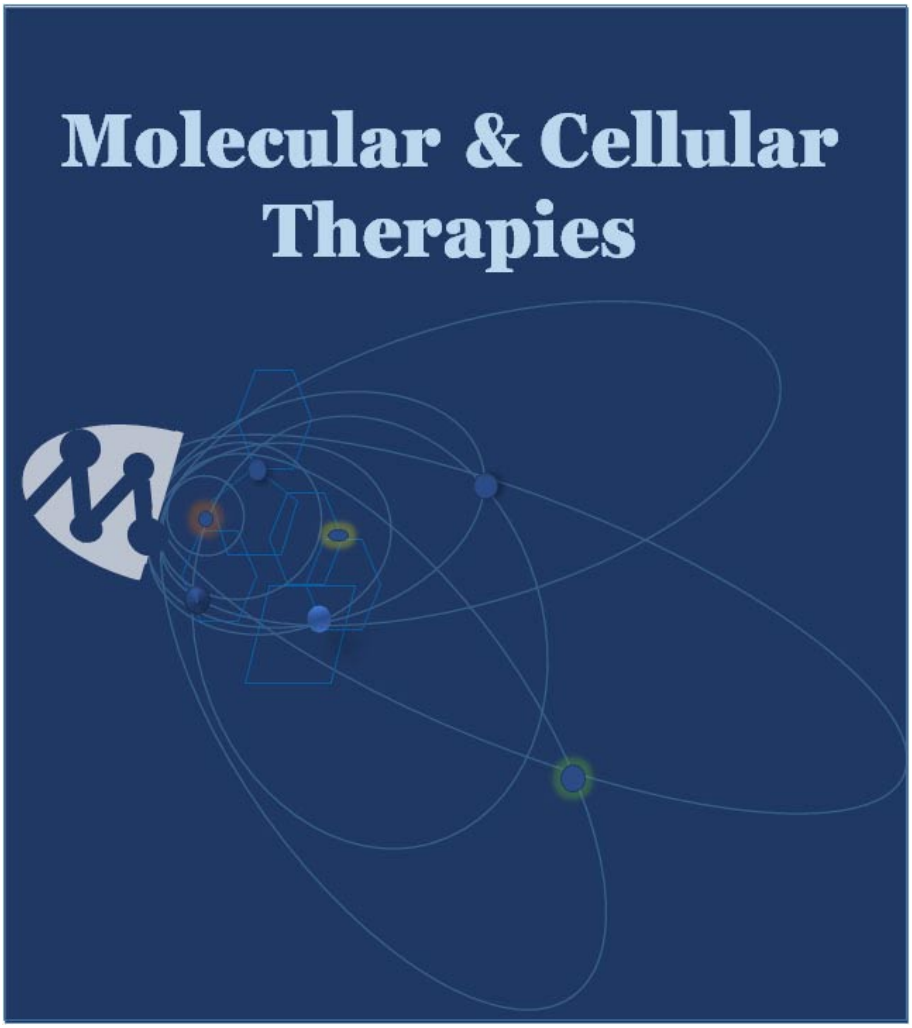

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Review

The role of mitochondria-targeted antioxidant MitoQ in neurodegenerative disease

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Abstract

The discovery of charged molecules being able to cross the mitochondrial membrane has prompted many scholars to exploit this idea to find a way of preventing or slowing down aging. In this paper, we will focus on mitochondria-targeted antioxidants, which are cationic derivatives of plastoquinone, and in particular on the mitochondria-targeted antioxidant therapy of neurodegenerative diseases. It is well known that the accumulation of amyloid-β peptide (Aβ) in mitochondria and its related mitochondrial dysfunction are critical signatures of Alzheimer' s disease (AD). In another neurodegenerative disease, Parkinson's disease (PD), the loss of dopaminergic neurons in the substantia nigra and the production of Lewy bodies are among their pathological features. Pathogenesis of Parkinson's disease and Alzheimer's disease has been frequently linked to mitochondrial dysfunction and oxidative stress. Recent studies show that MitoQ, a mitochondria-targeted antioxidant, may possess therapeutic potential for Aβ-related and oxidative stress-associated neurodegenerative diseases, especially AD. Although MitoQ has been developed to the stage of clinical trials in PD, its true clinical effect still need further verification. This review aims to discuss the role of mitochondrial pathology in neurodegenerative diseases, as well as the recent development of mitochondrial targeted antioxidants as a potential treatment for these diseases by removing excess oxygen free radicals and inhibiting lipid peroxidation in order to improve mitochondrial function.

