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Review article

Effect of aerobic exercise on mitochondrial DNA and aging

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Abstract

The aging process occurs at different rates among different tissues. The complication of the definition of aging is due to the occurrence of various diseases that modify body functions and tissue structure. Advances in medicine and public health have considerably increased life expectancy over the past 200 years. An enormous effort has recently been expended to understand how the aging process is regulated at the molecular and cellular levels with hopes to find a way to extend maximal life span. There are several determinants of life span, but one common thread that has emerged in a variety of species from yeast to rodents is regulation of life span by mitochondria. Mitochondria decay that occurs with age cannot be counteracted unless physical activity is enhanced. As the frontiers of understanding the senescence and life span increases, the countermeasures for reducing aging senescence has brought to light the effectiveness of enhanced physical activities in aging individuals. Regular aerobic exercise may increase healthy life expectance and prolong life through beneficial effects at the mitochondrial level.

Keywords: Aerobic exercise; Aging; DNA

Introduction

Aging affects all species and significantly influences the extent of our activities and quality of life, but the process of aging is not yet fully understood. The structural and functional changes related to diseases that are common in older persons are often hard to define from the aging process. Disease processes and environmental factors deeply influence the rate of aging. Additionally, the aging process occurs at different rates in different tissues, and the functional manifestations also differ. The complication of the definition of aging is due to the occurrence of various diseases that modify body functions and tissue structure. Advances in medicine and public health have considerably increased life expectancy over the past 200 years. An enormous effort has recently been expended to understand how the aging process is regulated at the molecular and cellular levels with hopes to find a way to extend maximal life span. There are several determinants of life span, but one common thread that has emerged in a variety of species from yeast to rodents is regulation of life span by mitochondria. Mitochondria decay that occurs with age cannot be counteracted unless physical activity is enhanced. As the frontiers of understanding senescence and life span increases, the countermeasures for reducing aging senescence has brought to light the effectiveness of enhanced physical activities in aging individuals. The purpose of this review is to investigate aerobic exercise and research regarding reduction of age-related decline with mitochondrial DNA (mtDNA) abundance. Regular aerobic exercise may increase healthy life expectance and prolong life through beneficial effects at the mitochondrial level.

Aging in aerobic species

Aging is an essential process to all organisms that are not capable of reproduction and would sap resources that could otherwise be available to reproducing progeny. From an evolutionary perspective, it seems advantageous for a species

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to have relatively short periods for reproduction, followed by death, to allow for more rapid selection of beneficial traits compared to a long-lived organism, which would continue to pass along its genetic code and slow the process of selection. Most humans, even after fulfilling obligations and capacity for reproduction, want to continue living. The average life expectancy of humans has increased remarkably over the past 200 years, largely as a result of advances of modern medicine for treatment of diseases such as diabetes, cancer, and cardiovascular diseases.[1] Although human interventions to improve health resulted in avoidance of premature deaths of humans and extended the life expectancy, the maximum life span of humans has changed very little. It seems that we are, at this point, helpless to avoid many deleterious cellular changes that ultimately lead to a senescent phenotype and eventually death.[1] The notion of changing the aging process has given rise to an enormous amount of research aimed at understanding the mechanisms of cellular aging. It is doubtful that any single process could entirely account for the emergence of the senescent phenotype. All species have the common cycle of birth, growth, aging, and death. All species are born with a set of genes that largely determine their lives. The expression of genes is usually influenced by environmental factors, which can result in the alteration of the rate of absolute growth, aging, and death.[1,2] Environmental factors not only affect the gene transcription but also gene translation and the modification of proteins. Proteins are the major determinants of alterations in body functions. Cellular functions depend on the ability to synthesize proteins with specific functions.[1] There is a gradual and progressive alteration in body functions from birth to death. The changes are rapid during the growth phase, but are, to a certain extent, slower during a rather prolonged period of aging from age 30 years to death.[1] The aging process is associated with diseases causing rapid deterioration of body functions in most species.

