Mitochondrial targeting peptide SS (Szeto-Schiller) selectively accumulated in the mitochondrial inner membrane has an antioxidant effect. By inhibiting the peroxidase activity of cytochrome c/cardiolipin complex, peptide SS reduces oxidized cytochrome C, and improves mitochondrial electron transport and ATP synthesis.[18] The most significant advantage of this peptide is that it does not change the mitochondrial membrane potential. However, mitochondrial dysfunction tends to have lower membrane potential, which might limit the intake of lipophilic cations that are dependent on membrane potentials. It is reported that SS-31 reduces β-amyloid protein-mediated cytotoxicity and improves the neurite outgrowth in the primary neurons

of APP transgenic mice.[19] In addition, this peptide restores mitochondrial transport and synaptic activity, and reduces the percentage of abnormal mitochondria,[20] suggesting a potential therapeutic value for AD. Another mitochondria targeting antioxidant is called Hemigramicidin-2,2,6,6-tetramethylpiperidine-1-oxyl (Hemigramicidin-TEMPO), which is composed of two parts, a high affinity for mitochondrial membrane gramicidin −S and ROS scavenger TEMPO. While gramicidin −S can be targeted to mitochondria without depending on membrane potential, TEMPO has been shown in animal experiments to improve the prognosis of sepsis-induced acute renal injury,[21] yet the effect of this drug has not been tested in AD.

Alternative mitochondria targeting strategy is to promote endogenous antioxidant mechanisms (Fig. 1A). Nrf2 (NF-E2-related factor 2) is a transcription factor that regulates the expression of antioxidant genes through its interaction with ARE (antioxidant response element).[22] It is known that Nrf2 is significantly reduced in the nucleus of hippocampal neurons in AD patients.[23] In the APP/PS1 transgenic mice, Nrf2-ARE activity is gradually attenuated with Aβ deposition; and tert-butylhydroquinone (TBHQ) application or Nrf2 gene transfer decreases Aβ-induced toxicity.[24] In addition, activation of Nrf2 may also promote the activity of autophagy adapter protein NDP52 (nuclear domain 10 protein 52) and reduce the level of phosphorylated tau.[25] Consistently, hippocampal injection of human Nrf2 gene improves the spatial learning in 9-month-old APP/PS1 transgenic mice, suggesting a potential therapeutic value of Nrf2.[26]

Curcumin is considered as a Nrf2 agonist and exhibits antioxidant,[27] anti-inflammatory[28] and amyloid depolymerizing[29] effect in animal experiments. It selectively reacts with Keap1 (Kelch-like ECH-associated protein 1), an endogenous inhibitor of Nrf2. The binding of curcumin to Keap1 promotes Nrf2 dissociation from Keap1, and thus activates Nrf2.[30] However, due to its poor water-solubility and low bioavailability, curcumin fails to improve cognition in clinical trials.[31] For this reason new delivery methods have been developed for AD treatment.[32] For