Keywords

Alzheimer's disease, mitochondria-targeted antioxidant, MitoQ, oxidative stress, Parkinson's disease

Introduction

Currently there are three pharmacological therapy approaches for mitochondrial disorders [1]: the first approach is to engineer compounds which selectively target to mitochondria; the second one is to design compounds that are not targeted to mitochondria but act on them based on their binding to specific targets; and the third one is to use compounds located outside the mitochondria but that ultimately affect the function of mitochondria [2]. Mitochondria-targeted antioxidants, 10-(6'-plastoquinonyl) decyl-triphenylphosphonium (SkQ1) and its analog plastoquinonyl decylrhodamine 19 (SkQR1), have been proved to slow down or even reverse the effects of aging [3, 4, 5]. Another important antioxidant is MitoQ, a synthetic analog of coenzyme Q10. As a mitochondria-targeted antioxidant, MitoQ can selectively accumulate in mitochondrial and remove excess oxygen free radicals, prevent lipid peroxidation and protect mitochondria and cell membranes against oxidative stress. An ever-increasing number of studies suggest that MitoQ possess some positive effect in treating neurological diseases with mitochondrial dysfunction and oxidative stress as main pathological features. In particular, the pathogenesis of neurodegenerative diseases, Alzheimer's and Parkinson' s disease, is very complex because of the involvement a vast number of factors. Since mitochondrial dysfunction and oxidative stress are among the most relevant factors [6] and they happen in the early onset of neurodegenerative diseases, they can be considered as essential and potential therapeutic targets for the early treatment of the disease.

Neurodegenerative diseases

Alzheimer's disease is a worldwide neurodegenerative disease typically correlated with aging. About 36.5 million people around the world are affected and this

number will rapidly increase in the future, especially in China, India, and Latin America [7]. In addition, young-onset cases have more frequently been reported and to date there is no effective treatment that can be used as a cure. This disease is characterized by wide spread synaptic damage and neuronal death with accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques of mainly Aβ [8]. In the early stages of AD, mitochondrial dysfunction induced oxidative stress can result in macromolecule damage, mainly lead by hydroxyl radicals [9]. The different aspects of the disease have been revealed through the studies on Alzheimer cells and transgenic mouse models which allow the direct observation of the pathogenic mechanisms of AD, especially the interaction between Aβ and mitochondria. Mitochondria are not only the target for amyloid precursor protein (AβPP) that releases and accumulates Aβ in the mitochondrial import channels, but also for Aβ which interacts with different proteins in the mitochondria, affecting normal mitochondrial function [10]. In humans, AβPP is present in many cellular structures like plasma membrane and many organelles such as endoplasmic reticulum, Golgi apparatus, as well as mitochondria. AβPP produces Aβ, a peptide of 39-43 amino acids in length, via the action of a β-secretase and then a γ-secretase enzyme [11]. Mitochondria, endosomes, Golgi and endoplasmic reticulum have been described as the major targets of Aβ. In mitochondria, Aβ can induce dysfunction of mitochondrial Ca^{2+}channels [12] and affect the activity of mitochondrial. Indeed, pyruvate dehydrogenase and α-ketoglutarate dehydrogenase can be altered decreasing NADH reduction, as well as the electron transport chain (ETC) enzyme complex IV, causing a reduction in the proton pumping across the inner mitochondrial membrane and hence altering the mitochondrial membrane potential [13]. The effect on complex V activity results in a decrease in ATP production along with an increasing in reactive oxygen species (ROS) production (Figure 1). Normally, excess ROS is removed by the antioxidant defense system, but oxidative stress may lead to a series of injuries due to an imbalance of antioxidant and prooxidant homeostasis, such as the damage of nucleic acids, proteins, and lipids [14]. On the other hand, excessive ROS negatively regulates presequence P (PreP) activity, hindering the normal degradation of Aβ and leading to an increase in Aβ content in mitochondria. Additionally, ROS induces mitochondrial peroxidation of macromolecules such as mitochondrial DNA and lipids, and it also damages the mitochondrial function by interfering with the fusion and fission processes of mitochondria, leading to mitochondrial fragmentation [15] and increased mitochondrial DNA mutations [10]. Besides, excess production of ROS also induces synaptic dysfunction by increasing tau hyperphosphorylation and neurofibrillary tangle formation, eventually leading to synaptic failure. There is wide evidence that oxidative stress plays an essential role in the pathological process of AD induced by Aβ. Therefore, it sounds to work on the elimination of free radicals and prevent them from being produced as a therapy for AD. In fact, many studies have been carried out with this scope. In one study, a mitochondria-targeted antioxidant, MitoQ, has been used to reverse the cognitive decline and to prevent early neuropathology in a transgenic mouse model of AD by acting against the attack of Aβ-induced toxicity and oxidative stress [16].

