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Minireview

Therapies for mitochondrial diseases and current clinical trials

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ABSTRACT

Mitochondrial diseases are a clinically and genetically heterogeneous group of disorders that result from dysfunction of the mitochondrial oxidative phosphorylation due to molecular defects in genes encoding mitochondrial proteins. Despite the advances in molecular and biochemical methodologies leading to better understanding of the etiology and mechanism of these diseases, there are still no satisfactory therapies available for mitochondrial disorders. Treatment for mitochondrial diseases remains largely symptomatic and does not significantly alter the course of the disease. Based on limited number of clinical trials, several agents aiming at enhancing mitochondrial function or treating the consequences of mitochondrial dysfunction have been used. Several agents are currently being evaluated for mitochondrial diseases. Therapeutic strategies for mitochondrial diseases include the use of agents enhancing electron transfer chain function (coenzyme Q_{10}, idebenone, riboflavin, dichloroacetate, and thiamine), agents acting as energy buffer (creatine), antioxidants (vitamin C, vitamin E, lipoic acid, cysteine donors, and EPI-743), amino acids restoring nitric oxide production (arginine and citrulline), cardiolipin protector (elamipretide), agents enhancing mitochondrial biogenesis (bezafibrate, epicatechin, and RTA 408), nucleotide bypass therapy, liver transplantation, and gene therapy. Although, there is a lack of curative therapies for mitochondrial disorders at the current time, the increased number of clinical research evaluating agents that target different aspects of mitochondrial dysfunction is promising and is expected to generate more therapeutic options for these diseases in the future.

1. Introduction

Mitochondrial diseases are a clinically and genetically heterogeneous group of disorders that result from dysfunction of the mitochondrial electron transport chain (ETC) and oxidative phosphorylation due to pathogenic variants in mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) encoding mitochondrial proteins [1,2]. In addition to a wide range of cellular perturbations such as aberrant calcium homeostasis, excessive reactive oxygen species (ROS) production, and dysregulated apoptosis, dysfunctional mitochondria are unable to generate sufficient energy to meet the needs of various organs, particularly these with high energy demand, including the nervous system, skeletal and cardiac muscles, kidneys, liver, and endocrine system. Energy deficiency in various organs results in multiorgan dysfunction leading to the variable manifestations observed in mitochondrial diseases including cognitive impairment, epilepsy, cardiac and skeletal myopathies, nephropathies, hepatopathies, and endocrinopathies [3,4].

With the advances in molecular and biochemical methodologies, the etiology and mechanism underlying these disorders have been better understood and the number of identified mitochondrial diseases has increased. However, advances in treating these conditions have been lagging behind. Thus, the treatment for the vast majority of mitochondrial diseases remains mainly symptomatic and does not significantly alter the course of the disease. With a limited base of evidence and little data from randomized clinical trials, the treatment of mitochondrial diseases is still largely anecdotal [5]. Over the past two decades, multiple agents have been evaluated through open-label and randomized clinical trials.

In this review, we present the current therapeutic options for mitochondrial diseases and existing clinical trials for treatment of mitochondrial diseases. Symptomatic treatment, exercise, and diet for mitochondrial diseases are presented first. Subsequently, different agents aiming to enhance mitochondrial function and treat the consequences of mitochondrial dysfunction are presented. These treatment include: 1) agents enhancing ETC function (coenzyme Q_{10} (CoQ_{10}), idebenone, riboflavin, dichloroacetate, and thiamine), 2) energy buffer (creatine), 3) antioxidants (vitamin C, vitamin E, lipoic acid, cysteine donors, and EPI-743), 4) amino acids restoring nitric oxide production

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Table 1
Agents used or being studied for treating mitochondrial diseases.

