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Mini Review

Treating Mitochondrial Myopathy: Can we Boost Oxidative Phosphorylation Activities by Enhancing Mitochondrial Biogenesis?

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Abstract

In clinical practice today, only symptomatic therapeutic approaches are available to patients with mitochondrial myopathies. A possible innovative strategy to ameliorate oxidative phosphorylation deficiency would be to increase the mitochondrial load of the patient's muscle tissue. Some of the most promising stimulators of mitochondrial biogenesis: resveratrol, quercitin, catechins and fibrates, are evaluated in this review. Results so far are promising, but there is need to determine if sufficient mitochondrial proliferation can be achieved to normalize OXPHOS function in patients with mitochondrial myopathy.

Keywords: Catechins; Fibrates; Mitochondrial biogenesis; Mitochondrial myopathy; Oxidative phosphorylation deficiency; Quercitin; Resveratrol

Abbreviations

EGCG: Epigallocatechin-3-Gallate; MELAS: Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-Like Episodes; OXPHOS: Oxidative Phosphorylation; PGC-1α: Peroxisome Proliferator-Activated Receptor-γ Coactivator α; PPAR: Peroxisome Proliferation Activated Receptor; SIRT: Sirtuin

Introduction

In humans, skeletal muscle is one of the tissues with the highest energetic demand. The majority of the necessary cellular energy is supplied by the mitochondria through Oxidative Phosphorylation (OXPHOS). The OXPHOS system consists of five multiprotein complexes embedded within the inner mitochondrial membrane: complex I (NADH:ubiquinone oxidoreductase), complex II (succinate:ubiquinone oxidoreductase), complex III (ubiquinol:cytochrome c oxidoreductase), complex IV (cytochrome c oxidase) and complex V (ATP synthase). Defects in the OXPHOS system are associated with a broad spectrum of clinical manifestations, not surprisingly often with prominent muscular problems [1]. Muscular complaints range from relatively benign myalgias to severe disabilities. The estimated incidence of OXPHOS defects in humans is approximately 1 in 5,000 live births. OXPHOS defects are complex due to the dual origin of genes involved and the specific nature of the mitochondrial genome. The mitochondrial DNA is present in multiple copies in individual cells, and co-existance of mutated and wild type variants, termed heteroplasmy, can occur. Due to this genetic complexity, pinpointing the origin of the defect is often a time-consuming process that requires thorough biochemical and molecular characterization of patient tissues. Diagnostic testing for OXPHOS deficiencies includes spectrophotometry and blue native-polyacrylamide gel electrophoresis, evaluating the activities of the individual OXPHOS complexes I-V [2].

Under physiological conditions, mitochondrial biogenesis is synchronized with changing energetic demands. The process of mitochondrial proliferation necessitates the coordinated expression of mitochondrial and nuclear genes and is governed by a complex system of transcription factors and co-activators, of which the peroxisome proliferator-activated receptor-γ coactivator α (PGC-1α) seems the master regulator [3,4]. Stimulation of PGC-1α activity results in increased mitochondrial mass and function. PGC-1α expression is controlled by the peroxisome Proliferation Activated Receptor (PPAR) family [5], and by deacetylation mediated by NAD^+-dependent protein deacetylase Sirtuin (SIRT) 1 [6,7].

So far, the development of effective therapies for OXPHOS deficiencies has been extremely limited [8]. A proposed therapeutic approach for OXPHOS patients would be to increase the number of mitochondria per cell, which could result in greater capacities to produce ATP (Figure), higher mitochondrial DNA content and increased mitogenesis has recently been suggested to protect mutation carriers from developping Leber's hereditary optic neuropathy [9]. In cybrids harbouring the classical m.3243A>G mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) mutation, PGC-1α overexpression improved OXPHOS complex III and complex IV deficiency [10].

This mini review will focus on some of the most promising stimulators of mitochondrial biogenesis, in relation to their potential to treat OXPHOS deficiencies.

Exercise

Physical activity results in increases in both mitochondrial content and function in skeletal muscle tissue [11], typically doubling the amount of muscle mitochondria. In elderly subjects, 8 weeks of high-intensity exercise training increased expression of PPARγ-1α and various OXPHOS components, and resulted in increased exercise endurance [12]. Significantly increased citrate synthase and OXPHOS complex I, III and IV activities were described in vastus lateralis of young and elderly healthy subjects [13]. A study monitoring patients with heteroplasmic mitochondrial DNA defects showed that, in

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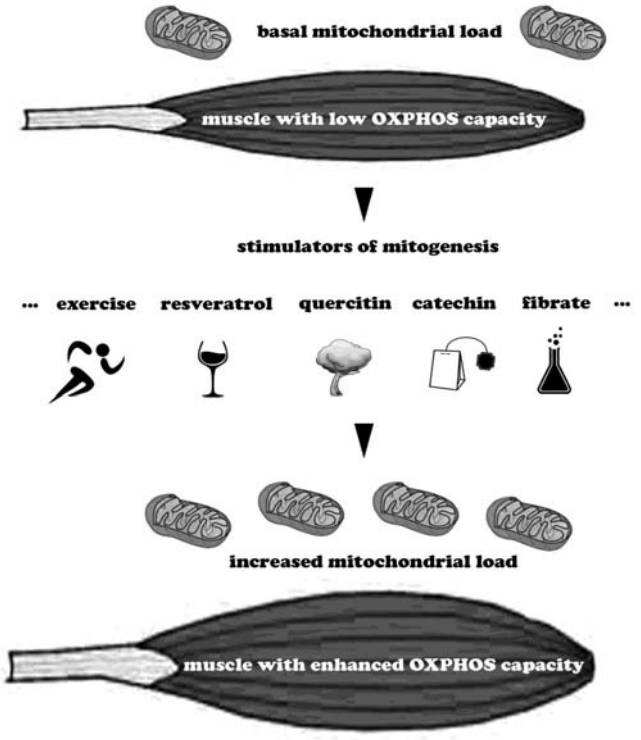

