RESEARCH ARTICLE

MITOCHONDRIAL DISORDERS AND THEIR CORRECTION IN NEUROLOGICAL DISEASES

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Abstract

Mitochondria are cellular organelles that produce energy in the form of ATP. For this reason, they are called "power stations" or "energy factories". Mitochondria have their DNA. Part of mitochondrial DNA in the process of phylogenesis moved into nuclear DNA. There are 4 types of metabolism in mitochondria: a) Transfer of electrons in the respiratory chain with the formation of ATP and oxygen, b) Fat metabolism with the participation of carnitine, c) Amino acid metabolism, d) Carbohydrate metabolism. There are 2 groups of mitochondrial pathology: Primary mitochondrial pathology is hereditary syndromes caused by mutations in genes responsible for mitochondrial proteins (Kearns-Sayre syndrome, Pearson syndrome, MELAS syndrome, MERRF syndrome, and others). Secondary mitochondrial pathology includes dysfunction of mitochondria as an important link in pathogenesis. Primary mitochondrial diseases are caused by mutations in mitochondrial DNA or nuclear DNA that affect the respiratory chain or mtDNA homeostasis. Secondary mitochondrial disorders have been identified in common sporadic neurological diseases, including Alzheimer's disease, Parkinson's disease, and other pathologies. ***ASEAN Journal of Psychiatry, Vol. 23(1) January, 2022; 1-9.***

Keywords: Sense of belonging, Scale, Adolescents

Introduction

Mitochondria are cellular organelles that produce energy in the form of ATP. For this reason, they are called "power stations" or "energy factories". Mitochondria have their own DNA. Part of mitochondrial DNA in the process of phylogenesis moved into nuclear DNA. a) Transfer of electrons in the respiratory chain with the formation of ATP and oxygen. b) Fat metabolism with the participation of carnitine. c) Amino acid metabolism. d) Carbohydrate metabolism. There are 2 groups of mitochondrial pathology: Primary mitochondrial pathology is hereditary syndromes caused by mutations in genes responsible for mitochondrial proteins (Kearns-Sayre syndrome, Pearson syndrome, MELAS syndrome, MERRF syndrome, and others). Secondary mitochondrial pathology includes dysfunction of mitochondria as an important link in pathogenesis. Primary mitochondrial diseases are caused by mutations in mitochondrial DNA or nuclear DNA that affect the respiratory chain or mtDNA homeostasis. Secondary mitochondrial disorders have been identified in common sporadic neurological diseases, including Alzheimer's disease, Parkinson's disease, and other pathologies.

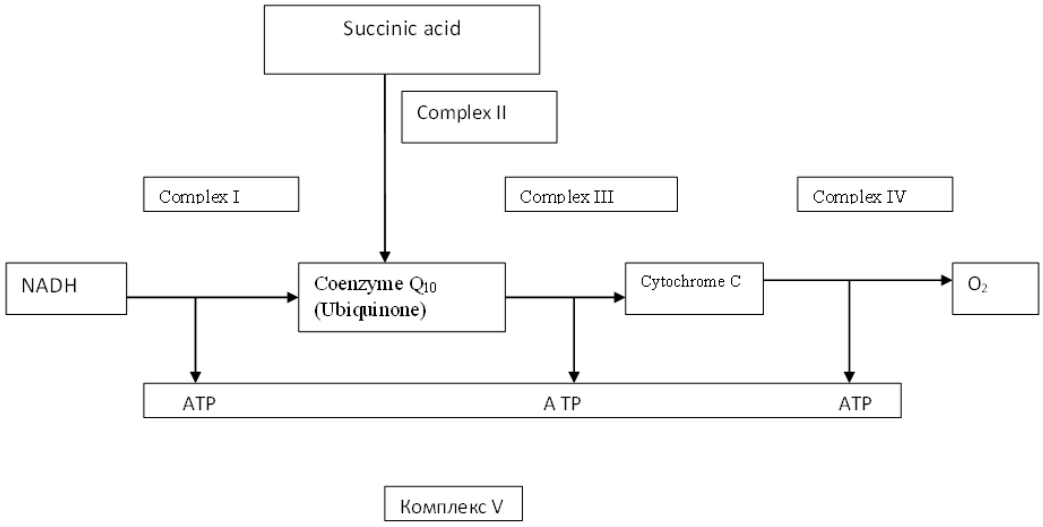

Figure 1 Complexes of the electron transport chain in mitochondria

Methods for the study of mitochondrial disorders

A method for the quantitative cytochemical determination of the activity of mitochondrial enzymes in peripheral blood lymphocytes was proposed by Pearse.