Parkinson's disease is the second prevalent progressive neurodegenerative disease that affects about 2% of people over the age of 60 [17]. One of the pathological characteristics of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta that causes motor symptoms. The other feature is the dopamine depletion in the striatum. PD is also associated with the presence of Lewy bodies in surviving dopaminergic neurons [18]. To date, the treatment of PD remains only on the surface, and current therapies cannot effectively slow or prevent the pathologic progression of the disease [19]. Although extensive studies have been carried out on PD, its precise etiology remains largely unknown despite some pathological mechanisms, such as mitochondrial dysfunction, oxidative stress and the ubiquitin-proteasome system disruption, as well as neuroinflammation have been brought forward. Under these assumptions, oxidative stress and mitochondrial dysfunction could be considered as reasonable candidates. In fact, mitochondrial DNA mutations have been shown to play a significant role in the death of dopaminergic neurons [20] and a great wealth of evidence suggests that mitochondrial dysfunction plays a vital role in the course of PD pathogenesis. One of the most significant research lines is the study of MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydrodropyrid ine), a Parkinsonian toxin which selectively depressed mitochondrial complex I inducing Parkinsonian syndromes [21]. Another toxic metabolite, originated by the action of monoamine oxidase on MPTP is 1-methyl-4-phenylpyridinium (MPP+) [22]. It is transported into the dopaminergic neurons by the dopamine transporter and accumulates in the mitochondria, causing adenosine triphosphate depletion through inhibition of complex I activity, changes in mitochondrial membrane potential, increases in the production of ROS and finally leads to apoptotic cell death [23]. Similarly, other complex I inhibitors for like rotenone, fenpyroximate and trichloroethylene also lead to dopaminergic neurodegeneration in many research models include human, all indicating mitochondrial dysfunction plays an important role in PD pathomechanism [24]. These toxic substances affect the normal functioning of mitochondria, result in a decreasing of function of electron transport chain [25] and mitochondrial mobility [26]. Furthermore, they can also induce an increase of the mitochondrial permeability transition and the production of ROS, as well as an increase in the activity of nitric oxide synthase. In PD patients, the function of complex I is impaired in the substantia nigra. The change in complex I structure is due to the absence of apoptosis inducing factors which does not cause neurodegeneration due to the loss of dopaminergic neurons, but makes the dopaminergic neurons more susceptible to neurotoxins

