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Research Article

Aerobic exercise affects mitochondrial quality control

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Abstract

Mitochondria play a significant role in morphological and physiological aspects of cells according to their known biological role. Any disruption in mitochondrial function weakens cell function and causes many cell diseases. On the other hand, mitochondria health is associated with cellular efficiency and causes health and physical performance. Evidence shows that one of the molecular mechanisms that regular physical activities, especially aerobic exercises, lead to health is mitochondrial health. Aerobic exercise can regulate and control the mitochondrial unfolded protein response (UPRmt), mitochondrial dynamics (fission and fusion) and mitochondrial. It seems that regulation of mRNA expression of proteins responsible for MQC signaling pathways, reduction of inflammation and oxidative stress is one of the mechanisms by which aerobic exercise benefits mitochondria.

Keywords:
Mitochondrial unfolded protein response, mitochondrial dynamics (fission and fusion), mitophagy, aerobic exercise

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1. Introduction

Regular physical activities, especially aerobic exercises, have health benefits. Evidence shows that aerobic exercise is one of the most effective non-pharmacological interventions to enhance health and is an integral part of human life, which has significant effects on maintaining health and preventing health disorders (1,2). A combination of aerobic exercise changes the cellular function, improves the functioning of the organs, and ultimately improves health. Reducing inflammation (3), oxidative stress (4), pathological apoptosis (5), endoplasmic reticulum stress (6), and improvement of mitochondrial function (7) are some of the cellular mechanisms through which aerobic exercise maintains and enhances health. In recent years, researchers have focused on mitochondria's role in improving cell functions. Mitochondria are intracellular organelles that evolved from bacteria endosymbiosis with eukaryotic characteristics (8). Mitochondria are unique, highly dynamic organelles that extract energy from energy sources through aerobic metabolism. They also control fatty acid synthesis, the production of intracellular reactive oxygen species (ROS), oxidative phosphorylation, thermogenesis, and intracellular calcium homeostasis. However, it is the regulatory center of cell signal transmission and controls many intracellular processes (9). Mitochondria's cellular roles are so diverse that its energy-generating role, which has made it the powerhouse of the cell, is one of the countless biological roles of this remarkable organelle (10). Due to mitochondria's multiple roles, any dysfunction in its function results in dysfunction in cells. This is one of the key mechanisms of various diseases and pathologies characterized by dysfunctional mitochondria (11).

Mitochondrial dysfunction is significantly related to a wide range of diseases including metabolic diseases, neurodegenerative disorders, cancer and many other diseases (12). Mitochondria's functional role in health and diseases has drawn researchers to this organelle more than other parts of the cell. The results of the studies of the last two decades show that aerobic exercises can improve health by affecting the structure and function of mitochondria (13).The evidence shows that aerobic exercises can lead to the maintenance and development of mitochondrial function and the development of health through the effect on the mitochondrial quality control system (MQC) (14,15).The three main mitochondrial quality control (MQC) mechanisms that regulate mitochondrial integrity and maintain mitochondrial function include the activation of mitochondrial unfolded protein response (UPRmt), mitochondrial dynamics (fission and fusion) and mitochondrial mitophagy (16). In this article, the effect of aerobic exercise on mitochondrial quality control mechanisms is investigated.

The effect of aerobic exercise on mitochondrial unfolded protein response

Mitochondrial unfolded protein response (UPRmt) is a critical pathway that maintains mitochondrial homeostasis and proteostasis under stress by stimulating the transcription of nuclear-encoded genes that protect and support mitochondria, and Facilitates cellular adaptation in response to pervasive mitochondrial stress. UPRmt activates mitochondrial specific chaperones and proteases, which results in protein folding or removal of mitochondrial proteins damaged by mtROS. This results in the preservation of mitochondrial quality control (17,18). Mitochondrial chaperone activity is critical for proper folding of folded and unfolded proteins in mitochondria. While proteases break down folded proteins to maintain mitochondrial proteostasis (19). Aerobic training has been studied in different tissues, especially skeletal muscle. One of the most significant features of mitochondria is the high flexibility of this organelle in response to aerobic exercise. This flexibility includes adaptations to their volume, structure and function, which leads to MQC (20). The evidence obtained from the studies shows that aerobic exercise has a significant effect on the activation of the UPRmt pathway, especially in skeletal muscle. The results of the studies show that aerobic exercise activates this pathway by affecting mRNA and proteins related to UPRmt. Exercise on a treadmill increased transcription factor Jun (c-Jun), heat shock protein 60 (HSP60) and CLpP (CLpP) in male C57BL/6J mice, which indicates activation of the classical UPRmt pathway (21). UPRmt pathway proteins decrease with age. Reported in rodents, mRNA levels of YME1L1 and CLpP of gastrocnemius muscle increased significantly along with mitochondrial content after aerobic training (22). These findings were confirmed in another study which showed that aerobic training enhanced skeletal muscle Yme1L1 and LONP1 mRNA levels along with PGC-1α and citrate synthase levels (23). These findings show that aerobic exercise can enhance skeletal muscle mitochondrial function in old age by stimulating the expression of UPRmt pathway proteins. It can also improve skeletal muscle function, which can increase rip strength, maximum running speed, and running distance. In obese mice fed high-fat diet, muscle function and mRNA levels of mitochondrial UPRmt pathway proteins decreased significantly. Four weeks of aerobic training increased grip strength, maximum speed, along with improving mRNA levels of Lon protease homolog, mitochondrial (LONP1), HSP60 ClpP, which shows that aerobic exercise can reduce the negative effects of obesity on skeletal muscle by increasing the function of the UPRmt pathway(24).The UPRmt response is one of the quality control mechanisms of MQC, which uses Activating Transcription Factor 5 (ATF5) to induce the expression of protective enzymes to maintain mitochondrial function. An increase in ATF5 expression after a bout of aerobic activity has been reported. This shows that the transcription factor ATF5 plays a crucial role in maintaining mitochondrial homeostasis and the proper response of muscle to physical activity to optimize mitochondrial quality control (25). In the hypothalamus, aerobic exercise increased the UPRmt markers of the hypothalamus. This was associated with maximum mitochondrial respiratory capacity in the brain, which confirms the role of aerobic exercise in the activation of the UPRmt pathway (26). Li et al. (2023)

