Revista Andaluza de
Medicina del Deporte
Rev Andal Med Deporte. 2011;2(4):77-83
www.elsevier.es/ramd

Revisión

ARTÍCULO EN INGLÉS

Pleiotropic effects of physical exercise on healthy aging

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History of the article:
Received January 8, 2011
Accepted March 7, 2011

Key words:
Aging.
Exercise.
Mitochondria.

ABSTRACT

Aging is a multifactorial process that affects all the organs and systems of the organism. Although the decline of physiological capacity associated with aging is, to date, unavoidable, practice of healthy life habits and physical activity can reduce the incidence of several aging-related diseases. In the present review we recapitulate the different effects of aging on the organism and show the new evidences that demonstrate how exercise is able to improve cell physiology in aged people. Moreover, the molecular mediators involved in the effect of exercise on aging progression are indicated.

Palabras clave:
Envejecimiento.
Ejercicio.
Mitocondria.

RESUMEN

Efectos pleiotrópicos del ejercicio físico en el envejecimiento saludable

El envejecimiento es un proceso multifactorial que afecta a todos los órganos y sistemas del organismo. Aunque la reducción de la capacidad física asociada al envejecimiento es, hasta la fecha, inevitable, la práctica de hábitos de vida sanos y de la actividad física pueden reducir la incidencia de varias de las enfermedades asociadas al envejecimiento. En esta revisión recapitulamos los diferentes efectos del envejecimiento sobre el organismo y presentamos las nuevas evidencias que demuestran cómo el ejercicio es capaz de mejorar la fisiología celular en las personas mayores. Además, se indican los mediadores moleculares implicados en el efecto del ejercicio sobre la progresión del envejecimiento.

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Introduction

Aging is a process, not a disease, which starts just after birthday. Even after conception, the developing organism starts a series of mechanisms that can affect positively or negatively further development including late years of life. These mechanisms are linked to the resistance of the organism to the decrease of the efficiency of physiological systems associated with aging. Scientific and clinical evidences demonstrate that the aging process can be accelerated by the malfunction of some genes such as Werner gene (Werner syndrome)[1] or the Lamin A gene (Hutchinson-Gilford progeria syndrome)[2] that causes progeria, a disease that produces rapid aging and begins in childhood. These evidences demonstrate that aging depends in part of the accurate function of key proteins encoded by these genes. Furthermore, several other evidences demonstrate that the deregulation of the metabolism in the organism also plays an important role in aging process and diseases bases in mutations in key components of cell metabolism ended in early death or senescence-like processes.

It is very difficult to disconnect the process of aging from the effect that some age-related diseases produce in the organism. In most cases, some diseases such as neurodegenerative diseases or metabolic-related diseases such as diabetes or obesity are aggravated during aging but also accelerate the aging process.

Although to date we cannot stop the aging process, we can improve health during last years of live of individuals. In this sense, increasing body of evidences has point to life habits as key factors that affect physiological activities during the last years. Among these life habits, nutrition, social activity and especially physical activity play an important role in the prevention of the impairment of age-related disease improving the activity and independence of individuals, in sum, their healthy aging. Thus, the aim of the present revision is to highlight the role of exercise at late years in the life.

Deleterious effect of aging on organism's physiology and beneficial effects of exercise

As a general phenomenon, aging affects all the organs and systems of the human being. Basically all the cells of the organism are losing their physiological capacities and become unable to maintain a functional equilibrium. This is the cause by which, although aging is not a disease, the progression of the incapability of cells and tissues increase the possibility to develop aging-related diseases.

In the following sections we will review the effects of aging on organs and systems and the most recent discoveries that demonstrate that the practice of physical activity even in old people is beneficial to maintain the capacity of the specific organs and also the whole organism.

Sarcopenia and frailty

Sarcopenia, the degenerative decrease in muscle mass and strength, is one of the main degenerative processes occurring during aging. During sarcopenia, muscle is replaced by fat and by connective tissue increasing fibrosis. Then, this progressive loss of muscle mass is directly responsible of the impaired mobility and higher frailty in the elderly. Furthermore, muscle injury linked to sarcopenia is accompanied by macrophage infiltration and increase of cytokine expression that resembles a systemic inflammation in muscle[3].