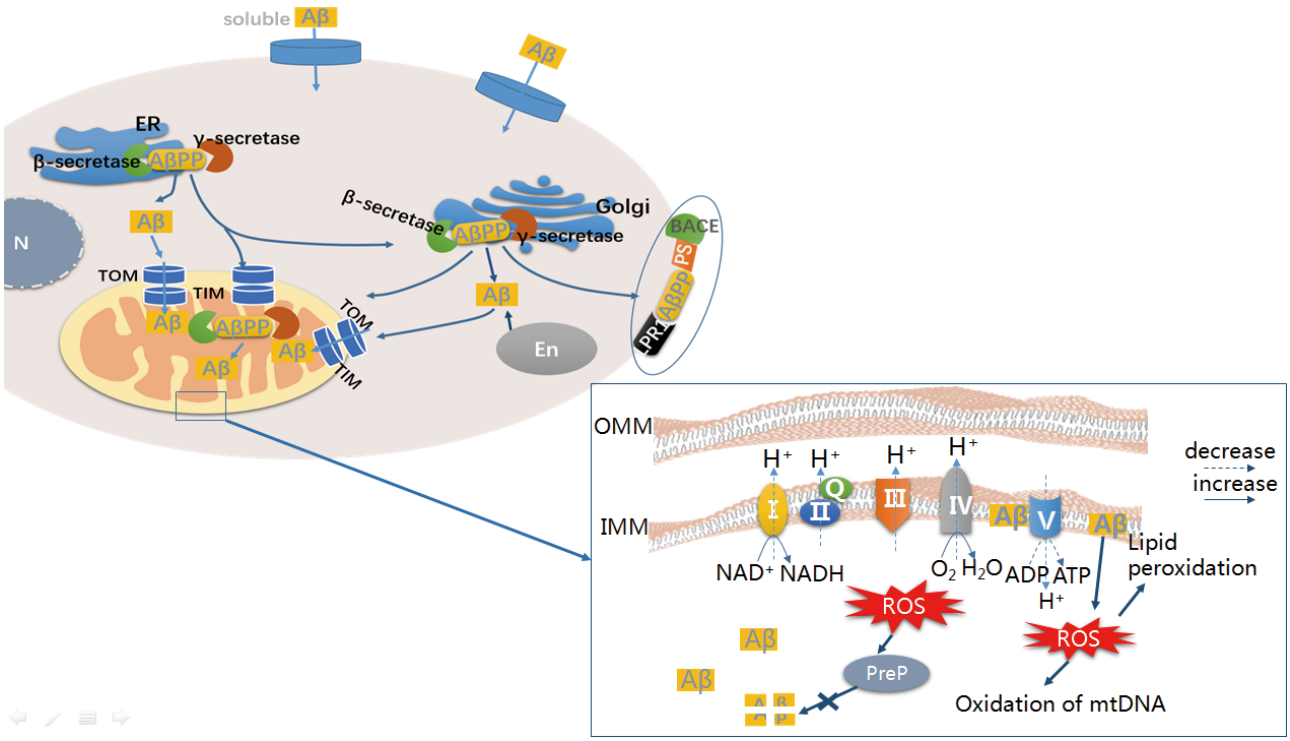

Figure 1. The generation and influence of Aβ. AβPP is synthesized in the endoplasmic reticulum (ER) and then directed to Golgi network, the cell surface or to mitochondria. In the plasma membrane, the apolipoprotein receptor LRP1 forms a complex with AβPP, together with other plasma membrane enzymes, such as the β-secretase BACE and the γ-secretase presenilin (PS), inducing the internalization of the amyloid precursor protein. AβPP produces Aβ, a 39-43 amino acid polypeptidevia the activity of β-secretase and then γ-secretase enzymes [11]. Aβ originates in the endosome (En), Golgi and ER, and it is especially present in Golgi or in late endosomes following the reuptake from the cell surface. Aβ enters into the mitochondrial matrix through TOM and TIM or is derived from mitochondria-associated AβPP metabolism. In mitochondria, Aβ can affect several enzymes inducing NADH reduction and the ETC enzyme complex IV, causing a reduction in the amount of protons and resulting in a decrease in ATP, which increases ROS production. Excessive amounts of ROS leads to lipid peroxidation and negatively regulates presequence P (PITM1/PreP) activity, hindering the normal degradation of Aβ and leading to an increase in Aβ content in mitochondria.

[27].