Method for quantitative cytochemical determination of enzyme activity in peripheral blood cells (formulation of reactions): Reactions are performed on blood smears prepared on fat-free slides. Smears are air-dried at room temperature for 10 minutes-15 minutes. The formulation of the reaction includes three stages: the fixation of smears, the reaction to detect the activity of enzymes, and the staining of the nuclei. Fixation of drugs is carried out in 60% acetone solution saturated with Trilon B at a pH is 5.2-5.4 at room temperature for 30second-40 seconds (for lymphocytes). After fixing, the preparations are washed with distilled water and dried at room temperature in the air. Composition of the incubation medium: for 40 ml of phosphate buffer, 13 mg of p-nitrotetrazolium violet, 13 mg of Trilon B, a specific substrate for a specific enzyme. The reaction is carried out at pH 7.3 and a temperature of 37°C for 60 minutes in an aqueous thermostat. After incubation, the smears are washed with water and immersed in a saturated solution of methyl green (nuclear dye) for 15 seconds-20 seconds, after which the smears are washed again and dried at room temperature in the air. The finished smears are microscopized under water immersion on a Micmed-6 microscope. The activity of the enzyme in the cell is judged by the number of dark purple formazan granules formed during the reduction of p-nitrotetrazolium violet (Figure. 2). To determine the enzyme activity in the lymphocyte population, the number of granules in 30 cells-100 cells is counted. The enzymatic activity when using this method is expressed in granules/lymphocyte, which corresponds to the average number of granules of the cytochemical reaction product-formazan.

Determine the activity of mitochondrial enzymes

-Succinate Dehydrogenase (SDH) - reflects the function of the mitochondrial respiratory chain (Figure 2).

-Lactate Dehydrogenase (LDH) - reflects the state of carbohydrate metabolism in mitochondria.

-Glutamate Dehydrogenase (DHD) - reflects the function of amino acid metabolism in mitochondria.

-Alpha-Glycerophosphatedehydrogenas (GPDH) - reflects the function of fat metabolism in mitochondria