reviewed the role of regular physical activities in preserving mitochondrial proteostasis in Parkinson's disease. The results of this study showed that regular physical activities maintain mitochondrial proteostasis by activating UPRmt, mitophagy. It regulates mitochondrial protein levels by regulating mitochondrial protein transport, reducing oxidative stress and improving body energy metabolism. Mitochondrial proteostasis regulation prevents and improves Parkinson's disease (27).

The effect of aerobic exercise on Mitochondrial dynamics (fission and fusion)

Mitochondrial dynamics includes the process of changing the morphology, quantity and position of mitochondria in eukaryotic cells, which is of great importance for the proper functioning of the cell, including energy production, differentiation, cell cycle, aging and apoptosis (28). Mitochondrial dynamics are vital in regulating many vital cell processes and maintaining mitochondrial homeostasis in response to stress (29,30). Mitochondrial dynamics consists of two opposite processes called fission and fusion. While fission separates mitochondria into globular organelles (31), fusion allows mitochondrial components to regenerate into an expanded mitochondrial network (32), facilitating mitochondrial metabolic remodeling and quality control. Disturbance in mitochondrial dynamics is one of the key mechanisms in the pathogenesis of many diseases such as diabetes, heart failure, Parkinson's disease, Huntington's disease, and cardiac hypertrophy, heart failure, myocardial infarction and ischemia-amyotrophic lateral sclerosis, in which mitochondrial dysfunction plays a role in all these diseases. Is important (33,34).

Physiological conditions cause mitochondria to adapt to cellular energy needs. These changes can occur through continuous cycles of mitochondrial fusion and fission, which allows for an adequate distribution of mitochondria within cells. Mitochondrial fission produces small mitochondria, while large interconnected mitochondria networks are produced through fusion (35). Mitochondrial fusion and fission are necessary to maintain critical cellular functions including mitochondrial respiratory activity, mitochondrial DNA (mtDNA) distribution, apoptosis and cell survival (36). It has been reported that twelve weeks of high-intensity aerobic interval training increased the volume and number of skeletal muscle mitochondria along with an increase in mitochondrial respiration and insulin sensitivity. OPA1, a regulator of fusion, was significantly increased following HIIT while FIS1, a regulator of fission, was significantly decreased following HIIT. The OPA1/FIS1 ratio was also significantly increased, indicating a balance between fission and fusion. This was positively correlated with improved respiration, insulin sensitivity, etc. Changes indicate increased fusion following HIIT with increased mitochondrial respiration, insulin sensitivity, and Vo2peak. This supports the idea that increased mitochondrial fusion is associated with significant health benefits of HIIT (37). In another study, twelve weeks of aerobic exercise improved insulin sensitivity, aerobic capacity, and fatty acid oxidation. Aerobic exercise decreased FIS1 and Parkin (regulator of fission) in skeletal muscle, while significantly affecting the expression of MFN1, MFN2, OPA1, and OMA1. (Fusion regulator) did not have. Aerobic exercise improves the ratio of fusion to fission proteins. These findings indicate that aerobic training changes the expression of mitochondrial fission and fusion proteins, and these changes may enhance insulin sensitivity and reduce metabolic disorders (38).

Mitochondrial dynamics are improved by aerobic exercise. Exercises that are very intense can reduce intrinsic mitochondrial function. It has been shown that aerobic exercise is beneficial depending on the intensity and duration of the program (40). In their review, Heo et al. (2017) showed that obesity disrupts mitochondrial dynamics and leads to an imbalance between fusion and fission by favoring fission or decreasing fusion proteins. Mitochondrial dysfunction and oxidative stress induce apoptosis, and mitochondrial apoptosis is induced by obesity in skeletal muscle. It is well known that regular physical activity is the most effective intervention to protect against obesity. Regular physical activity can reduce mitochondrial dysfunction and improve mitochondrial dynamics by reducing oxidative stress (41). Campos et al. (2023) showed that mitochondrial connectivity AND cycle dynamics are necessary to maintain physical fitness during aging. Regular physical activity can moderate aging's negative effects on skeletal muscle by regulating mitochondrial proteins (29).

