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IS AGING REVERSIBLE? – BENEFICIAL EFFECTS OF EXERCISE

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Factor(s) that substantially affect and determine longevity remain a mystery. Discovery of the elixir of life fascinated people for thousands of years. One of the best documented example is Chinese emperor Qin Shi Huang (259–210 B.C.). He did all he could to become immortal, so he tried to prolong his life by ingestion of mercury. But this plan failed, and he died (1).

Aging is a multifactorial process influenced by genetic factors, nutrition, and lifestyle. It is defined as an age-dependent or age-progressive decline in intrinsic physiological functions, leading to an increase in age-specific mortality rate and a decrease in age-specific reproductive rate (2). Mitochondrial dysfunction has long been considered a major contributor to aging and age-related diseases by oxidative phosphorylation dysfunction, progressive accumulation of mitochondrial DNA mutations and by deleterious effects of reactive oxygen species (3).

OVERVIEW OF MITOCHONDRIA – STRUCTURE AND FUNCTIONS

Mitochondria, originating from bacterial precursor cells that were able to generate energy, are essential for many cellular processes. Mitochondria comprise at least six compartments: outer membrane, inner boundary membrane of significantly larger surface area, intermembrane space, cristal membranes, intracristal space, and protein rich matrix (4). The primary function of mitochondria is to produce adenosine triphosphate (ATP) by the process of oxidative phosphorylation through the respiratory system (they synthesize more than 95% ATP for cellular utilization). The respiratory system is located in the inner mitochondrial membrane and is formed by four respiratory complexes (Complex I = NADH dehydrogenase; Complex II = succinate dehydrogenase; Complex III = cytochrome bc_1; Complex IV = cytochrome c oxidase), two individual mobile molecules – coenzyme Q (CoQ) and cytochrome *c*, and ATP synthase (Complex V). General view of the mitochondrial respiratory system is shown in Fig. 1. The oxidative phosphorylation is responsible for converting macronutrients (fatty acids, carbohydrates and amino acids) to ATP through a sequence of reactions. Electrons are transfered from electron donors (NADH a $FADH_2$) through the electron transport chain to the final electron acceptor – O_2.

The electrons travel from donors throught complex I (CI) or complex II (CII), they are transferred by coenzyme Q to complex III (CIII), then by cytochrome c to complex IV (CIV) and, in the end, the electrons reduce O_2 to H_2O. Electron transport is coupled with proton transfer through CI, CIII and CIV resulting in proton gradient formation in the intermembrane space. This proton gradient is used for creating of ATP from ADP and P_i by CV in mitochondrial matrix.

