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Review Article / Derleme

Exercise, mitochondrial biogenesis and disuse-induced atrophy

Egzersiz, mitokondriyal biyogenez ve kullanılmama atrofisi

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ABSTRACT

In addition to the physiological and cellular effects of exercise, many studies demonstrated that exercise could prevent skeletal muscle atrophy due to disuse. Mitochondria, which are powerhouses in cells, are at the top of the molecular mechanisms that control muscle function. Mitochondria play an essential role in regulating protein synthesis and degradation through various signaling pathways such as ubiquitin-proteolysis, mitochondrial biogenesis, fusion, and fission dynamics autophagy, and apoptosis. Regular exercise protects the skeletal muscle against different stresses by improving cellular oxidative capacity. Eventually, exercise controls the expression of proteins that have been shown to protect muscle from atrophy caused by disuse and activates many cellular signaling pathways. In this review, the role of mitochondria in muscle cells, the effect of disuse atrophy on mitochondria, and the effect of exercise on peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α) that plays a crucial role in mitochondrial biogenesis are discussed.

Keywords: *muscle atrophy, fusion and fission dynamics, Ca^{2+} homeostasis, mitochondrial disease*

ÖZ

Egzersizin fizyolojik ve hücresel etkilerine ek olarak, birçok çalışma egzersizin 'kullanılmama' nedeniyle oluşan iskelet kası atrofisini önleyebileceğini göstermiştir. Hücredeki enerji üretim merkezi olan mitokondri, kas fonksiyonunu kontrol eden moleküler mekanizmaların başında gelir. Mitokondri, ubikitin-proteoliz, mitokondriyal biyogenez, füzyon ve fisyon dinamikleri, otofaji ve apoptoz gibi çeşitli sinyal yolakları aracılığıyla protein sentezini ve degradasyonun arasındaki dengenin düzenlenmesinde önemli bir rol oynar. Düzenli egzersiz, hücrede oksidatif kapasiteyi artırarak iskelet kasını farklı streslere karşı korur. Sonuçta egzersiz, iskelet kasını 'kullanılmama' nedeniyle oluşan atrofiden koruduğu bilinen proteinlerin ifadesini kontrol eder ve birçok hücresel sinyal yolunu etkinleştirir. Bu derlemede, mitokondrinin kas hücrelerindeki rolü, kullanılmama atrofisinin mitokondri üzerindeki etkisi ve egzersizin PGC-α1 üzerindeki etkisi ve mitokondriyal biyogenezde oynadığı önemli rol tartışılmıştır.

Anahtar Sözcükler: *kas atrofisi, füzyon ve fisyon dinamikleri, Ca^{2+} homeostazisi, mitokondriyal hastalıklar*

INTRODUCTION

Skeletal muscles constituting 40-45% of human body weight, are responsible for the force production, body movement and breathing as well as glycemic control, regulation of metabolic genes and metabolic homeostasis. In addition to sarcopenia and cachexia, various conditions which are known as muscle disuse, where mechanical load or neural activation is lost or reduced such as denervation, limb immobilization, long term bed rest, sedentary lifestyle and physical inactivity result in skeletal muscle atrophy (1). The decrease in muscle contractile proteins will cause a decrease in functional capacities such as muscle strength and endurance and quality of life, as well as metabolic problems such as insulin resistance and type 2 diabetes, increase in morbidity and mortality and prolong recovery after diseases. As a result, skeletal muscle atrophy brings a serious economic burden on the health care system.

Disuse atrophy results in reduction of the cross-sectional area of the individual muscle fibers. On the cellular level, increase in protein breakdown (1), mitochondrial dysfunction (2, 3), deterioration in calcium homeostasis (4), and increase in reactive oxygen species occur (5, 6).