Theory proposed to explain the process of aging in aerobic species

A leading hypothesis of aging is based on the free radical theory of aging of Harman,[3] who argued that oxygen-free radicals (reactive oxygen species, ROS) produced during normal cellular respiration would cause cumulative damage to molecules, which would eventually lead to organismal loss of functionality and ultimately death. Because free radicals or ROS are produced in mitochondria in the electron transport chain, substantial attention has been focused on mitochondria and aging. The free radical theory was proposed in the 1950s.[4] According to the free radical theory of aging, all organisms age because of the accumulation of cell damage over time, and life span is an inverse function of metabolic rate.[3,4] Free radical theory encompasses aging and age-related diseases such as cancer, arthritis, atherosclerosis, Alzheimer's disease, and diabetes.[4] It is known that age causes structural and functional changes in skeletal muscle in humans. Muscle changes in humans start at age 40−50 years and can cause frailty and disabilities.[5] Related changes in body composition form the basis of many metabolic disorders, such as insulin resistance, type 2 diabetes, and hypertension.[4] Reduction in the synthesis rates of many muscle proteins, myosin heavy chains, and mitochondrial proteins occur with age.[1]

Aging in mammalian species

In humans, aging is different from that in most other species due to the relatively long duration of human life even after the genetic potential for growth is complete. Most of these reasons make it hard to study aging, and studies done in many other nonmammalian species cannot always be directly associated to human aging. Increasing evidence shows that, in rodents[6] and in humans,[4] muscle mitochondrial dysfunction occurs with age. Muscle mitochondrial function changes include decreases in mitochondrial DNA copy number, reduced muscle mitochondrial oxidative enzyme activities, decreased messenger RNA (mRNA) concentrations in genes encoding muscle mitochondrial proteins, and reduced mitochondrial protein synthesis.[4] The results are in conflict on whether the actual muscle mitochondrial adenosine triphosphate (ATP) production decreases with age.[6] It can be hypothesized that the muscle mitochondrial ATP production is a determinant of physical activity levels. The basis for the hypothesis is that humans and other species need ATP for muscle contractile activities. The availability of ATP may trigger, through an activity center, an alteration in activity levels. It can be assumed that the effects of mitochondrial ATP concentrations are natural activities under the control of the hypothalamus. The structural changes include reduction in muscle mass and muscle fibers and are associated with muscle weakness, reduced endurance capacity, and insulin resistance.[6] Muscle weakness is largely related to reduced mass but the muscle strength/unit mass of muscle also declines. In long-distance runners and in animal studies, type 1 fibers are rich in mitochondria and are relatively fatigue resistant. By contrast, the relative increase in type 1 fibers does not make older muscle fatigue resistant, perhaps because of a reduction in mitochondrial content with age.

Relating aging and mtDNA

A reduction in mitochondrial ATP production could contribute to reduced endurance and muscle weakness. Increased mtDNA oxidative damage with aging and cumulative DNA damage could explain an overall reduction in mtDNA copy numbers in oxidative tissue, such as skeletal muscle.[4] A reduced mtDNA copy number may contribute to reduced mRNA abundance, which results in reduced mitochondrial protein synthesis and enzyme activity. The overall effect is a reduced capacity for oxidative phosphorylation. The reduced availability of ATP may contribute to an overall reduction in the remodeling process that involves the synthesis and breakdown of proteins, both of which are energy consuming reactions in muscle. There are some data that indicate that the effects of aging on mtDNA abundance, gene expression, and the downstream effects may be traced back to

alterations and mutations to portions of DNA that encode mitochondrial proteins.[7] There is some uncertainty concerning the relevance of ROS to the aging process.[6] Skeletal muscle from older humans also exhibits higher levels of oxidation to proteins and lipids.[4] A link between cellular ROS and life span is suggested from studies where oxidant scavenging systems are either enhanced or decreased.[8]