Although muscle loss linked to sarcopenia is multifactorial[4], one of the most important risk factors for sarcopenia is sedentarism. Then, it is clear that, in an opposite way, the practice of exercise must be one of the main factors to maintain muscle mass and improve strength during aging. It seems that one of the main factors involved in atrophy of muscle fibers accompanying sarcopenia is the increase in dysfunctional mitochondria. Following the mitochondrial theory of aging, the accumulation of dysfunctional mitochondria during aging due to a higher oxidative damage and a lower mitochondrial turnover by decreasing mitophagy is responsible of the main physiological dysfunction that accumulates in aged people[5]. Furthermore, a recent study performed in a transgenic mouse showing a higher ratio of mutations in mitochondrial DNA due to the presence of a proofreading-deficient version of the mitochondrial DNA polymerase gamma, demonstrated a higher incidence of sarcopenia in these animals. Sarcopenia was affected by the deficit in mitochondrial activity due to anomalous assembly of functional electronic transport chain complexes that reduces oxidative phosphorylation although without increasing oxidative stress in these animals[6]. Another mouse model lacking the cytosolic version of the superoxide dismutase antioxidant enzyme (SOD1), shows high levels of oxidative damage and an accelerated sarcopenia. In this case, sarcopenia is also accompanied by a decline in mitochondrial bioenergetics, higher mitochondrial-dependent apoptosis and higher levels of reactive oxygen species (ROS)[7].

In a very recent review, Parise et al[5] show that resistance exercise improve mitochondrial phenotype in aged skeletal muscle increasing the number of functional fibers and the proportion of functional mitochondria in these fibers. Moreover, endurance exercise has been able to prevent mitochondrial DNA depletion and mutations in a transgenic mouse showing higher ratio of mutation due to abnormalities in DNA polymerase gamma[8]. These studies demonstrate that endurance exercise is able to maintain mitochondrial remodeling improving bioenergetics and increasing the capacity of muscle fibers. Thus, a correct turnover of mitochondria during aging permitting balanced bioenergetics equilibrated with the necessities of the organism is important to avoid sarcopenia in the elderly.

However, the type of exercise and the amount must be clearly fixed for each individual depending on its specific characteristics because an inadequate exercise must produce deleterious effects on muscle due to increases in oxidative stress-induced damage[9].

Osteogenesis

As in the case of sarcopenia, bone mass also shows involution with aging. Physical activity, even at low frequency, is able to increase bone mass and reduce the bone loss associated with age[10]. Furthermore, the decrease of estrogens after menopause is one of the responsible factors of bone loss in women since bone remodeling depends in part of estrogen receptor alpha[11]. As exercise is able to stimulate this receptor, the combination of exercise with estrogen therapy in postmenopausal women would maintain higher bone mass during aging.

Insulin resistance, obesity and diabetes

Sedentarism is one of the main causes of the epidemic increase of obesity and metabolic syndrome and its related risks as cardiovascular diseases, type 2 diabetes, hypertension, and other diseases including cancer[12]. One of the main factors involved in the impairment of the

homeostasis of the whole organism associated to obesity and diabetes is insulin resistance. Aging is accompanied in most of the cases by the increase of insulin resistance mainly because physical inactivity[13] and by the prevalence of the metabolic syndrome[14]. Insulin resistance perturbs the use of glucose by muscle and adipose tissue and produces the accumulation of fat in other parts of the organism such as liver impairing the activity of this organ. Further, insulin resistance aggravates several other processes including atherogenesis, dyslipidemia, increase of visceral adiposity, etc.

The practice of both aerobic and resistive exercise modifies body composition and is one of the main therapies to avoid obesity and increase insulin sensitivity in the whole organism even in older adults[15-18]. Short-term exercise has been able to improve pancreatic beta-cell function and ameliorate insulin resistance in old people[19]. However, it has been recently shown that training significantly improves insulin sensitivity in muscle in control and diabetic patients[20] although mitochondrial ROS release tended to be higher in diabetic patients, indicating a putative problem of re-adaptation of mitochondria in these patients.

As in the case of sarcopenia, mitochondria activity seems to be importantly involved in the onset of insulin resistance in diabetes and aging[21]. Although it is unclear whether exercise can prevent, reverse or delay the onset of insulin sensitivity, several evidences and studies indicate that exercise may reverse insulin resistance by affecting mitochondrial activity[22].

Exercise and hormones

Estrogen and other hormones production decrease during aging. In addition to its known effect on sexual cycle and activity, estrogens are important effectors that affect several other activities in the organisms. They affect bone remodeling, muscle mass maintenance, lipid deposition, prevent neurodegeneration and some kind of cancer, etc. Then, the maintenance of estrogen hormones above a determined level can be important to preserve tissue activity during aging.