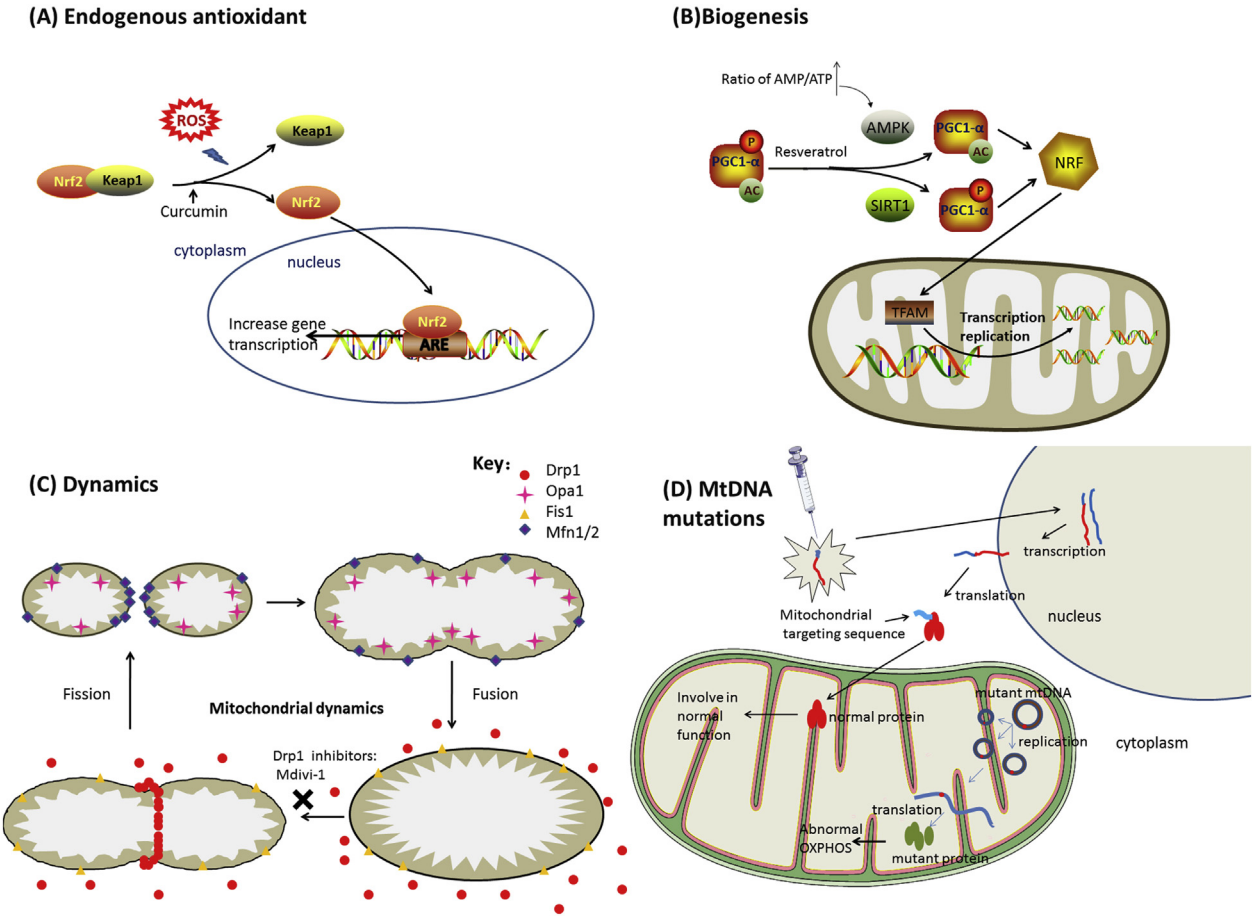

Fig. 1 Mitochondria targeting strategies in Alzheimer's disease: A) Endogenous antioxidant system agonist that increases endogenous antioxidative gene expression through Nrf2-ARE pathway; B) Promotion of mitochondrial biogenesis by PGC1-α-NRF-TFAM; C) Maintenance of mitochondrial dynamics by inhibiting Drp1; D) mtDNA mutations and gene therapy. Exogenous DNA encoding the normal mtDNA products can be transported to the mitochondria resulting in corrections of mtDNA mutations. (ROS: reactive oxygen species, Nrf2: NF-E2-related factor 2, Keap1: Kelch-like ECH-associated protein 1, ARE: antioxidant response element, PGC1α: peroxisome proliferator-activated receptor gamma coactivator 1-α, AMPK: AMP-activated protein kinase, SIRT1: sirtuin 1, TFAM: mitochondrial transcription factor A, drp1:dynamin-1-like protein, opa1: optic atrophy 1, fis1: fission 1 protein, mfn1/2: mitofusin-1/2.)

example, Marrache and Dhar[33] found that a mitochondria-targeted polymeric nanoparticle system (NPs) can significantly increase mitochondrial uptake of curcumin. However, it is worth noting that not all types of nanoparticles have the ability to enter mitochondrial bilayer membranes, depending on the size and volume of the surface charge.

Mitochondrial biogenesis

Mitochondrial biogenesis plays an important role in maintaining mitochondrial numbers, cell renewal, adapting to cell damage and the demand for energy supply.[34] This process is regulated by peroxisome proliferator-activated receptor (PPAR), and coactivators PGC1α, nuclear respiratory factor (NRF) and mitochondrial transcription factor A (TFAM). PGC1α is a key regulator of mitochondrial biogenesis and plays a pivotal role in the energy balance and metabolism.[35] The activity of PGC1α can be regulated by SIRT1 (sirtuin 1) or AMP-activated protein kinase (AMPK) respectively.[36] Sirtuins (SIRT1-7) are NAD^+ dependent histone deacetylase protein family members. SIRT1, SIRT6 and SIRT7 are found in the nucleus, while SIRT2 is mainly located in the cytoplasm, and SIRT3-5 are in mitochondria.[37] SIRT1 deacetylates PGC1α and promotes nuclear transfer.[38] AMPK is a sensor of AMP/ATP ratio. At low energy state, AMPK promotesPGC-1α phosphorylation and therefore regulates glucose transport, fatty acid oxidation and mitochondrial biogenesis. TFAM controls the expression of mtDNA replication and transcription, and participates in mtDNA base excision repair process.[39] Study has shown that the expression of PGC-1α, NRF 1, NRF 2 and TFAM are significantly decreased in the hippocampus of AD, suggesting an abnormal mitochondrial biogenesis in AD.[40] Interestingly, overexpression of PGC-1α can reduce the mitochondrial damage and improve biogenesis.[40]