Pathological mutations in many genes such as Parkin, α-synuclein, LRRK2 and DJ-1, PINK1, directly or indirectly demonstrate that mitochondrial dysfunction plays a role in PD patients [17]. Parkin, the E3 ubiquitin ligase, has been associated with the function of the respiratory chain. A lack of Parkin in mice and flies, for instance, would show a reduction in the level of proteins involved in mitochondrial function, reduced activity of complex I and complex IV of the electron transport chain and disrupted mitochondrial integrity [28]. Mutations in Parkin cause autosomal recessive juvenile PD. Similarly, mutations in PINK1 (PTEN-induced putative kinase 1) can also lead to an autosomal recessive form of PD, and such form is familial and early-onset. In cell culture models of Parkinsonism, mutationsin PINK1 result in decreasing mitochondrial respiratory chain function, leading to reduced ATP synthesis and the increase of α-synuclein aggregation [29]. PINK1 localizes to mitochondria via a multisubunit complex that includes the outer membrane protein TOM40 and the inner membrane protein TIM23. Upon translocation, it is cleaved by MPP and PARL proteases leading to its degradation. However, under stress conditions or in damaged mitochondria, it cannot be cleaved and stabilizes in the outer membrane leading to autophosphorilation and serine phosphorylation of ubiquitin and Parkin, promoting ubiquitination of the mitochondrial outer membrane protein to trigger selective mitochondrial autophagy (Figure 2) [30-32]. Parkin and PINK1 knockouts in *Drosophila*, has also shown that they are on same functional pathway, and that PINK1 has the ability to upregulate Parkin [30]. Thus, pathological changes in Parkin and PINK-1 disrupt normal mitochondrial function and well-balanced mitophagy. The mutation of DJ-1 lead to a rare and early-onset form of Parkinsonism, such form of PD is also autosomal recessive. Human who carry this gene mutation exhibit damage to the oxidative respiratory chain in mitochondria, decrease membrane potential, and increased levels of ROS in mitochondria, as well as altered regular mitophagy [33].

To date, no specific drug has been developed to slow down the progression of PD. Consequently, new therapies are urgently needed. Coenzyme Q, a vital antioxidant in the respiratory chain, is located in the lipid layer of mitochondria. Coenzyme Q10 possess neuroprotective effects that could protect against mitochondrial toxins, for example, MPTP. Although this antioxidant has been shown to be safe and patient tolerant, it has not shown any clinical value in the phase III of clinical trials that have already been carried out [34]. MitoQ is another powerful mitochondria-targeted antioxidant, which accumulates in the mitochondria and resists the damage induced by oxidative stress. However, a study using MitoQ did not revealed a slowdown in the progression of PD [35].

Mitochondria-targeted antioxidant therapy

The two most common approaches for the use of small molecules *in vivo* as mitochondrial targeted antioxidants are: conjugation to a lipophilic cation or absorbtion into mitochondria-targeted peptides.

Lipophilic cations can readily pass through the phospholipid bilayer, such as plasma membrane or the mitochondrial membrane, due to the effective distribution of charge cations in a large and hydrophobic surface that reduces their activation energy and enables their passage across the membrane [36]. These lipophilic cations can cross lipid bilayers without the need of ionophores or carrier proteins and accumulate in the mitochondrial matrix thanks to the negative-inside mitochondrial membrane potential. Triphenylphosphonium (TPP) cation is the most widely used lipophilic cation to transfer antioxidants into mitochondria. It consists of an intermediate positive charge of phosphorus and a surrounding hydrophobic surface. Therefore, TPP can quickly cross the phospholipid bilayer and retain the positive charge. Such positive charge is used to drive TPP cation first into the cell and subsequently into the mitochondrial matrix. The plasma membrane potential is 30-60 mV (negative inside), which favors a 10-fold higher concentration of TPP in the cytoplasm than outside the cell. Similarly, the much greater mitochondrial membrane potential, ~140-160mV, strengthens the reallocation of lipophilic cations from