In skeletal muscle, mitochondria are responsible for ATP production through oxidative pathways and are particularly significant for metabolic processes and contraction functions (7). However, in advanced conditions, including exercise or immobilization, mitochondria play a critical role in regulating redox homeostasis and apoptosis, controlling the balance between reactive oxygen species (ROS) production and antioxidant defense system (8, 9).

Although there is a great deal of evidence for the preservation of mitochondrial functions with certain chemical agents

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(10, 11), exercise is known to be the most effective treatment in improving muscle mass and strength and preserving mitochondrial functions. This review focused on a brief discussion on mitochondrial dysfunctions caused by immobilization and the importance of regular exercise in mitochondrial protection.

The role of mitochondria in disuse atrophy

Energy production

Adenosine triphosphate (ATP) is produced in mitochondria, and the cell uses ATP as the only energy form. The primary role of mitochondria is to convert products especially from carbohydrate, and fat metabolism to carbon dioxide and water through the electron transport chain's key enzymes localized in the inner membrane. During these reactions, electrons pass through NADH dehydrogenase (Complex I), succinate dehydrogenase (Complex II), cytochrome bc1 (Complex III), and cytochrome c oxidase (Complex IV) complexes while protons (H^+) are pumped from the matrix into the intermembrane space (Fig. 1). Thus, a proton gradient is formed, and this gradient is vital in performing ATP synthesis by the ATP synthase enzyme (Complex V). This process, called oxidative phosphorylation, involves the production of ATP by oxidation of substrates in the mitochondria, and the regular functioning of this process is extremely critical for various tissues and organs.

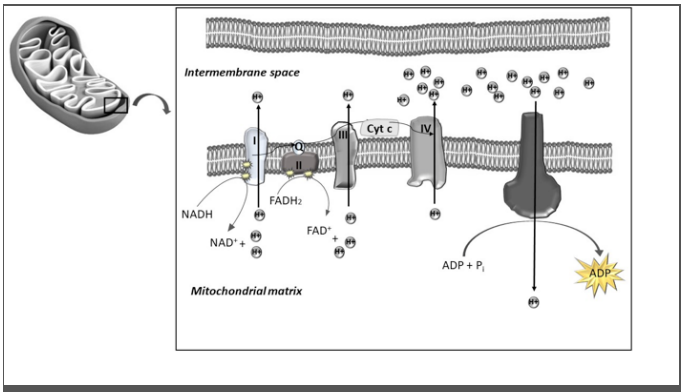

Figure 1. ***Mitochondrial Electron Transport Chain.*** *The electron transport chain is a sequence of electron transporters implanted in the inner mitochondrial membrane that transports electrons from NADH and $FADH_2$ to molecular oxygen.*

ROS generation

During energy production by oxidative phosphorylation, the products coming from glycolysis and Krebs cycle passing through the electron transfer chain (ETC), some oxygen (0.2% - 2%) taken into the cells even under normal conditions are transformed into ROS (12). This is because the electrons coming to the ETC accumulate as protons pass through complex I and III and combine with oxygen. Electrons combined directly with oxygen form the superoxide anion and with further reduction, the hydroxyl radical ($OH^{\cdot}$), a powerful oxidizer. Dysfunction of these mitochondrial complexes may also play an essential role in the pathogenesis of some chronic diseases, as a deterioration in mitochondrial function often accompanies the occurrence of metabolic disorders.

Ca^{2+} homeostasis

In addition to producing energy in the cell, mitochondria also perform a crucial function in maintaining intracellular calcium (Ca^{2+}) balance. Precise regulation of Ca^{2+} uptake and release to the cytoplasm is necessary to maintain Ca^{2+}homeostasis regarding cellular functions. Mitochondria respond to calcium concentration changes via mitochondrial calcium buffering capacity and by interacting with other channels or organelles to keep the intracellular Ca^{2+}concentration at a certain level (13). Indeed, a network of Ca^{2+} transport and buffering systems regulate intracellular Ca^{2+} concentration. The endoplasmic reticulum (ER) acting as Ca^{2+} storage within the cell and mitochondria are in contact to control intracellular Ca^{2+} homeostasis. This contact is exceptionally critical in regulating aerobic metabolism and cell survival (14, 15). Exposure to high concentrations of Ca^{2+} for a long time negatively affects vital activities (16). Moreover, a disruption in Ca^{2+} transfer between the sarcoplasmic reticulum and mitochondria causes an increase in Ca^{2+} concentration and this increase is a signal that activates apoptosis-related mechanisms in the cell (16, 17).