Resveratrol, one of the main active components of wine, is a polyphenolic compound. Many studies have noted that resveratrol can induce Sirt1 expression, increase AMPK activation, and activate PGC-1α (Fig. 2B).[41,42] Through Sirt1, PGC-1α and P53 signaling, resveratrol reduces hippocampal degeneration and learning impairment in AD models.[43] In vitro, resveratrol inhibits Aβ-induced apoptosis through Sirt.[44] Long-term resveratrol diet reduces learning and memory impairment, decreases amyloid and phosphorylated tau by activating AMPK and Sirt1.[45] A recent multicenter, randomized, double-blind, placebo-controlled Phase II clinical trial for mild to moderate AD shows that resveratrol is safe and well tolerated, and causes a certain degree of AD biomarker changes (plasma and cerebrospinal fluid Aβ40).[46] Resveratrol and glucose and malate mixed drug are undergoing phase III clinical trial (NCT00678431), which is expected to become a treatment choice for mild to moderate AD.

PPAR (α, β/δ, γ) agonist bezafibrate is commonly used to treat dyslipidemia. Recent research finds that PPARs can regulate mitochondrial function through PGC-1α.[47] Bezafibrate mainly activates PPARα, but also regulates PPARβ and PPARγ activity.[48] It is known that bezafibrate significantly reduces tau protein level and microglia activation, promotes mitochondrial biogenesis and improves behavioral activities in P301S mice.[49] In COX10 knockout mice, bezafibrate increases mitochondrial ATP synthesis, decreases astrocyte proliferation and inflammatory factors,[50] suggesting a potential significance of bezafibrate in the treatment of neurodegenerative diseases.

Thiazolidinedione drugs (TZDs) such as rosiglitazone, pioglitazone that are PPARγ agonists used for the treatment of diabetes, have been shown to improve the awareness of mild to moderate AD. Animal study shows that TZDs enhances mitochondrial biogenesis and respiratory function.[51]

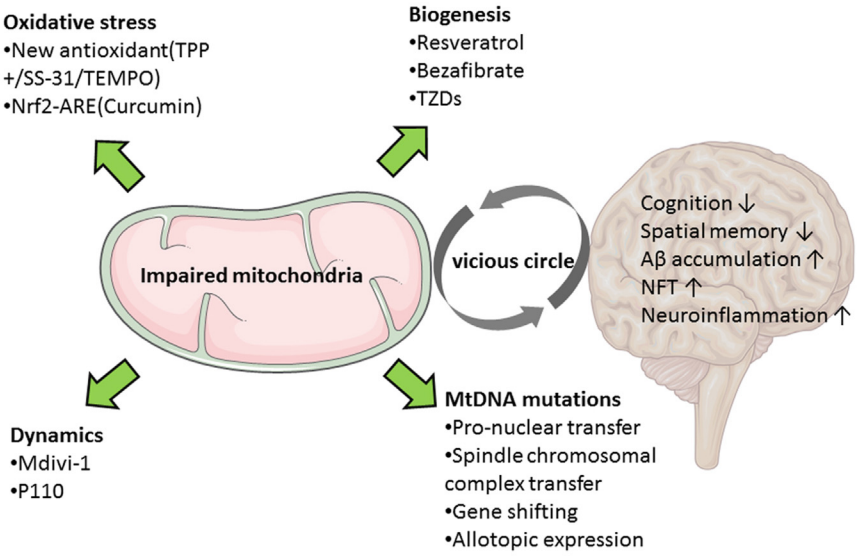

Fig. 2 Mitochondrial dysfunctions interact with the pathological changes of Alzheimer's disease, creating a vicious cycle. New drugs and technologies targeting mitochondria may relieve or prevent AD progression. (TPP+: triphenylphosphine, TEMPO: 2,2,6,6-tetramethylpiperidine-1-oxyl,Nrf2: NF-E2-related factor 2,ARE: antioxidant response element, TZDs: thiazolidinedione drugs, Aβ: amyloid β peptide, NFT: neurofibrillary tangles.)

