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Short Communication

Correction of Mitochondrial Dysfunction of the Brain in Ischemia

Fliuryk S., Dremza I., Bon L.I *., Khalko S.A

Grodno State Medical University, Grodno.

***Corresponding Author:** Bon L.I, Grodno State Medical University, Grodno.

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Abstract

The problem of treating mitochondrial dysfunction remains unresolved. This is primarily due to the complexity of cellular adaptation processes, including in neurons, which require substantial correction of the energetic status and normalization of mitochondrial function under any type of injury. The optimal therapeutic strategy involves agents that are equally effective across various forms of mitochondrial dysfunction: as symptomatic therapy in primary mitochondrial diseases and as pathogenetic therapy in secondary mitochondrial disturbances.

Kew Words: correction; mitochondrial dysfunction; brain; ischemia

Introduction

Energy insufficiency is a mismatch between the energy demands of the brain and the body as a whole and the limited amount of adenosine triphosphate (ATP) that is available at a given moment to support the structural integrity and functional activity of tissues. Mitochondrial damage and insufficient oxygen supply (hypoxia) play the key roles in the development of energy insufficiency; therefore, this term has recently been replaced with *mitochondrial dysfunction.*

The problem of treating mitochondrial dysfunction remains unresolved. This is primarily due to the complexity of cellular adaptation processes, including in neurons, which require substantial correction of the energetic status and normalization of mitochondrial function under any type of injury. The optimal therapeutic strategy involves agents that are equally effective across various forms of mitochondrial dysfunction: as symptomatic therapy in primary mitochondrial diseases and as pathogenetic therapy in secondary mitochondrial disturbances [1]. Such agents should possess a number of pharmacological properties, including: correction of the consequences of free-radical processes - particularly lipid peroxidation (LPO); attenuation of Krebs cycle enzyme inhibition; enhancement of mitochondrial oxygen utilization to prevent uncoupling of oxidation and phosphorylation and to stabilize membranes; and compensation for the loss of components of the respiratory chain through formation of redox systems that can bypass electron overload. Additional goals of drug therapy include reducing oxygen consumption and inhibiting auxiliary oxygen-consuming pathways that are not essential for survival under critical conditions. Antioxidants and antihypoxants are most commonly used to address these tasks. Current therapeutic strategies for mitochondrial dysfunction rely primarily on combinations of coenzyme Q10, L-carnitine, B-group vitamins, and antioxidants, which improve respiratory chain function and neutralize reactive oxygen species. These agents increase ATP synthesis without increasing lactate production, while reducing cellular expenditure of macro-energy compounds on processes unrelated to survival during critical conditions [2].

Antioxidant enzymes capable of eliminating oxygen anion radicals - such as superoxide dismutase, catalase (which decomposes H_2O_2), and glutathione peroxidase with glutathione-S-transferase - play a central role in regulating LPO processes in the body. Alongside free-radical oxidation, biological systems also generate substances possessing antioxidant activity, referred to as stable radicals. These radicals cannot extract hydrogen atoms from most cellular molecules, but they can react with specific molecules that contain weakly bound hydrogen atoms [2]. The brain is highly sensitive to free-radical reactions under ischemic (hypoxic) conditions due to several physiological characteristics. It consumes about 20% of the body's total energy, making its cells especially vulnerable to ATP deficiency. The brain contains a high level of phospholipids and, consequently, a low protein-to-lipid ratio - ten times lower than in skeletal muscle. It also contains low levels of vitamin A, transferrin, and ceruloplasmin, and displays deficient antioxidant systems, extremely low glutathione peroxidase activity, and nearly complete absence of catalase, while simultaneously having a high concentration of divalent iron ions. For these reasons, parenteral administration of antioxidants is currently viewed as one of the most promising approaches for treating mitochondrial dysfunction in the brain. In recent decades, active research has focused on developing drugs capable of activating metabolic processes - so-called metabolic agents [3]. Their effects should manifest under any pathological condition, and they should represent either natural metabolic substrates or modulators of their synthesis. Under conditions of injury, disease, or stress, agents in this group should prevent or reduce the pathological effects of hypoxia and support oxidative phosphorylation. This therapy helps maintain vital brain and systemic

