Biochimica et Biophysica Acta 1842 (2014) 1282–1294

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Mitochondria-targeted antioxidants for treatment of Parkinson's disease: Preclinical and clinical outcomes ☆

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ARTICLE INFO

Article history:
Received 25 July 2013
Received in revised form 10 September 2013
Accepted 11 September 2013
Available online 20 September 2013

Keywords:
Mitochondrial dysfunction
Mitochondria-targeted antioxidant
Neuroprotection
Oxidative stress
Parkinson's disease

ABSTRACT

Parkinson's disease is a progressive neurodegenerative disease in the elderly, and no cure or disease-modifying therapies exist. Several lines of evidence suggest that mitochondrial dysfunction and oxidative stress have a central role in the dopaminergic neurodegeneration of Parkinson's disease. In this context, mitochondria-targeted therapies that improve mitochondrial function may have great promise in the prevention and treatment of Parkinson's disease. In this review, we discuss the recent developments in mitochondria-targeted antioxidants and their potential beneficial effects as a therapy for ameliorating mitochondrial dysfunction in Parkinson's disease. This article is part of a Special Issue entitled: Misfolded Proteins, Mitochondrial Dysfunction, and Neurodegenerative Diseases.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects more than 1 million individuals over the age of 60 years in the United States [1]. According to a recent article, about 50,000 new cases are diagnosed annually, and this figure is expected to increase substantially as the median age of the population continues to rise in the coming decades [2]. Epidemiological studies suggest that sporadic late-onset PD accounts for 90% of cases, whereas the remaining 10% are early onset cases that mainly occur in familial clusters [3,4]. Pathologically, PD is characterized by the loss of dopaminergic neurons within the substantia nigra pars compacta (SNc) and the ensuing depletion of dopamine in the striatum. This loss of dopaminergic neurons causes most of the motor symptoms of PD. By the time PD motor symptoms are clinically recognized, 60% of dopaminergic neurons and 80% of putamen dopamine have been lost [5]. PD is also associated with the presence of ubiquitin- and α-synuclein-positive cytoplasmic inclusions known as Lewy bodies within surviving dopaminergic neurons [6]. In addition to the nigrostriatal dopaminergic defects, emerging clinical evidence suggests that extranigral degeneration and non-motor symptoms are key features of early stages of PD pathogenesis [7–10].

Currently, the available therapies for PD only treat the symptoms; none slow or prevent progressive neuronal degeneration in the dopaminergic system [11,12]. Dopamine replacement therapy, i.e., levodopa administered orally or stimulation of dopamine receptors, has been the most widely used treatment option for PD, but the beneficial effects of dopaminergic therapy wear off over time and its clinical efficacy gradually declines as the disease advances [13].

Despite extensive research, the precise cause of sporadic PD or non-familial PD remains unknown, but several pathogenic mechanisms have been proposed, including oxidative stress, mitochondrial dysfunction, impairment of the ubiquitin-proteasome system, and neuroinflammation. Convincing evidence from postmortem brain tissue, cell culture and animal models of PD and the analysis of human genetics support the involvement of oxidative stress and mitochondrial dysfunction in PD pathogenesis [14,15]. Mitochondrial dysfunction due to oxidative stress, mitochondrial DNA deletions, altered mitochondrial morphology and the interaction of pathogenic proteins with mitochondria all result in dopaminergic neurodegeneration. Thus, therapeutic approaches targeting mitochondrial dysfunction and related oxidative stress may

Abbreviations: MTA, mitochondria-targeted antioxidant; PD, Parkinson's disease; SNc, substantia nigra pars compacta; ETC, electron transport chains; $O_2^{\bullet -}$, superoxide anion; ROS, reactive oxygen species; NO, nitric oxide; TCA, tricarboxylic acid cycle; $ONOO^-$, peroxynitrite; RNS, reactive nitrogen species; H_2O_2, hydrogen peroxide; SOD, superoxide dismutase; GPx, glutathione peroxidase; TPx, thioredoxin reductase; OH•, hydroxyl radical; RO_2•, peroxyl radical; HOCl, hypochlorous acid; RO•, alkoxyl radical; HO_2•, hydroperoxyl radical; GSH, glutathione; GSSG, glutathione disulfide; NOS, nitric oxide synthase; CoQ_{10}, coenzyme Q_{10}; mtDNA, mitochondrial DNA; Apocynin, 4-hydroxy-3-methoxyacetophenone; TPP, triphenylphosphonium; MitoQ, mitoquinone; MitoVitE, mitotocopherol; TEMPOL, 4-hydroxy-2,2,6,6,-tetramethyl-piperidine-1-oxyl; Ang II, angiotensin II; DMT, dimethyltyrosine; PLGA, poly-lactide-co-gylcolide; CAT, catalase; tBHP, t-butyl hydroperoxide; 3NP, 3-nitropropionic acid; Aβ, amyloid beta