TZDs also promotes β-amyloid plaque clearance, reduces tau phosphorylation and improves synaptic plasticity.[52] Clinical trials show that rosiglitazone increases whole-brain glucose metabolism.[53] Patients with mild AD or MCI receiving six months of rosiglitazone (4 mg/day N = 20) exhibit better delayed recall (4 months and 6 months).[54] Another study investigated the effect of rosiglitazone in 511 mild to moderate AD patients, in which rosiglitazone significantly improves cognitive function in APOEε4 allele-negative but not in APOEε4 allele-positive patients.[55] A recent prospective cohort study has shown that long-term use of pioglitazone reduces the risk of dementia in patients of diabetes.[56] A meta analysis suggests that PPARγ agonists, especially rosiglitazone may be beneficial for early stages of mild to moderate AD, and the tolerability has been widely praised.[57]

Mitochondrial dynamics

Mitochondrial dynamics are also known as fission and fusion. The dynamic changes regulate mitochondrial morphology, which in turn can affect the mitochondrial energy synthesis and quality control. In many neurodegenerative diseases, mitochondrial dynamics are affected.[58] Several proteins play important role in fission and fusion. Mfn1, Mfn2, Opa1 are three main proteins controlling mitochondrial fusion (Fig. 1C). The dimmerization of Mfn1 and Mfn2 in the outer membrane and OPA1 localized in the inner membrane are shown to promote membrane fusion.[59] On the other hand, Drp1 and Fis1 contribute to fission. Drp1 (also known as Dlp1 and Dnm1) is located in the cytoplasm and functions through self-assembled spiral polymers to surround mitochondrial membrane and uses GTP hydrolysis to initiate fission.[60] Fis1 is responsible for recruiting Drp1 from cytoplasm to the outer membrane.[61]

Manczak[62] reports that in the frontal cortex of AD patients, Drp1 and Fis1 are increased at mRNA and protein levels, while the fusion gene Mfn1, Mfn2 and OPA1 expression are significantly reduced, suggesting that the imbalance of mitochondrial fission and fusion is an important mechanism involved in neuronal dysfunction. Study has shown that the interaction of Drp1 with Aβ and tau may cause excessive mitochondrial fission, resulting in synaptic dysfunction and cognitive decline.[63] A study by Reddy et al.[64] demonstrates that partial inhibition of Drp1 prevents the toxic effects of Aβ and tau, stables mitochondrial dynamics and increases mitochondrial biogenesis and synaptic activity. DRP1 is also found to be associated with GSK3β, CDK5 and p53,[64] but their relevance in AD has not been exactly clarified. Overall, the close association of Drp1 with Aβ and tau suggests that Drp1 might serve as a potential therapeutic target in AD.[65]

Mdivi-1, a Drp1 selective inhibitor, can inhibit Drp1 self-assembly and GTP activity.[66] Cells treated with mdivi-1 show anti-apoptotic properties presumably due to the inhibition of the mitochondrial membrane permeability. Mdivi-1 alleviates apoptosis in tubular and acute kidney injury through inhibiting mitochondrial fission.[67] In addition, mdivi-1 has been widely studied in animals models of epilepsy,[68] ischemia,[69] oxygen − glucose deprivation.[70] Qi et al[71] find that p110, another Drp1 peptidase inhibitor, can block Drp1 activity and its interaction with Fis1, thereby reduces mitochondrial fragmentation and ROS production, and neurotoxicity. These findings suggest that mdivi-1 might have therapeutic effects in AD.

Mitochondrial DNA mutations

Human mitochondrial DNA (mtDNA) contains a total of 37 genes, 13 of which are involved in oxidative phosphorylation (OXPHOS). In most cases, disease-causing mutations are recessive. Clinical symptoms do not appear until OXPHOS is damaged by a substantial proportion of mutations.[72] The muscle and brain tissues require high energy and thus are particularly rich in mitochondria, in which frequent mtDNA mutations may cause a variety of neuromuscular disorders. Unlike nuclear DNA (nDNA)that are protected by histones,[73] mtDNA are highly sensitive to mutagenic and cytotoxic ROS, the mutations of which are 10 times more than those of nDNA. As a result, abnormal products including NADH dehydrogenase, cytochrome C oxidase (COX) and ATP synthase, would eventually cause more electron leak and ROS generation. This so-called "vicious circle" plays an important role in aging. A recent mitochondrial gene polymorphism study demonstrates that mitochondrial haplogroup may increase genetic susceptibility to AD independent of APOE4.[74] A technique called pro-nuclear transfer has been developed to replace mtDNA in female carriers with mtDNA mutations. The nuclear chromosomes in her fertilized eggs can be transferred to a new fertilized egg where its own nuclear chromosomes are removed, so that the fertilized egg contains patient's nDNA and the new mtDNA derived from egg donors. Another similar technique is to transfer nDNA in the egg before being fertilized in vitro.[75] While these technologies have been successful in some animal experiments, the efficacy and safety issues should be carefully addressed before human clinical applications.