functions until normal metabolism is restored [4]. Energy-tropic agents that enhance the transport and oxidation of fatty acids in mitochondria to generate ATP, as well as facilitate electron transfer in the respiratory chain, commonly include metabolic cofactors (L-carnitine, B-group vitamins), antioxidants (succinic acid derivatives, reamberin, coenzyme Q), combined agents (cytoflavin), and trophic agents (actovegin). Coenzyme Q10 and succinic acid, in addition to replacement activity, also exert regulatory (signaling) effects: even at microdoses they normalize key stages of cellular energy metabolism and initiate mitochondrial renewal. One of the promising agents capable of targeted action on mitochondrial dysfunction is **Cytoflavin** [12]. It is a combination of two metabolic substrates (succinic acid - an endogenous intracellular Krebs cycle metabolite with universal energy-generating function - and inosine - a precursor of ATP) and two cofactor vitamins (riboflavin, vitamin B2 - an activator of succinate dehydrogenase, and nicotinamide, vitamin PP - an activator of NAD-dependent Krebs cycle enzymes). The balanced composition of Cytoflavin enables a wide range of metabolic effects: antihypoxic, antioxidant, anti-asthenic, energizing, neuroprotective, and anti-ischemic. In acute cerebral ischemia, the primary target of the drug is the so-called *penumbra zone*, where a cascade of events leads to acute ischemic mitochondrial dysfunction.

Most of the aforementioned agents act at the level of the Krebs cycle but do not influence reduced cytochrome c expression. In this context, the drug **Cytochrome C** deserves special attention - an original antioxidant/antihypoxant with a dual mechanism of action [5]. Cytochrome c is a natural heme-containing protein involved in cellular respiration and regulation of redox processes in tissues. By enabling the transition of the heme iron from the oxidized Fe(III) to the reduced Fe(II) state, cytochrome c activates electron transfer between coenzyme Q–cytochrome c reductase and cytochrome c oxidase complexes, without binding oxygen, while participating in tissue respiration [6,7]. Under hypoxic conditions, mitochondria lose components of the electron transport chain; exogenous cytochrome c acts as a form of replacement therapy. Experimental studies have shown that exogenous cytochrome c penetrates cells and mitochondria under hypoxia, integrates into the respiratory chain, and contributes to the normalization of energy-producing oxidative phosphorylation. It has proven effectiveness in improving tissue respiration under conditions marked by impaired redox processes, including in the therapy of complications of acute myocardial infarction and correction of hypoxic states [5,7]. A comparative study of cytochrome c and ethylmethylhydroxypyridine succinate in elderly patients with coronary artery disease complicated by chronic heart failure and/or arrhythmia demonstrated superior efficacy of cytochrome c, shown by improved exercise tolerance and significant reduction in ventricular extrasystoles [8]. Preventive administration of cytochrome c at 0.3 mg/kg exerts a cerebroprotective effect, preventing or reducing pathological processes such as intra- and extracellular brain edema [9]. Cytochrome c also promotes normalization of S100b protein levels - a marker of neuronal damage [10,26]. In clinical practice, it is particularly important for patients with chronic or acute manifestations of mitochondrial dysfunction to use drugs with simple and brief administration regimens. In all hypoxic conditions, cytochrome c is administered at 10 mg intravenously or intramuscularly once daily. After a 10-day break, the course should be repeated. Its bioavailability is identical for intravenous and intramuscular routes. Notably, cytochrome c is the only antihypoxant approved for the treatment of fetal asphyxia and permitted for pediatric use. It is derived from bovine heart tissue and is a natural-origin drug [7]. Further research will help elucidate its role in correcting mitochondrial dysfunction, including potential combinations with other agents such as antioxidants. Thus, one of the promising approaches for the prevention and treatment of mitochondrial dysfunction is the use of antihypoxants that reduce or eliminate hypoxic disturbances by supporting and enhancing energy production within the mitochondrial oxidative phosphorylation system.

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