Postmenopausal women show a clear decline of hormone levels that not only affects estradiol but also testosterone levels. This decline would affect physical capacity since it has been demonstrate that sex and estrogen may attenuate the indices of post-exercise muscle damage and enhance muscle contractile properties[23]. Once again, some studies have demonstrated the effect of estrogens on mitochondrial capacity for oxidative phosphorylation at the same time that decrease production of ROS indicating that mitochondrial decline with aging can be also reduced by maintaining higher levels of estrogens during aging, especially in women[24]. Then, the reduction of estrogens levels during aging would be one of the main factors involving in the decrease of physical capacity during aging.

Several studies have been developed to determine the effect of exercise on estrogens levels. Although a fist hypothesis would indicate higher levels of hormones after exercise, a recent study have shown that sexual hormones such as estradiol or testosterone show an inverse association with physical activity during menopausal transition[25]. However, in general, most of the studies have demonstrated that exercise is able to induce an increase in circulating androgens in both sexes. This effect is observed after both, resistance and endurance acute exercise[26]. However, in the cases of chronic training, the picture is less clear and, in some cases, exercise can lead to a decrease in circulating androgens.

On the other hand, it has been demonstrate in men that the practice of long-term intensive training produce deleterious effects on semen production and reduction in the levels of testosterone in serum whereas these levels recover after a recovery period of low-level exercise practice[27]. This effect has is known as the «exercise-hypogonadal male condition» and the causes are not clear but it seems that the hypothalamic-pituitary-testicular regulatory axis suffers a readjustment due to chronic endurance exercise[28]. These results indicate that physical activity is important to maintain estrogen levels in the organism but it must be indicated at a correct level for each age. The balance between beneficial and detrimental effects of high levels of estrogens in the organism must be considered in old people to plan a specific training protocol depending on the age and the specific characteristics of the person.

Another important issue is concerning the adrenal hormones such as dehydroepiandrosterone (DHEA) and DHEA-sulfate. These secretory products of the adrenal gland dramatically decline with aging. Due to the cardioprotective, antiobesity, antidiabetic and immuno-stimulatory effects of DHEA, its age-related decline must be one of the most important factors in senescence[29]. Thus, it has been suggested that restoration of DHEA levels to young adult levels may have beneficial effects on age-related diseases. Most of the studies performed in aged people have been focused on the effect of DHEA together with exercise in patients showing different diseases. In fact, few recent works indicate that exercise increase the levels of DHEA[30,31] although other have not found changes in older but do in young adults[32]. Further, other studies have found that DHEA can be metabolized in muscle to locally increase the levels of testosterone[33]. Knowing the effects of steroids on muscle and several other organs, increase of DHEA by exercise could be one of the main factors involved in healthy aging. However, the mechanism by which exercise is able to increase DHEA remains to be clarified.

Immune senescence and inflamm-aging

One of the most known processes affected by aging is immunity. Immune system suffers reduction of its capacity even at lower years of the life. As a clear mark of the effect of aging, the innate immune system, based on non-specific response against pathogens increases whereas the adaptative system based on lymphocyte activity and antigen-dependent response, is reduced during aging. In this way, the inflammatory response increases during aging and produces several auto-immune diseases such as systemic arthritis, diabetes, lupus and other diseases and also increase the risk for infectious diseases and tumorgenesis. As a chronic disease, the increase of pro-inflammatory response in the organism during aging has been named as inflamm-aging[34].

Some studies have shown that physical exercise does not result in major restoration of the senescent immune system in humans[35]. However, people that practice exercise for long time seem to have a relatively better preserved immune system. However, newer studies performed on clinical relevant models such as the response to vaccines and novel antigens that decreases due to immunosenescence, suggest that exercise can be used as therapy for restoring immune function in the elderly[36]. Long-term exercise protocols have been reported to improve antibody titer, T-cell function, macrophage response and alterations in the cytokine balance, pro-inflammatory cytokines and naive/memory cell ratio. These results indicate a general positive effect of exercise on immune system[36].

As inflammation increases during aging, exercise training has been considered as treatment against chronic inflammation in the elderly[37]. In fact, several of the diseases linked to aging have been related to the increase of inflammatory cytokines such as C-reactive proteins and