The mitochondrial adaptation to disuse atrophy

Mitochondria are programmed to adapt to the various conditions since they have to provide the required energy for continuing cellular processes in skeletal muscle. These adaptations are regulated by fusion and fission events (Fig. 2). Excessive ROS production is known to be closely associated with skeletal muscle atrophy in mice (18). However, the exact mechanism is still unclear. Fusion and fission are not only involved in the structural regulation of mitochondria but are also remarkably important in transmitting intracellular ROS production-related redox signals and regulating apoptosis pathways (19, 20). Two of the best characterized mitochondrial fusion factors are mitofusin 1 and 2 (Mfn1/2), responsible for the attachment and fusion of outer mitochondrial membranes (21). Optic atrophy protein 1 (OPA1) controls the mitochondrial inner membrane fusion (22). Concurrently, two essential proteins that promote mitochondrial fission include dynamin-related protein-1 (Drp1) and Fission 1 (Fis1).

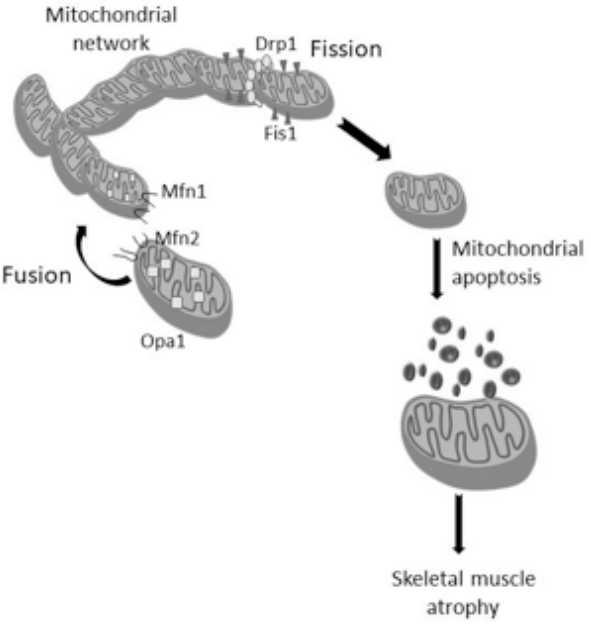

Figure 2. ***Mitochondrial adaptation during disuse atrophy.*** *The fusion progression requires mitochondrial outer membrane fusion via Mfn1/2 and mitochondrial inner membrane fusion via Opa1.*

There is evidence that the increase in mitochondrial fission is associated with increased apoptosis in some cell types and increased atrophy in skeletal muscle fibers (19, 23, 24). For instance, it has been shown that Drp1 activity inhibition may delay caspase activation and apoptotic cell death in cells exposed to apoptotic stimuli. Moreover, the inhibition of Fis1 may also protect against apoptosis, while the overexpression of Fis1 promotes apoptotic cell death (19). Similarly, mice lacking Mfn1/2 in skeletal muscle exhibit both mitochondrial dysfunction and profound muscle atrophy (25). It has also been shown irregularity of the mitochondrial inner membrane, the release of cytochrome c, and increased apoptosis in cells lacking Opa1 (26).