Primary causes for decrease in mitochondrial activity with aging

The primary causes of the decrease in mitochondrial biogenesis and ATP production seem to be a decrease in mitochondrial DNA and mRNA.[9] Reduced ATP production could explain the reduced muscle protein turnover, which requires energy. It can be explained that a reduction in tissue mitochondrial ATP production makes the hypothalamic centers reduce unplanned physical activities.[10] Physical activities are regulated by cognitive centers and could alleviate the progressive decline in mitochondrial functions occurring with age.[10] ATP is produced through a set of exquisitely coupled and coordinated reactions where macronutrients are oxidized, oxygen is reduced to water, and adenosine diphosphate (ADP) is phosphorylated to ATP.[1,2] The maintenance of the mitochondrial membrane potential by the electron transport chain is critical to proper function of the organelle and, therefore, the cell. The role of mitochondria in the aging process has been a topic of intense interest for many years. Human studies have focused largely on skeletal muscle because it is a postmitotic tissue, tissue samples are relatively easy to acquire, and it is a determinant of physical function which is known to decline dramatically with aging.[1] Skeletal muscle is also a highly metabolically active tissue, accounting for glucose disposal following a meal and vital for peripheral glucose disposal. Electron microscopy has been used to demonstrate that mitochondrial volume density decreases with aging in skeletal muscle.[2] Less abundant mitochondria would logically lead to a decreased capacity for oxidative phosphorylation. Indeed, we find that the maximal rate of mitochondrial ATP synthesis declines over the life span. The age-related decline in mitochondrial capacity may reflect reduced content of the organelle in skeletal muscle.[1] However, when ATP production rates are expressed/unit of mitochondrial protein, which accounts for differences in mitochondrial content, there are persisting age effects. Thus, the effects of age on mitochondrial function are compounded by reduced mitochondrial content as well as impaired intrinsic activity of the mitochondrial machinery.[10] Measurements of mitochondrial function are generally in agreement with the concept that mitochondrial function declines with aging,[2] although some reports show that the effects of old age are more modest.[10] These types of *in vitro* measurements in isolated mitochondria permit functional assessment of distinct levels of the respiratory chain and tricarboxylic acid cycle. However, *in vivo* assessment of mitochondrial function by magnetic resonance spectroscopy is advantageous from the standpoint of physiological relevance (intact circulatory and regulatory systems). Numerous *in vivo* studies also find that oxidative capacity is reduced in older adults.[11] Although several others find that oxidative capacity is similar in young and older adults with similar physical activity levels.[3]

Effect of decreasing mtDNA mutations/deletions in aging

The importance of physical inactivity as a determinant of the aging phenotype is something to be taken into consideration. In an effort to understand the mechanisms responsible for this age-related decline in mitochondrial function, numerous investigators have examined various molecular and cellular disturbances with aging. Age-related changes at multiple levels between the expression of genes and the assembly of the functional organelle appear to be responsible for the overall decline in mitochondrial function.[1,2,11] Aging affects the expression of genes encoding mitochondrial proteins, as evidenced by decreased mRNA transcript levels,[5] possibly due to reduced gene transcription or mRNA instability with aging. Mitochondrial DNA copy number decreases with age,[5] which could account for the reduction of mitochondrial gene transcripts and, therefore, the proteins encoded by these genes. Protein expression is not only affected by mRNA template availability, but also by the rate of protein synthesis, which declines with age.[5] Whether aging affects the synthesis rates of mitochondrial proteins encoded by both genomes in the same way has yet to be determined. This question is now addressable, due to recent advances in measuring the synthesis rates of individual mitochondrial proteins.[2] Specific rates of mitochondrial protein breakdown have yet to be measured *in vivo*, but observations that expression of Lon protease, a key enzyme for mitochondrial proteolysis, is reduced in older mice suggesting that mitochondrial protein turnover is likely to be reduced with aging.[11] An overall decrease in protein expression may result from the mismatch between rates of protein synthesis and degradation. Importantly, decreased protein turnover may lead to accumulation of oxidatively damaged dysfunctional proteins, such as protein carbonylation[11] and nitrotyrosine-modified proteins.[2] Nucleic acids also demonstrate increased levels of oxidative damage with aging, particularly mtDNA, whose susceptibility is increased by its proximity to the source of damaging ROS and the lack of protection by histones. Mitochondrial fusion and fission appear to be critical for the maintenance of mtDNA,[11] but a causal link to aging and mtDNA damage remains in its nascent stages.[5]

Countermeasures for aging: aerobic exercise

Aerobic exercise and resistance exercise augment muscle protein synthesis and mitochondrial biogenesis.[12] Insulin and amino acids can improve muscle mitochondrial biogenesis and mitochondrial protein synthesis. The insulin-induced augmentation of muscle mitochondrial ATP production is defective in type 2 diabetic patients with insulin resistance.[12] Dissociation between increases in insulin sensitivity and muscle mitochondrial biogenesis after exercise has been noted