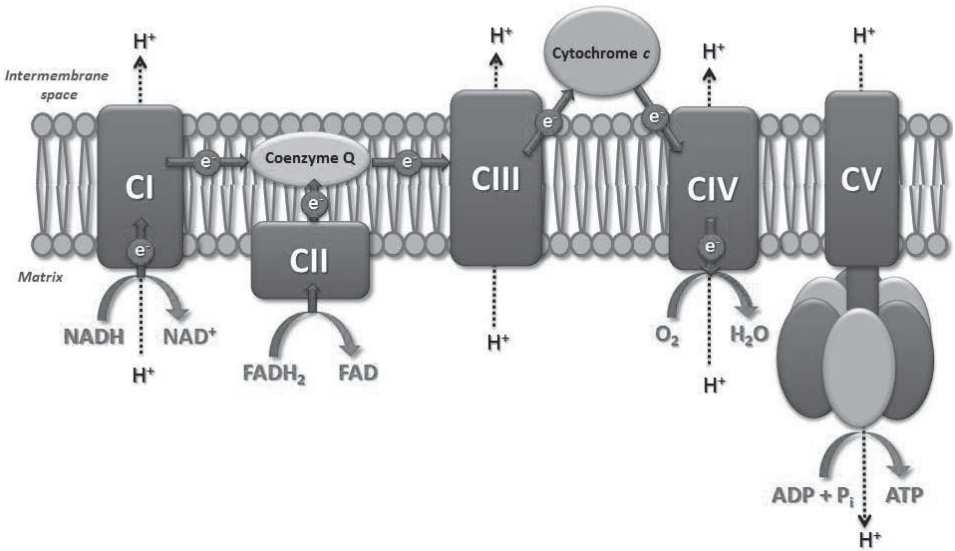

Fig. 1 Schematic representation of oxidative phosphorylation system. In the picture, respiratory chain complexes CI–CIV, ATP synthase (CV) and two mobile electron carriers (coenzyme Q and cytochrome *c*) are shown. Electrons are transferred from electron donors (NADH a $FADH_2$) through the electron transport chain to the final electron acceptor – O_2. The electrons travel from donors throught complex I (CI) or complex II (CII), from them they are transferred by the coenzyme Q to complex III (CIII), then by cytochrome c to complex IV (CIV) and then the electrons reduce O_2 to H_2O. Electron transport is coupled with proton transfer through CI, CIII and CIV resulting in proton gradient formation in the intermembrane space. This proton gradient is used for creating of ATP from ADP and P_i by CV in mitochondrial matrix

In addition to energy, oxidative phosphorylation also generates reactive oxygen species (ROS). Mitochondria are the major source of cellular ROS production. Beside this, mitochondria play a crucial role in apoptosis, cell cycle regulation, Ca^{2+} signalling, non-shivering termogenesis, metabolism etc. (5–8).

Mitochondria contain their own genetic system, which is separate and distinct from the nuclear genome of the cell. DNA molecules have usually circular structure and they are present in multiple copies per organelle. Human mitochondrial DNA contains 37 genes coding for two rRNAs, 22 tRNAs and 13 polypeptides involved in electron transport and oxidative phosphorylation (1).

IS AGING REVERSIBLE? EFFECT OF EXERCISE

A decline in muscle mass, strength and exercise efficiency accompanies aging in humans. Physical inactivity accelerates muscle catabolism, mitochondrial dysfunction, oxidative stress accumulation, and reduces aerobic capacity (9). The beneficial effects of exercise on mitochondrial function are well documented. In 1967, Holloszy's pioneering work dealing with impact of exercise on mitochondrial oxygen uptake and respiratory enzymes activities in skeletal muscle was published (10). Since then, exercise training has been shown to be an effective strategy to improve mitochondrial functions (11).

During physical exercise, the metabolic rate increases greatly, as quantified by oxygen consumption and heat production, which results in an enhanced generation of ROS (12). Oxygen radicals generating physiological responses at moderate levels are important modulators of muscle contraction, antioxidant protection, and oxidative damage repair (13). The increased production of ROS associated with the inefficiency of the antioxidant defence system can lead to oxidative stress (14) that is a common response to exercise. Nevertheless, the levels of ROS generated can substantially differ among various tissues and cells (12). The modest and regular exercise can induce positive cellular defence against stronger oxidative stress thus promoting health and reducing risk of diseases (15). In contrast, the enhanced formation of ROS in response to extensive physical activities in unprepared body can lead to oxidative modifications of lipids (lipid peroxidation as measured by the formation of malondialdehyde), proteins, nucleic acid (oxidative DNA damage as measured by 8-hydroxydeoxyguanosine), and other cellular compounds (16).