Effect of aerobic exercise on Mitochondrial mitophagy

Mitophagy is selective autophagy of damaged mitochondria (42). Mitophagy is a multi-step process that is very complexly regulated and causes the selective destruction of damaged/dysfunctional mitochondria by autophagy and has common aspects with other types of selective autophagy. From a morphological point of view, mitophagy is the placement of mitochondria inside an autophagic vacuole called a mitophagosome (43). In general, mitophagy is a fundamental biological mechanism in all cells or tissues and is regulated by cellular energy needs.

Mitophagy amounts are different in all tissues. In tissues such as the nervous system, kidney, skeletal muscle, heart and liver, it is more than the spleen and thymus (44).

Biological evidence shows that damaged mitochondria are not only unable to produce ATP and other biosynthetic products, but also produce higher levels of reactive oxygen species. This can disturb the intracellular balance. If reactive oxygen species cannot be cleared in time and accumulate in cells, it leads to pathological apoptosis (45).

Mitophagy keeps mitochondria in optimal condition by removing dysfunctional mitochondria. Mitochondrial homeostasis is maintained by the balance between elimination and bioproduction, which can be disrupted by uncontrolled mitophagy (46). Disruption in mitophagy can be associated with diseases such as type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular diseases, neurodegenerative diseases and old age (47). PTEN-induced putative kinase 1 (PINK1) and Parkin (also known as PARK2) are two key proteins that play a crucial role in mitochondrial quality control (48). PINK1 is a serine/threonine kinase located in mitochondria. It protects cells from mitochondrial dysfunction and stress. When mitochondria are damaged, PINK1 accumulates in the outer membrane of dysfunctional mitochondria. PINK1 acts as a signal for the selective destruction of damaged mitochondria through mitophagy. It attracts Parkin to the damaged mitochondria and removes these organelles (49). Parkin is an E3 ubiquitin ligase that regulates protein degradation through the ubiquitin-proteasome system. It also controls mitochondria and mitophagy (50). When PINK1 accumulates in damaged mitochondria, it phosphorylates Parkin and activates it.

Upon activation, Parkin ubiquitinates various proteins on the mitochondrial outer membrane. This marks them for degradation and facilitates the recruitment of the autophagic machinery to engulf and destroy damaged mitochondria (51). Like UPRmt and mitochondrial dynamics, aerobic exercise positively affects mitophagy in aging, obesity and various diseases. It has been reported that aerobic exercise increases the proteins of the mitophase pathway, especially Parkin, along with the improvement of mitochondrial function in the myocardium (52). On the other hand, aerobic exercise reduced age-related muscle mass destruction in rodents by activating the PINK/Parkin signaling pathway and regulating mitophagy (53). These findings have also been reported in old rats' myocardial tissue after aerobic exercise (54). An increase in the expression of PINK/Parkin protein with an increase in mitophagy, improving mitochondrial function, increasing the volume and number of skeletal muscle mitochondria and aerobic performance after aerobic exercise has also been reported (55). High-intensity interval training significantly increased mitochondrial biogenesis and mitophagy in parallel with reducing inflammation and oxidative stress in skeletal muscle. These changes were associated with an increase in fatigue time (56). These findings have been confirmed in the skeletal muscle of obese elderly people after intermittent exercise with high intensity, which indicates the regulatory effect of aerobic exercise on mitophagy (57).

Conclusion

The review of studies showed that mitochondrial health is directly related to health and cell function. In addition, mitochondrial disorders are the pathogenesis of many diseases such as metabolic diseases, neurodegenerative disorders, and cancer. Aerobic exercise can develop mitochondrial quality control and improve health and physical performance by affecting the three mechanisms of mitochondrial unfolded protein response (UPRmt), mitochondrial dynamics (fission and fusion) and mitochondrial mitophagy. In fact, aerobic exercise enhances health by increasing the levels of mRNA and proteins responsible for the signaling pathway (UPRmt), mitochondrial dynamics (fission and fusion) and mitochondrial mitophagy.

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Compliance with ethical standards

Conflict of interest None declared.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

Conceptualization: F,A. M,A,A. SH,R,M. L,M ; Methodology: F,A. M,A,A. SH,R,M. L,M ; Software: F,A. M,A,A. SH,R,M. L,M ; Validation: F,A. M,A,A. SH,R,M. L,M ;Formal analysis: F,A. M,A,A. SH,R,M. L,M ;Investigation: F,A. M,A,A. SH,R,M. L,M ; Resources: F,A. M,A,A. SH,R,M. L,M ;Data curation: F,A. M,A,A. SH,R,M. L,M ; Writing - original draft: M.H, M.G, R.Z, P.E; Writing - review & editing: M.H, M.G, R.Z, P.E; Visualization: F,A. M,A,A. SH,R,M. L,M; Supervision: F,A. M,A,A. SH,R,M. L,M ;Project administration: F,A. M,A,A. SH,R,M. L,M; Funding acquisition: F,A. M,A,A. SH,R,M. L,M.

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