in older persons.[8] Exercise can enhance the effectiveness of muscle mtDNA in rodents.[13] The reduced physical activity as a contributor of age-related mitochondrial dysfunction is not determined. Physical activity in the form of resistance and aerobic exercise stimulates muscle protein synthesis in both young and older persons.[4] Resistance exercise programs increase muscle mass[14]; therefore, it is likely that the synthesis of structural proteins is enhanced by resistance exercise. By contrast, many metabolic changes occur with aerobic exercise with no increase in muscle mass.[10] It is therefore likely that aerobic exercise stimulates the synthesis of many muscle proteins involved in metabolic processes. There is evidence in various species, from worms[4] to rodents,[13] that physical activity levels decrease with age. Although it is a common belief, supported by some experimental evidence that physical activity levels decrease with age, further direct evidence is needed to verify this in humans. Spontaneous activities decline with age in response to declining peripheral tissue mitochondrial function.[15] This, together with a reduction in voluntary activities, further reduces mitochondrial biogenesis and functions as well as the synthesis rates of contractile proteins.[15] Maintaining voluntary physical activities will partly prevent the age-related decline in muscle mitochondrial and contractile functions.[15] Moreover, physical activities and related changes are also likely to delay or prevent insulin resistance. Physical activity such as voluntary exercises continues to hold much promise for increasing healthy life expectancy in humans, but remains to show any impact to increase maximal life span.[16]

In addition to expanding mitochondrial volume and increasing the capacity for oxidative ATP synthesis, endurance exercise has also been shown to reduce mitochondrial ROS production and protect against mitochondrial-mediated apoptosis.[16] Researchers have found that although exercise actually increases the formation of ROS, the net cellular ROS load is reduced by regulated oxidant scavenging systems.[16] Given that many documented adaptations to endurance exercise are the same factors that are impaired with aging, there has been much interest in the utility of exercise to attenuate the deterioration of mitochondrial function with aging. Beneficial adaptations to aerobic training seem to be maintained across the life span, as evidenced by increases in VO_2 peak mitochondrial enzyme activities,[10] mitochondrial content, protein synthesis rates,[9] mtDNA copy number,[1] and gene transcripts for mitochondrial proteins.[14] Studies in older rodents provide evidence that exercise training is able to decrease ROS production, attenuate DNA oxidative damage and increase the activity of DNA repair processes[17] to aid in the removal of oxidatively damaged proteins.[14] Although exercise delays the onset of many mitochondrial changes associated with aging, there are several factors that cannot be attenuated even by vigorous endurance exercise programs. In spite of this high level of physical activity, there remains substantial age related declines in mtDNA copy number and expression of several mitochondrial respiratory chain proteins.[18] Thus, it seems that exercise can help delay the onset of many age-related detriments, but there is a component of mitochondrial aging that is an inevitable function of chronological age. The aforementioned studies of exercise adaptations with age and other studies involving careful control of health and physical activity patterns[19] indicate that environmental and lifestyle factors can account for much of the aging phenotype. This study proposes that voluntary physical activities increase muscle mitochondrial capacity. In mice, an aerobic exercise program increased muscle mtDNA abundance and ATP production rate, which was associated with increased activity. Long-term aerobic exercises largely prevented age-related declines in mitochondrial DNA abundance and function in humans.[14] It was seen to increase spontaneous activity levels in mice.[13] Wang et al[5] showed that acute exercise loading causes a deletion in mtDNA in rat skeletal muscle, and concluded that the oxidative stress induced by acute exercise modifies mtDNA. Jafari et al[13] demonstrated that one session of aerobic exercise does not cause mtDNA deletion in rat skeletal muscle. Mirzaei et al[20] examined dynamic changes of deleted mtDNA in human leucocytes after endurance exercise. Regular aerobic exercise and prevention of adiposity by healthy diet may increase healthy life expectancy and prolong life span through beneficial effects at the level of the mitochondrion.

In conclusion, the connection between mtDNA and aerobic exercise has important implications for aging because it supports the notion of a relation between mitochondrial function and spontaneous physical activity; that is, endurance training increases mitochondrial function, stimulates spontaneous physical activity, and is a viable approach to interrupt the vicious cycle of aging. It is clear that mitochondria play a role in the cell that goes well beyond their dogmatic function as the "powerhouse of the cell". It is likely that the mitochondrial decay that occurs with age cannot be counteracted in humans who are not on caloric restriction unless physical activity is voluntarily enhanced. As we advance the frontiers of our understanding of how senescence and life span are regulated, it may become possible to not only decrease the incidence of age-related comorbidities, but also extend maximal life span. Addressing the latter without regard to the former would create an undesirable situation of a rapidly expanding population of individuals who would stress an already overburdened health-care industry with little contribution to society. Further work is needed to elucidate the mechanism responsible for the positive effect of aerobic exercise on mtDNA damage. Also, further work is needed to examine the effect of aerobic training on mtDNA deletion, oxidative DNA damage biomarkers, and mtDNA content.

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