Some studies suggest that insulin signaling underpins mitochondrial electron transport chain integrity and activity by maintaining the NAD(+)/NADH ratio, the mediator of the pathway for mitochondrial biogenesis and function (17). Mitochondria normally enhance insulin sensitivity upon redox regulation of protein tyrosine phosphatase and insulin receptor. Development of insulin resistance, i.e. a state where normal concentrations of insulin produce less than normal biologic response (18), is tightly linked to muscular glucose uptake, mitochondrial dysfunction and endurance exercise (19, 20). Many studies have shown that patients with type 2 diabetes mellitus exhibited changes in mitochondrial morphology, functions and genes coding for key enzymes (21–25). Amati et al. studied the effect of exercise on insulin sensitivity in younger and older endurance-trained athletes, younger and older normal-weight subjects, and younger and older obese subjects using a glucose clamp. They did not find any difference between younger and older athletes, or younger and older normal-weight subjects, or even younger and older obese subjects. Regardless of age, athletes were more insulin sensitive than normal-weight sedentary subjects, who in turn were more insulin sensitive than obese subjects (26). This finding was confirmed by the work of Lanza et al., who measured insulin sensitivity and ATP production in mitochondria isolated from vastus lateralis biopsies of healthy sedentary and endurance-trained young (18–30 years old) and older (59–76 years old) subjects. Their results showed that insulin-induced glucose disposal and suppression of endogenous glucose production were higher in the trained young and older subjects, but no age effect was noted (27).

Several other studies were devoted to changes in the expression of nuclear and mitochondrial genes and transcription factors controlling mitochondrial biogenesis (28–30). Melov et al. evaluated healthy aging gene expression profile in skeletal muscle before and after a six-month resistance exercise-training program. They found 596 genes differentially expressed in relation to aging. After exercise training, the transcriptional signature of aging was markedly reversed back to that of younger levels for most genes (31).

Several studies documented increase in total mitochondrial copy number and mitochondrial protein synthesis rates after exercise training (28, 29). Short et al. reported the effect of a 16-week aerobic exercise program or control activity performed by men and women aged 21–87 years on insulin sensitivity and muscle mitochondria. They found that exercise led to an increase in mRNA levels of mitochondrial genes (COX4, ND4) and genes involved in mitochondrial biogenesis (PGC-1alpha, NRF-1 and TFAM). Further, their findings showed an increase in peak oxygen uptake (VO_{2peak}) and activity of muscle mitochondrial enzymes as citrate synthase and cytochrome c oxidase. They also observed reduction of abdominal fat (5%) and concentration of plasma triglycerides (25%) (28).

There is an ample evidence that physical activity improves mitochondrial respiratory functions (28, 29, 32–34), e.g. Menshikova et al. examined the effects of exercise on skeletal muscle mitochondria in older men and women. Exercise enhanced mitochondrial electron transport chain activity in older human skeletal muscle, particularly in subsarcolemmal mitochondria, which is likely related to the concomitant increase in mitochondrial biogenesis (29). Melov et al. concluded that healthy older adults show evidence of mitochondrial impairment and muscle weakness that can be partially reversed at the phenotypic level and substantially reversed at the transcriptome level following six months of resistance exercise training (31). Ghosh et al. confirmed that exercise reverses the mitochondrial phenotype (proteome and function) of old mitochondria (35). Indeed, exercise has also been shown to increase complex IV activity of the electron transport chain (it may have an indirect antioxidant effect in older adults and may improve function in daily activities) (36), heat shock proteins levels or antioxidant enzymes activities (37–39).

Multiple lines of evidence suggest that regular exercise training is not beneficial only for exercising muscles but also for other organs, particularly the brain (40, 41). Mechanisms that contribute to the improvement of neuronal functions at the cellular level are only partially known and remain to be further explored. To date, two specific hypotheses have been proposed: 1. Stimulation of mitochondrial biogenesis, authophagy and antioxidant enzymes activity in response to physical exercise. 2. Increased synthesis and release of neurotransmitters (e.g. dopamine) and trophic factors that in turn promote neuroplasticity, reduce neural apoptosis and may delay the neurodegeneration process (41, 42).

Nonmuscular systemic beneficial effect of exercise on mitochondrial functions was also documented in the brain, liver, and kidney of mice subjected to regular moderate exercise at the age of 28 weeks for maximally 50 weeks (43). This training protocol increased activities of mitochondrial complexes I and IV not only in skeletal and cardiac muscles, but also in the liver and kidney. Also in the aged rats, moderate regular exercise led to significantly reduced oxidative lesions in both nuclear and mitochondrial DNA of the liver (44).