The plasticity of skeletal muscle largely depends on mitochondria's ability to change their shape and size in response to both intracellular and extracellular signals (27). Many studies suggested that disuse negatively affects mitochondrial homeostasis, and it may be the primary cause of defects in muscle structure and function (28). Indeed, experimental atrophy models have shown a significant reduction in mitochondria density. For example, Kang et al. showed that the mitochondrial density in mice tibialis anterior muscle decreased after the 14-day hindlimb immobilization (29).

Mitochondrial biogenesis is organized principally by peroxisome-proliferator activated receptor γ (PPARγ) andperoxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α) in which stimulates the expression of nuclear-encoded mitochondrial proteins Nrf-1 (Nuclear respiratory factor 1) and Nrf-2(*Nuclear respiratory factor 2)*, and Tfam (Transcription factor A, mitochondrial), the key controller of mitochondrial DNA (mtDNA) biosynthesis (30). Kang et al. emphasized that PGC1α expression, which plays an essential role in mitochondrial biogenesis, is suppressed during immobilization. Moreover, after five days of remobilization following 14 days of hindlimb immobilization, PGC1α expression decreased in TA (tibialis anterior) muscle and then reached control levels on the 10th day of remobilization. The same study reported that PGC1α overexpression also improved the oxidant-antioxidant balance (31). Similarly, 14-day denervation causes a decrease in muscle cross-sectional area. Nrf2 levels are also significantly reduced (32), accompanied by a decrease in Tfam (29).

Mitochondrial caspase-3 dependent apoptosis is another critical signaling pathway in disuse-induced muscle atrophy (33). Impairment of calcium homeostasis during disuse causes an increase in intracellular calcium concentration and activates caspase-3, which is involved in protein degradation in the cell (34). Besides, increasing Ca^{2+} levels triggers the activation of the pro-apoptotic protein Bax to the mitochondria's outer membrane by creating Bax/Bax-homo-oligomerization. Bcl2, an anti-apoptotic Bcl-2 family protein that inhibits Bax, can prevent the formation of Bax/Bax-homo-oligomerization. The reduction in the Bax/Bcl-2 ratio leads to pro-apoptotic release from mitochondria that activate caspase-9 and caspase-3 (35). Hu et al. reported an increase in Bax/Bcl-2 and cytochrome C release from mitochondria in the gastrocnemius after 14 days of HLU (36). Therefore, both ROS overproduction and Ca^{2+} overload play an important role in disrupting protein synthesis following immobilization.

Many studies have been conducted in recent years, emphasizing the importance of mitochondrial integrity in disuse-induced muscle atrophy in skeletal muscle cells. Among these studies, the importance of PGC-1α was noted not only in maintaining a healthy muscle mass, but also in terms of susceptibility to metabolic diseases (37). Indeed, the multiple roles and apoptotic cascades of PGC-1α in the cell to control mitochondrial biogenesis and fusion-fission dynamics have gained importance for muscle physiology research. This shows that explaining the cellular mechanisms of muscle atrophy can provide information for developing relevant treatment strategies for patients suffering from muscle wasting.

Exercise and mitochondrial biogenesis

Exercise positively affects multiple organ systems, including the musculoskeletal system. Many studies demonstra-

te that a sedentary lifestyle significantly increases the relative risk of various chronic diseases such as coronary artery disease, insulin resistance, type 2 diabetes, osteoporosis, and some cancers (38-40). On the other hand, regular exercise is significantly associated with increased life expectancy and quality (41) and may also be beneficial to moderate or slow the progression of many metabolic diseases such as obesity, metabolic syndrome, type 2 diabetes. Indeed, regular exercise is known to improve metabolic gene regulation and glycemic control and increase whole-body oxygen uptake capacity (42).

The most prominent response of organisms to external stress factors that increase the need for aerobically produced energy is mitochondrial respiration adaptations. These adaptations have involved some modifications in the mitochondria, facilitating the diffusion of O_2 and substrates used for ATP synthesis to provide the energy required in stress conditions. Increased energy requirement during exercise is essential in mitochondrial biogenesis. The energy requirements of the cell are fulfilled by regulating the size and content of mitochondria in response to exercise. Indeed, even an acute exercise can trigger mitochondrial regulation (43).