other cytokines: metabolic syndrome and diabetes, osteoporosis, cardiovascular disease including atherosclerosis, hypertension, etc. In some cases, the cause and the consequence of this inflammatory process are confusing. For example, the accumulation of adipose tissue in obesity contributes to the production of TNF-α, IL-6, IL-1 receptor antagonist and C-reactive protein[38] whereas this pro-inflammatory status may contribute to insulin-resistance that produces fat accumulation. Studies performed in rats, have demonstrated that the practice of moderate exercise is enough to significantly reduce the inflammatory levels in these animals[39]. Recent studies have also demonstrated that the practice of mixed exercise, aerobic and resistive, in obese people together with the maintenance of diary activity produces a significant anti-inflammatory effect on these patients[40]. However, other studies indicate that resistance exercise training is able to reduce pro-inflammatory markers whereas aerobic exercise does not produce any effect[41]. As a mechanism of action it has been postulated that TNF-α is one of the responsible of insulin resistance. Exercise stimulates the production of IL-6 by muscle fibers that would stimulate the presence of anti-inflammatory cytokines such as IL1-ra and IL-10 in circulation that would inhibit the production of TNF-α. Decrease of TNF-α levels would then reduce its effect on insulin resistance[38] decreasing several of the deleterious effects related to higher levels of glucose in blood such as adipogenesis, atherosclerosis or liver adiposity.

Besides the increasing body of evidences indicating that the practice of exercise, even in older adults, improves immune system activity[42], the mechanism by which this effect is produced remains to be elucidates. In some cases[36], it has been suggested that hormones regulate the activity of the immune system[43]. In fact, the imbalance that is produced during aging in the ratio between cortisol and DHEA can be one of the factors involved in immunosenescence since they show opposite effects on immune function being DHEA immunostimulatory and cortisol immunoinhibitory. The increase of DHEA levels found in people that practice exercise[30] indicates that this would be the cause of the improvement in immune response found in active people.

Cardiovascular system

Aging also affects cardiovascular system that result in alterations in cardiovascular physiology affecting mechanical and structural properties of the vascular wall. These modifications lead to the loss of arterial elasticity and an increase in stiffness of the arterial system. Arterial compliance is also reduced in aging-related disease states such as hypertension or diabetes[44]. Even more, coronary artery disease occurs with increasing frequency as age increases. The loss of elasticity results in increased overload on the left ventricle, increase in systolic blood pressure, and left ventricular hypertrophy and other changes in the left ventricular wall that prolong relaxation of the left ventricle in diastole. Furthermore, atrial pacemaker cells suffer a dropout resulting in the decrease in intrinsic heart rate. Finally, cardiac skeleton suffers calcification in the base of the aortic valve and β-adrenergic receptor reduces their responsiveness to neurotransmitters[45]. All these changes produce systolic hypertension, diastolic dysfunction and heart failure, defects in atrio-ventricular conduction and aortic valve calcification, all diseases have been seen in the elderly[45].

There are several evidences that demonstrate a positive effect of exercise on cardiovascular dysfunction associated with aging or age-related diseases. Most of the clinical trials confirm that lifestyle interventions (dietary modification and increased physical activity) reduce the risk of progressing or hypertension and improve endothelium-dependent dilatation in the aorta and resistance arteries of the heart. Moreover, short-term training is able to increases endothelial function in coronary conduit arteries[46]. In a study performed on middle-aged men during 33 years of physical training, the results demonstrated that exercise produced a favorable effect on cardiovascular system during aging reducing loss of oxygen uptake, no rise in resting blood pressure and not changes in body composition[47]. Moreover, chronic exercise also reduces the deficiency in the autonomic nervous system controlling cardiovascular system[48] and maintains the morphology and morphometry and number of cardiac neurons in Wistar rats[49].

Regeneration of endothelial tissue also decreased during aging. Circulating endothelial progenitor cells (EPCs) contribute to the integrity of the endothelium and its function whereas cardiac stem cells (CSCs) can differentiate into cardiomyocytes, endothelial or smooth muscle cells in the heart. During aging, both EPCs and CSCs suffer a reduction in their number and functional capacity[50]. It has been suggested that regular physical activity can increase the activity of these cells during aging maintaining a higher ratio of cardiovascular tissues regeneration. This higher capacity of endothelial function can also improve neurological activity by increasing the metabolic support of some brain regions increasing regional capillary density[51].

Neurological effects of exercise

Although with a different sense that the currently known, the Roman poet Decimus Iunius Iuvenalis (Juvenal), wrote the sentence «mens sana in corpore sano» in its Satire X. The current use of this sentence is related to the beneficial effects of exercise on brain and several studies have demonstrate that the practice of exercise, especially in aged people, can produce beneficial effects on brain activity and delay the progression of known age-related neurodeficiencies such as Parkinson's or Alzheimer's diseases. In a recent revision, Dishman et al, indicate that recent evidences are accumulating about the protective benefits of physical activity in neurological diseases that aggravate during aging such as Parkinson's disease, Alzheimer's disease, and ischemic stroke[52]. In a recent work carried out with a significant human population it has been reported that the incidence rate of dementia in aged population practicing exercise almost 3 times per week was significantly lower 1.3% vs. 1.97% than in sedentary population[53].