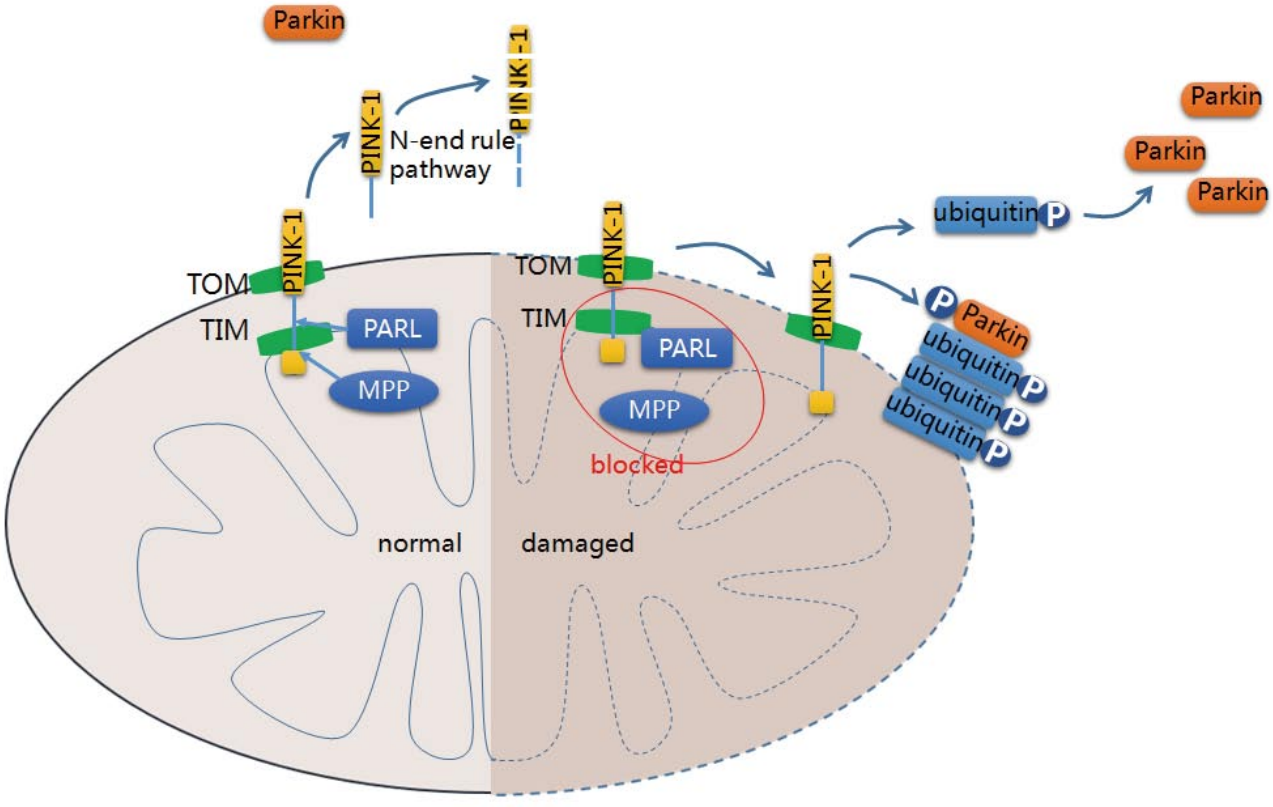

Figure 2. The PINK-1–Parkin pathway. In the normal conditions, PINK1 is imported to the mitochondria through TOM and TIM complex, on the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM), respectively. After entry, PINK-1 is sequentially cleaved by inner mitochondrial membrane proteases MPP and PARL, between amino acids 103 and 104. The remaining N-terminal fragment is then degraded via the N-end rule pathway in the cytosol. However, when mitochondria are damaged or the TIM complex is non–functional due to mitochondrial depolarization, PINK1 processing by MPP and PARL is restrained because of lack of import into the inner membrane. Instead, PINK1 accumulates on the OMM bound to the TOM complex, where it phosphorylates ubiquitin at Ser65. This stimulates the recruitment of cytosolic Parkin to the mitochondrial surface via the direct binding to phospho-ubiquitin chains. Parkin is then also phosphorylated by PINK1 and activates it.

the intracellular space into the mitochondria, leading to ~200-400 fold accumulation of TPP in the mitochondrial matrix [37]. Based on this principle, researchers targeted many antioxidants to mitochondria by conjugation to the TPP cation, including MitoQ.