The role of PGC-1 appears to be prominent in most studies explaining the role of exercise in mitochondrial biogenesis. PGC-1α has been shown to interact directly and activate multiple nuclear receptors to increase oxidative metabolism and mitochondrial biogenesis in most cell types (Figure-3). Overexpression of PGC-1α in muscle tissue of transgenic mice activates mitochondrial biogenesis, leading to an increase in type I and oxidative type IIa fibers and consequently, an increase in resistance to muscle fatigue (44). In contrast, the absence of PGC-1α in muscle leads to a significant reduction of mitochondrial respiration, gene expression encoding enzymes in the electron transfer chain and reduced exercise performance (28).

Exercise stimulates mitochondrial biogenesis in skeletal muscle following acute exercise by various cellular signals: **a)**increased intracellular Ca2+ concentration and **b)** energy balance disruption due to muscle contraction. These signals caused by exercise induce the expression of PGC-1α, nuclear respiratory factors 2 (NRF-2) and mitochondrial transcription factor A (Tfam) in the nucleus (45). During muscle contraction, increased Ca^{2+} concentration activates the PGC-1α transcription through calcium-dependent protein phosphatase, calcineurin and calmodulin-dependent kinase. It has been shown that PGC-1α is a particular element for type I fibers that use energy in the skeletal muscle aerobically (44). On the other hand, mice with skeletal muscle-specific PGC-1-KO (PGC-1-MKO) have displayed a decreased maximum exercise capacity, muscle function damage and decreased oxidative metabolism capacity (46).

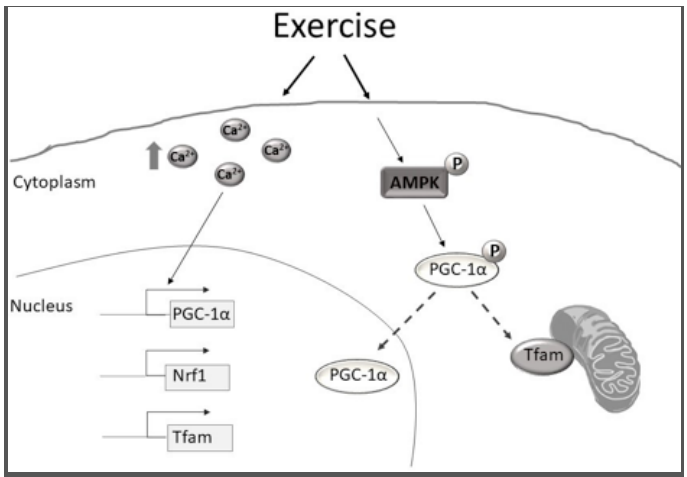

Figure 3. Exercise effects on mitochondrial biogenesis: Exercise triggers mitochondrial biogenesis in skeletal muscle by the activation of various signaling pathways. PGC-1α translocates to the nucleus to stimulate transcription factors and nuclear receptors. AMPK: *5′ AMP-activated protein kinase;* NRF1: *nuclear respiratory factor-1;* PGC-1α: *peroxisome proliferator-activated receptor gamma coactivator 1-alpha;* Tfam: *Transcription factor A, mitochondrial.*

The deterioration in the ATP/ADP ratio during exercise activates AMP-activated protein kinase (AMPK) (47). AMPK phosphorylation results in the phosphorylation of PGC-1α (48, 49). It has been reported that the increase in AMPK phosphorylation in skeletal muscle is an important factor to activate the mitochondrial function of PGC-1α (50). PGC-1α is mostly found in the cytosol in an inactive form in the resting state, but when exposed to stress such as endurance exercise, PGC-1α is phosphorylated and translocated from the cytosol to the nucleus, and the nuclear protein level increases. It has also been reported that PGC-1α passing into the nucleus also affects the expression of Tfam (51).