Figure: Rationale for treating oxidative phosphorylation (OXPHOS) deficiencies by stimulating mitochondrial biogenesis. Therapeutic measures stimulating mitochondrial proliferation include exercise and administering mitogenetic compounds, resveratrol, quercitin, cathechins and fibrates. In theory, they enhance the OXPHOS capacities, but this needs to be proven in a therapeutic setting.

response to exercise, levels of the mitochondrial marker citrate synthase increased 50%, while OXPHOS activities went up 20% on average [14], resulting in improved muscle symptoms [15]. In a cohort of patients with chronic progressive external ophtalmoplegia due to single, large-scale mtDNA deletions, 12 weeks of resistance training led to increased muscle strength and a 2-fold significant increase in satellite cell numbers [16]. These data offer promising, yet somewhat unequivocal findings, as different types of exercise were performed and the number of patients enrolled often was low. Although exercise training is regarded a highly efficient means of increasing muscle function, there is an important drawback. Many patients have difficulties maintaining a regular exercise program, which makes other strategies involving nutritional supplements and drugs an attractive alternative.

Caloric restriction

Myriad animal studies have taught us that caloric restriction has the potential to prolong lifespan and diminish aging-associated changes. In the mechanisms responsible for these beneficial effects, increased mitochondrial biogenesis and activity are important players [17]. Caloric restriction increased PGC-1α expression significantly in the gastrocnemius of rats [18]. In a cohort of healthy overweight patients, 25% caloric deficit was shown to increase mitochondrial content and associated makers of biogenesis in vastus lateralis, however, without changing OXPHOS complex IV activity [19]. It needs said that in human due to poor compliance, implementing caloric restriction is not a reliable therapeutic approach.

Resveratrol

Resveratrol (3,5,4'-trihydroxystilbene) is a natural polyphenol present in the skin of red grapes presumed to boost mitogenesis by activating PGC-1α via SIRT1 [20,21]. Significantly increased mitochondrial biogenesis was shown in resveratrol fed mice [21], an effect comparable to the one achieved in PGC-1α overexpressing mice [22]. An *in vitro* study assaying the effect of resveratrol in cultured skin fibroblasts from patients with OXPHOS complex I and complex IV deficiency showed stimulated mitochondrial biogenesis and increased OXPHOS protein levels, resulting in corrected deficiency (measured through oxygen uptake rates) in 6 out of 16 patients' cell lines [23]. In our own *in vitro* study however, resveratrol was unable to normalize mitochondrial enzyme activities in a series of fibroblast cell lines from patients with isolated complex II and complex IV deficiencies, and seemed to necessitate a threshold of residual OXPHOS activity to generate a response [24]. At this time, the first results are beginning to surface addressing the effects of resveratrol in patients. A study evaluating the benefits of exercise in elderly healthy subjects showed no additional gain of adding resveratrol to the study protocol [12].

Quercitin

Quercitin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one) is a widely distributed plant pigment that gets its name from the oak tree (quercus). It is present in many foods, including red onions, apples and berries [25]. Seven days of quercitin feedings significantly increased a set of mitochondrial markers in murine soleus muscle, among which PGC-1α and SIRT1 expression, and resulted in increased maximal endurance capacity and voluntary wheel-running activity [26]. In humans four-week quercitin treatment achieved a small but significant performance effect in young healthy adults [27]. Combined with additional antioxidants and caffeine, a six-weeks supplement has been shown to improve endurance in a bicyle test [28].

Catechins

Epigallocatechin-3-Gallate (EGCG) is known for its anti-cancer and mitogenetic properties. It is present in large quantities in tea leaves and protects mitochondria from oxidative stress. The reduced OXPHOS complex I and complex V activities observed in EBV-immortalized lymphoblasts and fetal skin fibroblasts from subjects with Down's syndrome, were restored to normal levels by treating the cells *in vitro* with 20μM EGCG for 24h [29].

Fibrates

Fibrates are amphipathic carboxylic acids that act as PPAR agonists. They are routinely used for treating diabetes mellitus and metabolic syndrome. Bezafibrate was reported to boost residual OXPHOS enzyme activity that lead to normal oxygen consumption rates in the treated cells [30]. Four-day bezafibrate treatment of cybrids carrying homoplasmic mitochondrial tRNA gene mutations resulted in increased PGC-1α mRNA expression and ATP synthesis. It also increased activities of citrate synthase and OXPHOS complex IV [31].

Conclusion

Based on the literature reviewed, one can conclude that stimulators of mitochondrial biogenesis could be of benefit to patients with

inborn OXPHOS deficiencies. However, this remains to be tested thoroughly in humans. Also, development of potent derivatives of the known mitogenetic compounds could increase therapeutic responses further.

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