MitoQ is a mitochondria-targeted ubiquinol, it consists of an ubiquinone moiety covalently attached to a TPP moiety by a ten-carbon aliphatic carbon chain [38]. The TPP moiety on MitoQ can cross the plasma membrane due to the plasma membrane potential and then accumulate hundreds-fold in the mitochondrial matrix compared to cytosol due to its greater membrane potential [16]. Once MitoQ accumulates in the matrix side of the inner membrane, it persistently removes peroxyl radicals, peroxynitrite, superoxide, prevents lipid peroxidation as well as mitochondrial injury [39, 40]. After detoxifying oxidants, the ubiquinol is oxidized to ubiquinone and recycled by the electron transport chain complex II [41, 42]. Consequently, this directionally accumulates MitoQ in the mitochondrial matrix where it is continually recycled, making this targeted-antioxidant hundreds-fold more powerful than other antioxidants [38]. On the other hand, the ubiquinol moiety of MitoQ can also react directly with superoxide and protect against peroxynitrite [43]. However, in some cases, due to the redox cycle of quinone, it may be pro-oxidant and pro-apoptotic and generate superoxide [44]. MitoQ has been shown to possess a protective effect in a large number of animal models of diseases related to oxidative stress such as neurodegenerative disease (including Alzheimer's disease, Parkinson's disease etc.) [16, 20], ischemia-reperfusion [45], type 2 diabetic [46] and hypertension [47].

To evaluate the potential effect of MitoQ on Alzheimer' s disease, different mouse models were analyzed and it has been reported that MitoQ was able to prevent the accumulation of Aβ, inhibit Aβ induced oxidative stress and reverse the reduction of synapses and early cognitive decline. In particular, MitoQ protected neurons against Aβ in a transgenic mouse model of AD and diminished the neurological deficits in the mice [16]. In cultured mouse sympathetic neurons, deprivation of nerve growth factor induced cell death but MitoQ treatment blocked apoptosis by preventing increased mitochondria-derived ROS and subsequent cytochrome c release, caspase activation, and mitochondrial damage by scavenging mitochondrial superoxide [48]. Several studies have shown that MitoQ can not only increase life span, postpone Aβ induced paralysis, but also improve mitochondrial lipid cardiolipin depletion, as well as protect the ETC enzymes complex IV and complex I [49]. In SH-SY5Y cells, it could effectively inhibit mitochondrial fragmentation caused by 6-hydroxydopamine [50]. In another study, MitoQ effectively inhibited neurotoxicity induced by both MPP^+- and MPTP in cell cultures and in a preclinical PD mouse model [51]. MitoQ inhibited the decrease in dopamine and tyrosine hydroxylase levels, as well as the loss of mitochondrial membrane potential caused by MPP^+. It could also alleviate the depletion of dopamine and its metabolites caused by MPTP toxicity. In PD animal models, MitoQ decreased caspase-3 activation which was induced by MPP^+ and alleviated mitochondrial aconitase inactivation which was mediated by MPTP, maintaining normal operational tricarboxylic acid cycle, and decreasing oxidative damage [51]. In one study, a PD mouse model was treated with high levels of MitoQ for up to 28 weeks and showed no evidence of toxicity on whole-body physiology. This result indicated that mitochondria-targeted antioxidant, MitoQ, can be safely administered long-term in mice [52]. MitoQ has undergone phase I and II clinical trials in Hepatitis C virus patients and was proved to be an effective strategy, demonstrating the potential therapeutic efficacy of MitoQ in chronic liver diseases [53]. However, in another double-blind clinical trial of PD patients, it failed to demonstrate any benefit in slowing down the pathologic process of PD during 12 months [35]. A potential explanation for these conflicting results is that the extent of dopamine neurons damage has exceeded the neuroprotective effect of MitoQ. In general, approximately fifty percent of dopamine neurons have been lost by the time there is a clinical diagnosis of PD. Thus, it is possible that the treatment on the remaining neurons is no longer able toprevent the progression of the disease. Although the beneficial effects of MitoQ in PD have been proved both *in vitro* and *in vivo*, further detailed studies are needed to test and verify its potential for treatment. However, it is not only neurodegenerative diseases the targets of MitoQ therapies. In 2015, a new clinical trial aimed to study the effects of MitoQ on improving physiological functions including vascular, motor, and cognitive in middle aged and elderly people was registered on clinicaltrials.gov [54]. In a recent study on human skeletal muscle feed arteries from 44 subjects, it has been shown that MitoQ could reverse age-related endothelial vascular dysfunction [55]. Furthermore, MitoQ could reduce the severity of renal damage in renal is chemia-reperfusion injury in rat models [45]. All this suggest that mitochondrial targeted antioxidants, such as MitoQ can be applied as treatment to a wide variety of diseases.

