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REVIEW ARTICLE

Mitochondria as a therapeutic target in Alzheimer's disease

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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

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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