Pathogenic mtDNA mutation and wild-type mtDNA coexist in the cell, known as heterogeneity.[76] Current mitochondrial gene therapy strategies aim to reduce the pathogenic mtDNA to a below threshold level, which is to increase the ratio of wild-type mtDNA to mutant mtDNA. These measures include designing anti-gene sequences to bind mutant mtDNA and inhibit its replication, or using mitochondrial targeting nuclease such as peptide nucleic acids, restriction enzymes and zinc-finger nuclease enzymes, to selectively degrade mutant mtDNA. The feasibility of these methods has been validated in several animal models, but many problems have not been solved. For instance, the size of the carrier may inhibit mtDNA from passing through inner mitochondrial membrane. In addition, mtDNA degradation is difficult to control, especially for tissues and cells containing high levels of mtDNA mutations.[77] Some studies suggest that the use of retroviral vector gene therapy may lead to upregulation of proto-oncogene and cause malignant transformation of cells.[78]

Allotopic expression is another technique that uses nDNA to express genes originally encoded by mitochondrial genome (Fig. 1D). A section of exogenous DNA that encodes the normal mtDNA is made to reintegrate into nDNA, and

the gene products are then transported to mitochondria. Using this method, Guy J et al[79] have successfully repaired the mutation (11778G> A) of ND4 subunit of complex I in Leber hereditary optic neuropathy (LHON).Today the gene therapy trials of allotopic expression for LHON are recruiting patients.[80] It is believed these gene therapy strategies would provide important information for treating AD and other neurodegenerative diseases.

Other treatments

Dimebon was first considered as blocking H1-histamine receptors,[81] and was used to treat allergic diseases in the early 1980s. Studies suggest that Dimebon is also an inhibitor of NMDA receptors and voltage-gated calcium channels,[82] It maintains mitochondrial function by inhibiting Aβ25-35 induced mitochondrial permeability transition pore (MPTP) opening.[83] Clinical trial shows that Dimebon is safe and effective, well tolerated, and dramatically improves the clinical symptoms of mild-to-moderate AD.[84] However, in phase III clinical trials Dimebon fails to demonstrate a significant effect.[85]

Melatonin, a major pineal hormone widely presented in the cell, is considered as a powerful free radical scavenger.[86] Study shows that melatonin upregulates anti-apoptotic factor Bcl-2 expression, downregulates the expression of pro-apoptotic Bax, inhibits Aβ-induced cell death and stabilizes mitochondrial function.[86] Melatonin also indirectly inhibits the opening of the mitochondrial transition pore (MTP), blocks MTP-dependent cytochrome C release. Transgenic AD mice receiving melatonin (10 mg/kg) for 4 months exhibit reduced levels of oxidative stress and pro-apoptotic markers.[87] Long-term melatonin treatment improves cognition in mice and reduces the expression of amyloid deposition and inflammatory cytokines.[88] Clinical studies also reveal the therapeutic effect of melatonin in AD.[89,90]

α-Tubulin deacetylation by histone deacetylase 6 (HDAC6) is a key factor to ensure axonal transport, destruction of which is an important pathophysiological process of AD. Studies show that HDAC6 inhibitor tubastatin A restores Aβ-induced dysfunction of axonal transport of mitochondria,[91] and HDAC6 knockout mice exhibit improved learning and memory,[92] suggesting that HDAC6 inhibitor may serve as a potential target for AD.

Conclusions

The exploration of mitochondrial targeting treatment still remains in animal experiments. Many drugs that show therapeutic effect in AD mouse model do not achieve the desired results in clinical studies. The reason may be that the majority of AD mice are constructed by amyloid deposition, while the real development of the human disease might be more complicated. In addition, as mitochondrial dysfunction is an early manifestation of AD, it might be too late to start drug therapy. AD is always diagnosed when disease develops to the late stage, thus the early diagnosis and preventive treatment should be very important. Nonetheless, owing to the important role of mitochondria in the pathophysiology of AD, we think that future therapy targeting mitochondria may open a new window in the treatment for AD.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

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