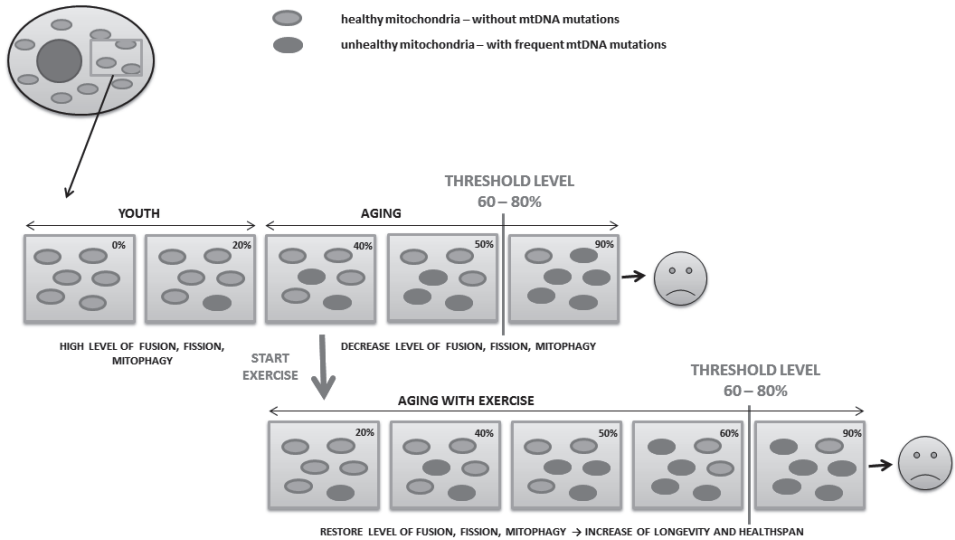

Fig. 2 Mitochondrial threshold effect and the effect of exercise on longevity. Pathological manifestation of the mutation depends on so-called threshold effect – situation, where the accumulation of dysfunctional product reaches certain level and the mitochondria are further unable to perform essential functions**.** Thanks to the multicopy nature of mtDNA, effect of the mutation is not immediately evident. During aging, ratio of mutated DNA increases and when it reaches certain level (60–80% of mutated mtDNA), there are no longer enough wild type copies of proteins and the cell dies because of the mitochondrial failure. Accumulation of mutated copies could be reverted or slowed down by regular exercise that stimulates mitochondrial turnover, which can result to extended cellular life span

CONCLUSIONS

Taken together, mitochondrial dysfunction is deeply involved in the process of aging. However, at least some negative consequences of aging could be prevented, reduced or even reversed by regular moderate exercise that can help to attenuate age-associated changes in mitochondria not only in the skeletal muscle, but also in the heart, brain, liver, and kidney (45–48). Putative systemic benefecial effect of exercise on mitochondrial functions should be further explored in non-muscular and non-neuronal tissues and cells. Schematic view is shown in Fig. 2.

SUMMARY

Aging is a multifactorial process influenced by genetic factors, nutrition, and lifestyle. Mitochondrial dysfunction has long been considered a major contributor to aging and age-related diseases. This review summarizes the major changes of mitochondria related to moderate exercise during aging and it tries to suggest an answer to the question: Can we prevent, slow down or even reverse aging-related processes?

Je stárnutí zvratný proces? – Pozitivní vlivy cvičení

SOUHRN

Stárnutí je multifaktoriální proces, jehož průběh je ovlivňován genetickými faktory, výživou a životním stylem. Mitochondriální dysfunkce jsou dlouho považovány za hlavního přispěvatele stárnutí a se stárnutím asociovaných chorob. Tento přehledový článek shrnuje hlavní změny mitochondrií spojené s mírným cvičením v průběhu stárnutí a snaží se nastínit odpověď na otázku: Můžeme předejít, zpomalit nebo dokonce zvrátit procesy související se stárnutím?

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