Protective role of exercise on mitochondria during disuse

Disuse atrophy causes a decrease in protein synthesis and an increase in degradation, causing skeletal muscle mass loss. It also causes mitochondrial dysfunction, creating a decrease in physical performance and reducing life quality. An increase in reactive oxygen species and mitochondrial dysfunction in disuse atrophy activate protein degradations and cell apoptosis signaling pathways (52, 53).

It is well known that regular exercise has positive physiological effects on the cardiopulmonary and neuroendocrine systems (54). Besides, exercise causes phenotypic changes, including cross-sectional muscle area, capillary density, fi-

ber type transition (55) and mitochondrial biogenesis, resulting in increased performance (56).

The fact that PGC1-α activation increases with exercise and decreases in disuse conditions (28) suggest that PGC1-α has a vital role in cellular protection. Therefore, since high-intensity endurance exercises will increase PGC1-α activation (57), regular endurance exercises will enable PGC1-α to be active (58, 59). Besides, human and animal studies have shown that an increase in antioxidant defense with exercise preserves mitochondrial biogenesis in a condition of subsequent atrophy (60, 61). it has also been determined that exercise causes an increase in mitochondria fusion by increasing the expression of Mfn1 / 2 proteins (43, 62).

Mitochondrial disease and exercise

Mitochondrial diseases include rare diseases that develop due to oxidative phosphorylation disorders in mitochondria caused by mutations in mitochondrial DNA (mtDNA) (63). The organs with higher metabolic requirements, especially the skeletal muscle are negatively affected by this condition. Mitochondrial myopathy, inadequate exercise capacity and low aerobic performance levels in skeletal muscle characterize mitochondrial disease (64). Although it is one of the most common neuromuscular disorders, it shows a variable estimated prevalence (65). For instance, Jeppesen et al. reported that 12 weeks of aerobic exercise significantly improved maximum oxidative capacity in 20 patients with four different mtDNA mutation types and various mutant loads. This improvement did not significantly affect activities of daily living in asymptomatic carriers of mtDNA mutations; however, VO2max improvement is significant in patients with severe oxidative defects (66). Similarly, Taivassalo et al. reported in a study involving ten patients with various heteroplasmic mtDNA defects that a 14-week cycling exercise improved the patients' quality of life by increasing exercise capacity and maximum O_2 utilization (67). This study has shown that 14 weeks of training increased oxidative capacity by 20-30% and systemic arteriovenous O2 difference by 20%. They also reported that in patients with Complex I and Complex IV defects, mitochondrial volume increased by 50% in biopsy samples taken from the vastus lateralis muscle and accompanied by increases in defective respiratory chain enzymes (67). These results are emphasizing that exercise may be a valuable method improving patients' quality of life by increasing exercise capacity, maximum O2 utilization, and endurance capacity for patients with mitochondrial disease (67, 68). Resistance exercises also trigger mitochondrial biogenesis in skeletal muscle cells (69) and cause an increase in muscle mass and strength (70). Murphy et al. showed that a 12-week resistance exercise on eight patients with large-scale deletions in mtDNA improved strength and a reduced mitochondrial DNA heteroplasia without any side effects (71).

CONCLUSION

Complications in mitochondrial biogenesis occurring in the muscle cell contribute significantly many health problems starting from the cellular level to increasing susceptibility to some chronic diseases. Mitochondria are susceptible to signals that occur in response to muscle contraction. Therefore, exercise plays an essential role in regulating mitochondrial biogenesis and maintaining its function. PGC-1 is a gene expression coactivator that controls mitochondrial biogenesis in muscle. Improvement of our understanding of exercise that regulates mitochondrial biogenesis and muscle function is critical for maintaining whole-body metabolic health.

Conflict of Interest / Çıkar Çatışması

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