Conclusion

In neurodegenerative diseases, the two main pathological markers are mitochondrial dysfunction and oxidative stress. In addition to these two hallmarks, there are other pathological features, such as excessive production of ROS, mitochondrial DNA mutations or impaired ATP synthesis. Mitochondrial dysfunction plays a central role in AD and PD, and can be an important target for treating these diseases. As a new therapeutic method, mitochondria-targeted antioxidants have good pharmacological effects in various animal and cell culture models. Among them, MitoQ has been the most extensively studied. In the phase II clinical trial on PD patients, its beneficial effect has not been proven though. This may be due to the fact that mitochondrial dysfunction may represent early stages of the pathological process

of the disease, while pharmacological effects are usually pursued at later stages of the disease after the clinical diagnosis. Mitochondrial dysfunction and oxidative stress can not only define these neurodegenerative diseases, but may also be a new therapeutic strategy and therefore a bigger effort should be made to push research forward before these diseases encroaching on more people.

Future outlook

So far, MitoQ, is the most studied mitochondrial-targeted antioxidant, which has already been used in human clinical trials. In human phase I clinical trials, MitoQ performed good pharmacokinetic characteristics when first administered to Parkinson patients to see if it could slow the progression of the disease [35]. Although mitochondrial targeted therapies inaugurated a new era in mitochondrial dysfunction, such procedure still has some unresolved limitations. First, these specific compounds are often required to be located in the mitochondrial matrix or the matrix-facing surface of the inner membrane. Second, these compounds are not yet targeted to specific organs and thus, they are commonly concentrated in organs with higher mitochondrial content. Moreover, mitochondria-targeted antioxidant MitoQ, has been shown to be safe for humans but still requires further clinical trials. The field of therapeutic mitochondrial compounds has only just begun, and there are many diseases caused by mitochondrial damage such as ischemia/reperfusion injury, diabetes and metabolic syndrome already waiting for this technology to mature. However, different diseases have diverse pathological features, which in turn, means further and specific testing.

Abbreviations

Aβ: amyloid beta
AD: Alzheimer’s disease
PD: Parkinson’s disease
SkQ1: 10-(6’-plastoquinonyl) decyltri-phenylphosphonium
SkQR1: plastoquinonyldecylrhodamine 19
AβPP: amyloid precursor protein
ROS: reactive oxygen species
NADH: nicotinamide adenine dinucleotide
ETC: electron transport chain
MPTP: 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydrodropyridine
MPP+: 1- methyl-4-phenylpyridinium
LRRK2: leucine-rich repeat kinase 2
DJ-1: Parkinson disease protein7
PINK-1: (PTEN)-induced putative kinase 1
TOM: translocase of outer membrane
TIM: translocase of inner membrane
TPP: triphenylphosphonium
ER: endoplasmic reticulum
PS: presenilin
En: endosome
PreP: presequence P
OMM: outer mitochondrial membrane
IMM: inner mitochondrial membrane

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