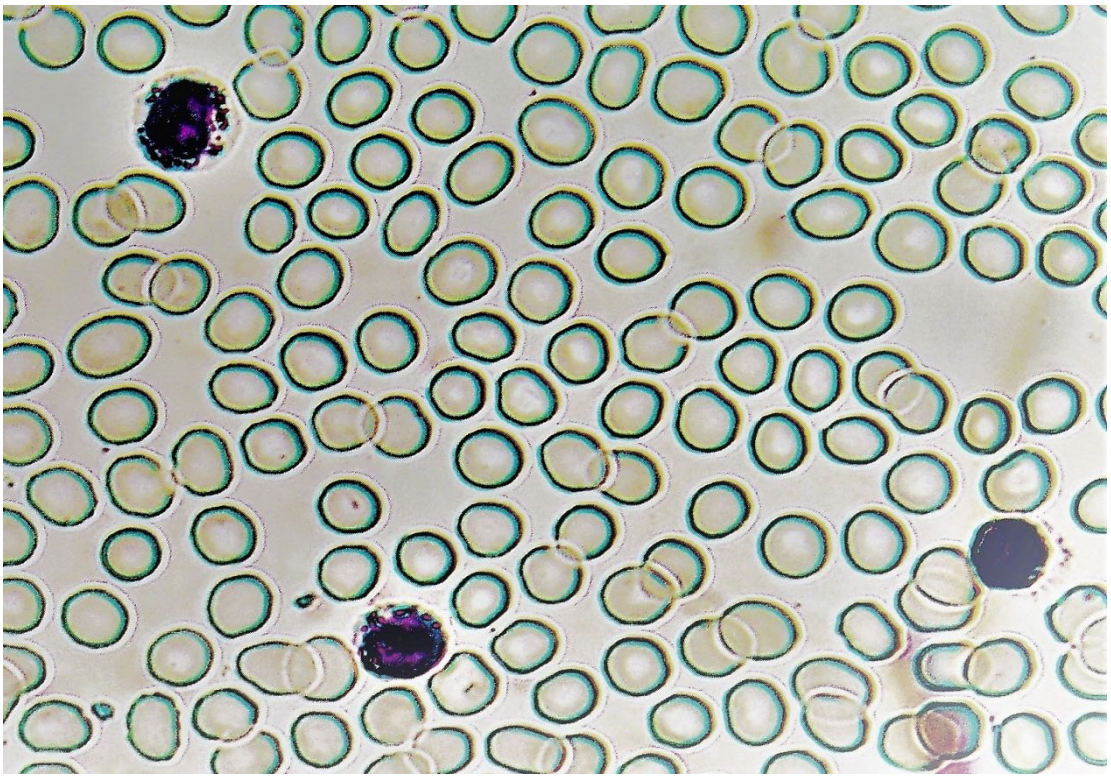

Figure 2 Revealing the activity of succinate dehydrogenase in lymphocytes by a quantitative cytochemical method (view under a microscope, magnification 600, dark granules according to the periphery of the cell - production).

The lactate level is determined in whole heparinized blood by the amperometric, enzymatic method using a substrate-specific electrode on a blood gas analyzer ABL800 FLEX. The study of lactate in the blood before meals and 1 hour after taking sugar or glucose dissolved in water at a dose of 1 g per kg of body weight.

Respirometry is the measurement of oxygen in biological material. The rate of consumption and concentration of oxygen by living cells and tissues is measured with the maximum approximation of the measurement to *in vivo*. Respirometry is performed using an oxigraph device Oxygraph-2k (Oroboros, Austria).

L. D. Lukyanova, the Corresponding Member of the Russian Academy of Sciences, made a great contribution to the study of the respiratory chain of mitochondria.

He coined the term energotropic medicines.

Energy medicines (specific antioxidants) are substances, the effects of which are aimed at correcting mitochondrial dysfunction and restoring

the energy-synthesizing function of the cell.

For Correction of disorders in the mitochondrial respiratory chain are used:

- Medicines of Coenzyme Q 10
- Medicines of succinate
- Cytochrome C
- ATP

Medicines of Coenzyme Q 10 (Complex III of the mitochondrial respiratory chain):

- Idebenone (well penetrates the blood-brain barrier).
- Coenzyme Q10 (poorly penetrates the blood-brain barrier)
- Daily requirement for coenzyme Q10 is 500 mg.
- Differences between idebenone and coenzyme Q10
- Significantly smaller size (5 times less than isoprenoid units in the side chain);
- Less pronounced hydrophobicity;
- Easily penetrates the blood-brain barrier;
- More significant antioxidant activity.

- Medicines of Idebenone:
- Noben, 1 capsule - 30 mg. Registered since 18 years
- Mnesis, 45 mg in a tablet
- Celestab, capsules 45 mg. Registered since 18 years
- Idebenone, Capsules 30 mg, 45 mg. Registered since 18 years
- Neuromet (no age limit) Capsules. 30 mg-45 mg
- Coenzyme Q10 medicines (Poorly penetrates the blood-brain barrier):
- Kudesan. 1 tablet 30 mg.
- Kudevita. Capsules 30 mg.

Idebenone and coenzyme Q10 medicines are prescribed under the control of blood pressure. It can decrease by 10 millimeters-20 millimetres of mercury (mm Hg).

If blood pressure drops, it is recommended-salty food, tea, vitamin B1 tablets 100 mg -200 mg each.

ECG is recommended once every 6 months. If extrasystoles appear, the dose of idebenone or coenzyme Q10 medicines should be reduced.