	Doses	Effect on mitochondrial function	Diseases for which agents are used
Agents increasing electron transfer chain function			
CoQ_{10}	Ubiquinone: 5–30 mg/kg/day divided in 2 doses Ubiquinol: 2–8 mg/kg/day divided in 2 doses	Improving the efficacy of electron transfer through ETC	Primary CoQ_{10} deficiency
Idebenone	30–300 mg/dose 3 times daily	Being a CoQ_{10} analog with higher efficacy	LHON
Riboflavin	50–200 mg/day divided in 2–3 doses	Being a flavoprotein precursor that is a key building block in complexes I and II	Acyl-CoA dehydrogenase-9 deficiency and multiple acyl-CoA dehydrogenase deficiency
Dichloroacetate	10–25 mg/kg/day divided in 2 doses	Increasing pyruvate dehydrogenase activity, thereby increasing the catabolism of pyruvate to acetyl-CoA	Congenital lactic acidosis
Thiamine	10 mg/kg/day (children) 100–1000 mg/day (adults)	Enhancing pyruvate dehydrogenase activity, thereby increasing the catabolism of pyruvate to acetyl-CoA	Leigh disease and thiamine transporter deficiency
Energy buffer			
Creatine monohydrate	100–300 mg/kg/day divided in three doses (children) 2–10 g/day divided in three doses (adults)	Acting as an intracellular buffer for ATP and an energy shuttle for high energy phosphates movement from mitochondrial to cytoplasm	Mitochondrial myopathies
Antioxidants			
Lipoic acid	25 mg/kg/day (children) 300–600 mg/day (adults)	Providing antioxidant action and being an essential factor for pyruvate and ketoglutarate dehydrogenases	MELAS and other mitochondrial diseases
RP103	–	Increasing intracellular glutathione levels by increasing cysteine availability	Leigh and other mitochondrial diseases, ongoing clinical study (https://clinicaltrials.gov/ct2/show/NCT02023866)
EPI-743	–	Protecting against excessive ROS and restoring reduced intracellular glutathione	Leigh disease, ongoing clinical study (https://clinicaltrials.gov/ct2/show/NCT02352896) Mitochondrial diseases, ongoing clinical study (https://clinicaltrials.gov/ct2/show/NCT01642056)
Restoration of nitric oxide production			
Arginine	150 to 300 mg/kg/day divided in 3 doses	Restoring NO production	MELAS Mitochondrial diseases, ongoing clinical study (https://clinicaltrials.gov/ct2/show/NCT02809170)
Cardiolipin protection			
Elamipretide	–	Binding to cardiolipin and protecting it from oxidation	Mitochondrial myopathy, ongoing clinical study (https://clinicaltrials.gov/ct2/show/NCT02367014)
Agents enhancing mitochondrial biogenesis			
Bezafibrate	–	Activating PPAR which activates PCG-1α pathway and induces mitochondrial biogenesis	Mitochondrial myopathy, ongoing clinical study (https://clinicaltrials.gov/ct2/show/NCT02398201)
Epicatechin	–	Enhancing mitochondrial biogenesis	Friedreich ataxia, ongoing clinical study (https://clinicaltrials.gov/ct2/show/NCT02660112)
RTA 408	–	Activating Nrf 2 which stimulates mitochondrial biogenesis	Mitochondrial myopathy, ongoing clinical study (https://clinicaltrials.gov/ct2/show/NCT02255422)

(ETC: electron transport chain; LHON: Leber hereditary optic neuropathy; ROS: reactive oxygen species; NO: nitric oxide; PPAR: peroxisome proliferative-activated receptors; Nrf 2: nuclear respiratory factor 2).

(arginine and citrulline), 5) cardiolipin protector (elamipretide), 6) agents enhancing mitochondrial biogenesis (bezafibrate, epicatechin, and RTA 408), and 7) nucleotide bypass therapy (Table 1). Finally, gene therapy and liver transplantation for mitochondrial diseases are discussed.

2. Symptomatic treatment, exercise, and diet

Examples of symptomatic treatment in mitochondrial diseases include physical therapy for hypotonia and motor delays, hearing aids or cochlear implants for hearing loss, slow infusion of sodium bicarbonate during acute exacerbation of lactic acidosis, cardiac pacing for rhythm abnormalities, surgical correction of ptosis, administration of pancreatic enzymes for exocrine pancreatic dysfunction, and treating diabetes with diet, sulfonylurea, and insulin [1,3].

Exercise can be helpful for mitochondrial disease. Lack of exercise in healthy individuals leads to an overall reduction in mitochondrial ETC activity, whereas endurance training can improve ETC activity and resistance training can stimulate the incorporation of satellite cells into existing muscle fibers. It has been suggested that resistance training in individuals with mtDNA mutations can lead to an overall reduction in the proportion of mutated mtDNA, as satellite cells contain a low or negligible amount of mutated mtDNA. Endurance training might also improve the mitochondrial function. Furthermore, exercise can result in mitochondrial proliferation through inducing PGC-1α, which is the master transcription regulator that stimulates mitochondrial biogenesis [6,7].

No specific dietary manipulation has shown consistent benefit for individuals with mitochondrial disorders. On the other hand, secondary mitochondrial dysfunction was observed with extreme malnutrition and individuals with mitochondrial diseases may have altered caloric needs and inadequate caloric intake because of feeding difficulties. As