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Editorial

# Possibility of pharmacological therapy for mitochondrial diseases

## Clinical position of mitochondrial diseases

Mitochondrial diseases appear as various systemic organ disorders mainly observed in brain, nerve, skeletal muscle, and heart which are organs with higher necessity of energy [1,2]. Mitochondrial malfunction usually results in reduction in adenosine triphosphate production and leads these organs to a shortness of metabolic energy as well as hyper-production of pyruvate or lactic acid [1]. Representative appearance of clinical mitochondrial encephalomyopathy can be classified as chronic progressive external ophthalmoplegia, myoclonic epilepsy with ragged red fibers and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) [1]. Mitochondrial cardiomyopathy is

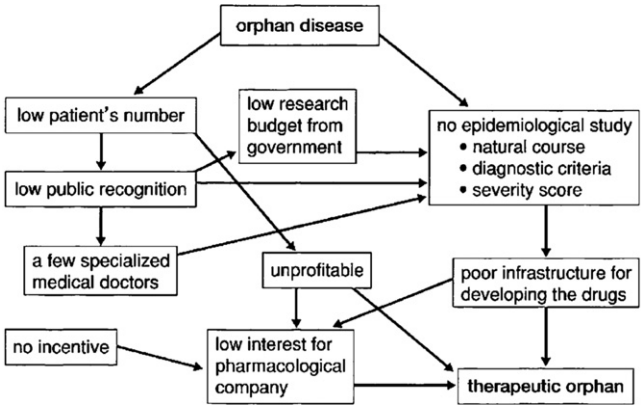


**Fig. 1.** Problems in clinical trials of therapies for orphan disease [2].

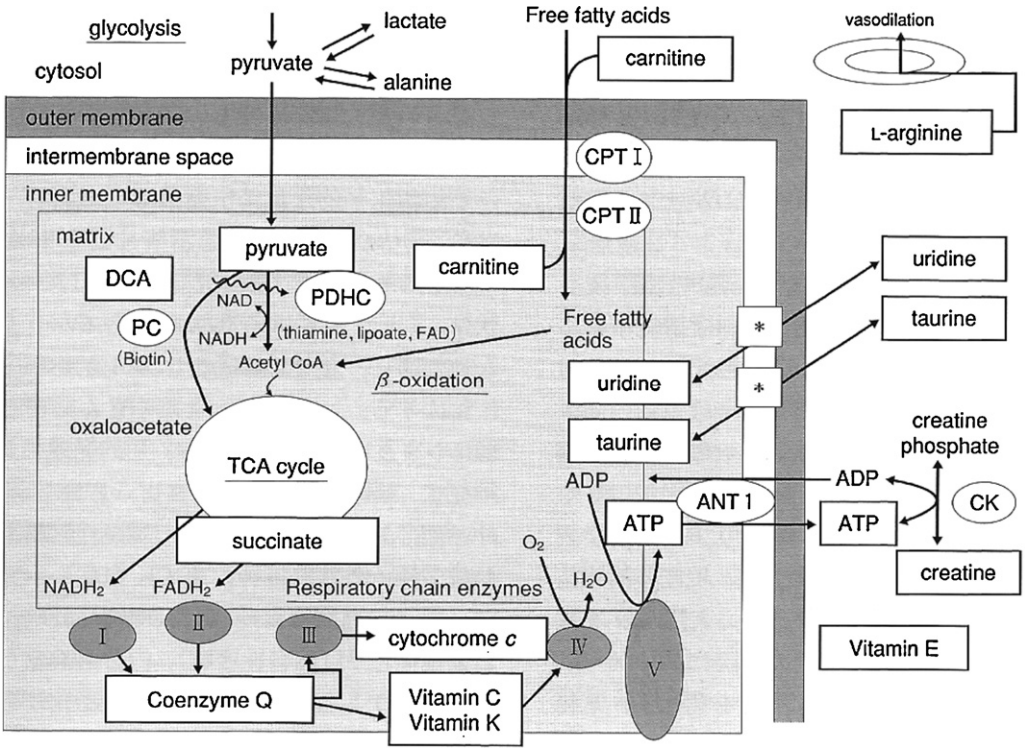


**Fig. 2.** Concepts of possible therapeutic materials for mitochondrial diseases [2]. CPT, carnitine palmitoyltransferase; DCA, dichloroacetic acid; PC, phosphatidyl choline; PDHC, pyruvate dehydrogenase complex; TCA, tricarboxyl acid; ANT1, adenine nucleotide translocator 1; ATP, adenosine triphosphate; ADP, adenosine diphosphate; CK, creatine kinase; $NADH_2$, dihydro-nicotineamide adenine dinucleotide; $FADH_2$, dihydro-flavin adenine dinucleotide. * specific transporter.

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also a phenotype of mitochondrial disease and is defined as abnormal structure and/or function of cardiac tissue caused by genetic abnormality involving mitochondrial respiratory chain without any other known heart disease [3–5]. These and the other types of mitochondrial diseases are rarely observed and termed as "orphan disease" and the population of the patients is considered less than 50,000 in total in Japan. Because of such a situation, even a precise classification as well as clinical trials for therapeutic approaches is limited (Fig. 1) [2]. Probably, the replenishment of lacking enzyme in abnormal mitochondria will be a fundamental approach, but such methodology cannot be anticipated because of restricted transferring function of mitochondria membrane.

## Possible pharmacological therapy for mitochondrial diseases

Concepts of possible therapeutic materials for mitochondrial diseases are summarized in Fig. 2 [1,2]. None of these materials were proven to be effective for any type of mitochondrial disease and all of the trials for the treatment involve off-label use. The most recent review, i.e. Cochrane Review 2006 [6], has realized the absence of any effective therapy for mitochondrial diseases, but it also mentioned several interesting reports. They were the reports about coenzyme Q10, creatine, dichloroacetic acid (DCA), and dimethylglycine as the therapeutic materials but the results were controversial [7,8]. However, some clinical trials, such as coenzyme Q10 for mitochondrial diseases, DCA for MELAS, and idebenone for Leber hereditary optic neuropathy are still on going. The possibilities of resveratorol and L-arginine have also been suggested by several reports [9,10]. In the case report of Vahdat et al. [11], a catastrophic condition of diseased heart was dramatically improved by the administration of a unique "mitochondrial cocktail" which contained respiratory chain co-factors (coenzyme Q10, thiamine, riboflavin), antioxidant (vitamin-E), biochemical materials (L-carnitine, creatine, folate), and vasodilator (L-arginine). Although the diagnosis itself of the patient was controversial, the effect of this therapeutic approach was dramatic and cardiac condition almost fully recovered at least in this case. Although it will be difficult to clarify the role of each material in this unique cocktail in mitochondrial diseases, this kind of "broad approach" might be effective in various types of mitochondrial diseases [12–14] and may show a novel pharmacological approach to mitochondrial diseases. However, strong attention should be paid to the dosage and method of administration of these materials because they can cause various types of side effects, including hypotension, peripheral vascular injury, cardiogenic shock, or life-threatening arrhythmias. The protocol for such broad therapy should be constructed carefully by considering case-by-case situations.

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