Succinic acid medicines (II complex of the mitochondrial respiratory chain):

- Mexidol.
- Mexiprim.
- Cytoflavin.

These medicines are not for a long time prescribed because of the possible stimulation of the proliferative process.

The medicine "Cytochrome C" is prescribed only parenterally.

ATP medicine in tablets
Perhaps this medicine contains less ATP than it is formed when taking idebenone, succinic acid and cytochrome C.
Do not simultaneously prescribe medicines from various complexes of the mitochondrial respiratory chain, since their effect is reduced due to competition for electrons.

Carnitine medicines

Carnitine is involved in fat metabolism. Violation of fat metabolism is defined as a change in activity alpha-glycerophosphate dehydrogenase by the Pearse method.

Carnitine is involved in the metabolism of fatty acids in the mitochondria, and not in the electronic transport chain of mitochondria. The daily dose of carnitine is 500 mg.

Carnitine medicines

- Karnitsetin. It contains an acetyl group, promotes the synthesis of acetylcholine and improves interneuronal conductivity. Registered from the age of 18.
- Karniten contanes levocarnitine with sugar and magnesium.
- Levocarnitine - elkar. In solution and powder for oral administration, in ampoules for parenteral administration.
- Carnitine chloride. For intravenous administration.

It is possible to simultaneously prescribe coenzyme Q10 medicines and carnitine preparations, since they have different points of applciation.

Medicines that reduce lactic acidosis:

- Dimephosphone
- Dichloroacetate
- Stimol (citrulline malate)
- Carnosine (L-carnosine, sevitin).

In 1903, the Russian scientist Gulevich discovered it in high concentrations in muscle and brain tissue.

His student Severin found out the function of these substances.

It turned out that if you add carnosine to the solution in which the isolated frog muscle was located, then, under the influence of an electric charge, it acquires the ability to work for hours without any fatigue.

This experience later entered physiology as the "Severin phenomenon. In the presence of carnosine, the muscle can accumulate colossal amounts of lactate.

Skvortsova V.I., et al. [1] studied the activity of mitochondrial enzymes (succinate dehydrogenase, alpha-glycerophosphate dehydrogenase and others) in the acute period of stroke. Changes in the activity of mitochondrial enzymes were revealed, which is an indication for the appointment of energotropic

medicineses.

Secondary mitochondrial disorders in stroke are also presented in the article by S.V. Kotova, et al. [2]. He investigated the activity of mitochondrial enzymes on the first day of stroke. The activity of succinate dehydrogenasa was compensatory increased. Succinate dehydrogenase is the second complex of the mitochondrial respiratory chain. The activity of alpha-glycerophosphate dehydrogenase was reduced. This enzyme is involved in mitochondrial fat metabolism.

Administration of Mexidol (a medicine of succinic acid) to patients accelerates the regression of neurological symptoms in ischemic stroke [3].

There is statistically significant differences were revealed in the severity of regression of neurological defects in patients of the control group and patients receiving Elcar (levocarnitine) in the acute period of ischemic stroke [4].

Carnosine is highly effective in animal models of ischemic stroke models.

Carnosine reduced the area of cerebral infarction by 29% [5]. A clear dose-response effect was observed and efficacy decreased when carnosine was administered more than 6 hours after ischemia. Carnosine administered before or after the onset of ischemia is highly effective in experimental ischemic stroke.

Histological examination of brain tissue in mice with experimental autoimmune encephalitis treated with L-carnosine showed less pronounced inflammatory infiltrates and demyelination compared with the control group [5].

At the onset of Parkinson's disease, a statistically significant compensatory increase in succinate dehydrogenase activity was noted as compared with the control group [6].

Russian patent [7] demonstrates an increase in the effectiveness of therapy for Parkinson's disease with a combination of carnosine with classical therapy.