☆ This article is part of a Special Issue entitled: Misfolded Proteins, Mitochondrial Dysfunction and Neurodegenerative Diseases.

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http://dx.doi.org/10.1016/j.bbadis.2013.09.007

hold great promise of a cure for PD. One potential approach to ameliorating complications arising from PD is to suppress mitochondrial reactive oxygen species (ROS) generation with specific antioxidants. Several small antioxidant molecules, such as ubiquinol and creatine, have shown promising neuroprotective effects in different models of PD [16,17]. However, a major limitation of using these compounds to treat PD is their failure to accumulate preferentially in the target organelle mitochondria. For this reason, several strategies to identify antioxidants with therapeutic potential that specifically target mitochondria have been developed. In this review, we will describe cellular changes in the progression of PD, and in our discussion of promising PD therapeutic strategies, we will focus on the mitochondrially targeted antioxidants as potential therapies for PD.

2. Production of mitochondrial ROS

Mitochondria play a central role in the life and death of cells. Physiologically, mitochondria perform a variety of fundamental regulatory processes in the cell, including ATP production [18], calcium homeostasis and modulation [19], amino acid and nitrogen metabolism [20], apoptotic cell death [21], ROS generation and detoxification [22,23], and heme and iron–sulfur center biosynthesis [24]. They supply the vast majority of cellular energy in the form of ATP through oxidative phosphorylation. During oxidative phosphorylation, electrons from reduced cofactors are transferred through a series of respiratory chain complexes (complexes I–IV) located in the mitochondrial inner membrane to oxygen, the ultimate electron acceptor. The flow of electrons simultaneously leads to the pumping of protons out of the mitochondrial matrix. This electrochemical reaction generates a transmembrane potential ($\Delta\Psi m$) yielding the energy for ATP synthesis from ADP and inorganic phosphate.

ROS can be generated within mitochondria in several sites of mitochondrial electron transport chains (ETC), in particular on complexes I and III, where electrons occasionally leak to oxygen and form a superoxide anion ($O_2^{\bullet -}$), the predominant ROS in mitochondria (Fig. 1) [25,26]. In fact, mitochondria are the major sites of cellular ROS production, with approximately 1–3% of mitochondrial oxygen consumption being converted to ROS [27]. In addition to formation from incomplete reduction of oxygen in ETC, a number of enzyme systems also generate superoxide, including the tricarboxylic acid cycle (TCA) enzymes α-ketoglutarate dehydrogenase [28] and aconitase [29], the non-TCA cycle enzymes pyruvate dehydrogenase, dihydroorotate dehydrogenase [30] and glycerol-3-phosphate dehydrogenase [31], and the mitochondrial outer membrane proteins such as methemoglobin reductase [32]. Because of its negative charge and poor membrane permeability, superoxide is relatively unreactive, but it can react rapidly with nitric oxide (NO) to form the potent oxidant and nitrating agent peroxynitrite ($ONOO^-$) and subsequently other reactive nitrogen species (RNS). Moreover, it is able to damage some mitochondrial iron–sulfur cluster-containing proteins [33]. Most cellular superoxide is rapidly converted to hydrogen peroxide (H_2O_2) either through spontaneous dismutation or dismutation reactions catalyzed by superoxide dismutase (SOD) [34]. Hydrogen peroxide itself is a reactive free radical that is stable, membrane permeable and has a relatively long half-life enabling diffusion within the cell. As a redox active species, H_2O_2 can inactivate some enzymes by oxidizing their thiol groups [35], although it is unable to oxidize DNA or lipids directly [33]. Hydrogen peroxide can be decomposed by cytosolic and mitochondrial antioxidant systems such as glutathione peroxidase (GPx), catalase (CAT), and thioredoxin reductase (TPx). However, if not removed, it can further produce the highly reactive hydroxyl radical (OH•) in the presence of Fe^{2+} cations via the Fenton reaction [36]. The OH• has a strong oxidizing potential and can damage virtually every type of macromolecule close to their site of origin, making it an extremely dangerous compound to the organism. Furthermore, unlike superoxide and hydrogen peroxide, which can be detoxified by an enzymatic conversion, no enzymatic routes are known for eliminating hydroxyl radicals. Nonenzymatic mechanisms for scavenging peroxyl radicals include several antioxidants such as vitamin E and glutathione. Other radicals derived from oxygen include peroxyl radical (RO_2•), hypochlorous acid (HOCl), alkoxyl radical (RO•), and hydroperoxyl radical (HO_2•), which are high-energy species and exhibit a broad array of biological actions. Additional endogenous sources of cellular ROS are macrophages, neutrophils, and eosinophils. ROS generation can also occur through a host of exogenous