There are primary and secondary mitochondrial disorders in neuromuscular diseases. S. Kotov et al. [8] examined 74 patients with neuromuscular diseases. The activity of 4 mitochondrial enzymes involved in carbohydrate metabolism (lactate dehydrogenase), amino acid metabolism (glutamate dehydrogenase), fatty acids (α-glycerophosphate dehydrogenase), and mitochondrial respiratory chain complex II (succinate dehydrogenase) was evaluated. For a cytochemical study of the activity of mitochondrial enzymes in peripheral blood lymphocytes, the method proposed by A. G.E. Pearse was modified by R. P. Narcissov.

Results

The greatest changes were revealed in cases with myotonic dystrophy: statistically significant decreases in the average activity value of all studied enzymes ($p<0.05$).In cases with hereditary motor-sensory neuropathy of type I the activity of succinate dehydrogenase and glutamate dehydrogenase is reduced ($p<0.05$), in cases with type II there are deviations in the activity indicators of mitochondrial enzymes, more pronounced compared with type I, but not statistically significant ($p>0.05$). In patients with myasthenia gravis, a decrease in the activity of α-glycerophosphate dehydrogenase and glutamate dehydrogenase ($p<0.05$) was noted. Average values of succinate dehydrogenase and lactate dehydrogenase activity indicators were also reduced ($p>0.05$). In cases with Landusi-Dejerine myopathy the activity of succinate dehydrogenase, α-glycerophosphate dehydrogenase and glutamate dehydrogenase were reduced, of which only for α-glycerophosphate dehydrogenase $p<0.05$. In the analysis of each case in groups of patients with the studied pathology, it was shown that in addition to patients with myotonic dystrophy, in which all patients decreased the activity of succinate dehydrogenase, α-glycerophosphate dehydrogenase and glutamate dehydrogenase, in other cases, in some patients, the studied enzyme activity did not change. P. Borum et al. shows muscle carnitine levels in patients with Duchenne myopathy is reduced by almost 3 times, with Becker's myopathy by almost 2 times [9].

At the World Muscular Society 2020 year G. Buese submitted material about slowing the development of respiratory disorders in Duchenne myopathy using idebenone [10].

Buyse and co-authors have shown a positive effect of idebenone on the function of the respiratory muscles in Duchenne myopathy [11]. The inspirational flow reserve of boys with Duchenne myopathy who received idebenone differed in a positive direction compared with patients who

received placebo.

McDonald, et al. [12] showed that idebenone reduces respiratory complications in Duchenne myopathy. The average frequency of broncho-pulmonary diseases in Duchenne myopathy in patients receiving idebenone and in patients receiving placebo.

At the Moscow Regional Clinical Research Institute (MONIKI), we prescribed idebenone to a patient with Becker's myopathy. The improvement came within 1 month. More significant after 3 months. And even more important after 6 months. After 1 month, the strength of the muscles of the arms increased from 3 points to 4 points. But the patient squatted 6 times, as before the treatment.

After 3 months, he was able to sit down 11 times. After 6 months, 13 times. The strength in the hands became 5 points.

Cognitive function improves in patients taking idebenone.

Russian neurologist Grinio Leonora Petrovna publicated the Book

"Coenzyme Q10 (ubiquinone) in clinical practice".

S.V. Kotov, et al. [13] reported the positive effect of energotropic therapy (L-carnitin, coenzim Q10) in patient with Becker muscular dystrophy based on the magnetic resonance imaging of limb muscles.

Grinio, L.P. [14] reported the role of carnosine in muscular diseases. The carnosine in skeletal muscles in Duchenne muscular dystrophy is significantly reduced. This is the basis for the use of carniosine (sevitin) as a remedy for this disease.

Dursun N., et al. [15] reported Carnosine treatment resulted in a significant reduction in cardiomyopathy in rats.

Conclusion

The appointment of energotropic medicines for hereditary neuromuscular pathology is relevant due to the lack of screening of newborns for most of these diseases and the appointment of gene therapy in the preclinical stage of the disease.

These medicine are effective for hereditary diseases. They also improve the course of the disease in other acute and chronic neurological diseases, since mitochondrial dysfunction plays a role in their pathogenesis.

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Received: 07 December 2021 **Accepted:** 10 December 2021