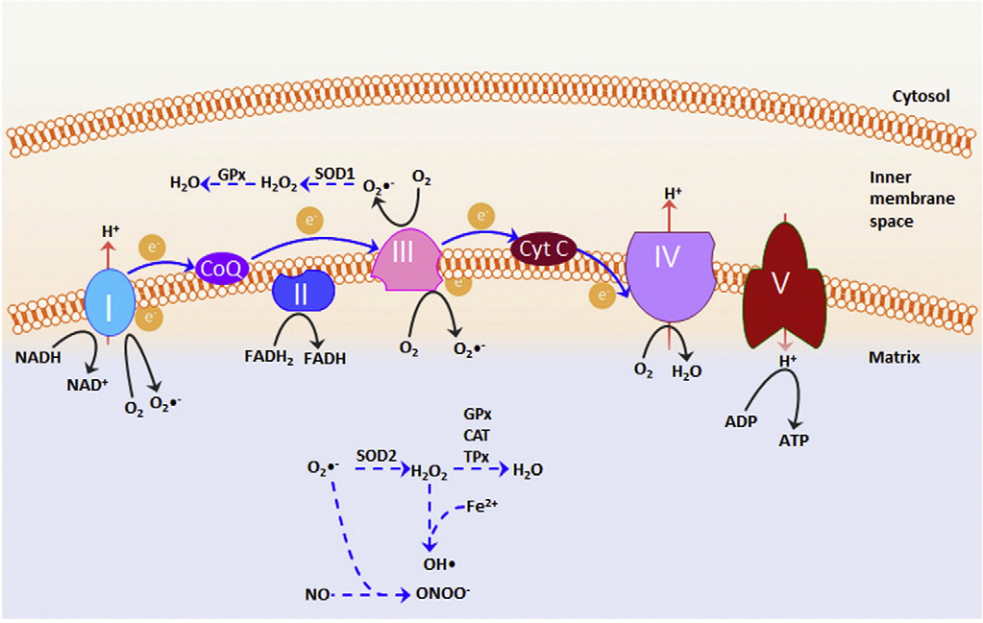

Fig. 1. Schematic presentation of the generation of ROS in mitochondria. ROS are generated from the transfer of electrons (e^-) to molecular oxygen to form superoxide ($O_2^{\bullet -}$) at the mitochondrial electron transport chain complexes I and III. Once generated, superoxide is decomposed enzymatically by superoxide dismutase 1 (SOD1) in the intermembrane space and by SOD2 (MnSOD) in the matrix to form hydrogen peroxide, which is further catabolized to water by the action of enzymes such as catalase (CAT), glutathione peroxidases (GPx), and thioredoxin reductase (TPx) to avoid possible buildup of oxidative stress. However, under mitochondrial stress, superoxide may react with nitric oxide to form the potent oxidant and nitrating agent peroxynitrite ($ONOO^-$). Hydrogen peroxide can also form the highly reactive hydroxyl radical (OH•) in the presence of Fe^{2+} cations. These highly reactive radicals may cause damage to proteins, lipids, and nucleic acids. CoQ, coenzyme Q; Cyt C, cytochrome C.