However, the main problem is to determine what kind of exercise and intensity is better to increase brain performance, memory or different brain activities. In a recent work Colcombe et al have reported that aerobic fitness training but not stretching and toning training affect brain volume in both gray and white matter and then, enhancing central nervous system function[54].

Hippocampus is the main brain region involved in memory. Recently, Kramer group has shown that there is a triple relationship between higher levels of aerobic fitness, higher hippocampal volume and better memory function[55]. Exercise enhances proliferation of neural stem cells increasing neuronal reparation. At the same time exercise is able to increase neurite growth and the survival of neuronal progenitor cells in mice dentate gyrus of hippocampus[56]. Furthermore, continued exercise reduces the age-dependent decline in adult neurogenesis[57]. These results have demonstrated that the practice of physical activity might contribute to higher cerebral capacity during aging by increasing neurogenesis even in adults although the effect has been higher in young that in old animals[58].

The mechanism by which exercise improves brain activity is not completely clear. Although only few factors have been already discovered, it have been demonstrated that exercise increases the levels of insulin growth factor-1 (IGF-1) in brain and this factor enhances the production of neurotrophic factors such as brain derived neurotrophic factor (BDNF). BDNF is one of the main factors involved in the complex activity of brain. Very interestingly, caloric restriction, the dietary manipulation able to increase both, mean life-span and maximum life, also affects both, IGF-1 and BDNF in brain[59]. BDNF is a factor that protects against neurodegeneration and modifies neuronal plasticity[60]. As in other systems involved in the decline of physiological activity during aging, BDNF also affects mitochondrial activity modifying brain metabolism[61].

Molecular mechanisms involved in the effect of exercise on aging

To explain how exercise produces the above described protective effects on aging we have to focus on the main factors involved in aging. However, to date there is not a theory that is generally accepted to explain aging. We know that accumulation of damage along life and the incapacity to remove damaged components of cells and tissues is directly related to the malfunction of cells and the deterioration of physiological functions that aggravates during aging. However, the main cause is not clear although oxidative stress and the effect of oxidized macromolecules seem to be one of the more accepted mechanisms. As mitochondria are the main ROS producers in the cell, growing dysfunction of mitochondria could explain most of the problems occurring during aging[62].

Experiments carried out in mouse demonstrate that exercise is able to reduce the incidence of mitochondrial mutations that induce accumulation of dysfunctional mitochondria. Recently, several papers indicate that the exercise-dependent induction of mitochondrial biogenesis in muscle is able to protect muscle against mitochondrial damages[8,63]. Several factors are involved in mitochondrial biogenesis. They can be clustered in three main groups: ubiquitous transcription factors (SP1, YY1, CREB, MEF-2/E-Box), nuclear respiratory factors (NRF-1, -2, MT1- to -4) and co-activators (PGC-1α, 1B and PRC)[62]. Other factors are also involved in the metabolic adaptation to fasting and energy requirements such as peroxisome proliferator activated receptor (PPAR) that together with PGC-1α increase mitochondrial biogenesis.

The most recent results indicate that PGC-1α is required for training-induced prevention of the decline in mitochondrial activity and expression of antioxidant enzymes in skeletal muscle[64]. Among the molecular components involved in mitochondrial turnover we found PGC-1α as common component. Biogenesis of new mitochondria is stimulated by the PGC-1α-NRF1 pathway. PGC-1α is the first stimulator of mitochondrial biogenesis whereas NRF1 is an intermediate transcription factor which stimulates the synthesis of transcription factor A mitochondrial (TFAM). In mitochondria TFAM activates the duplication of mitochondrial DNA molecules. One of the reasons by which mitochondria activity decreases during aging is because this pathway is impaired[65]. Since aerobic exercise is able to activate mitochondriogenesis in young animals, activation of this system would be one of the mechanisms by which exercise increases muscle capacity and improves physiology of other organs during aging

The modulation of mitochondrial activity is also related to the improvement of insulin resistance found after the practice of exercise. Regulation of the AKT/mTOR pathway by exercise improves endothelial function and regulates muscle activities improving cell response[66] and reducing insulin resistance.

The response of the organism to environmental agents characterized by a low dose stimulation of beneficial effects whereas high doses produce toxic and also deleterious effects is called hormesis[67]. As in the case of ischemia, dietary restriction or low doses of phytochemicals, exercise also induces mild stress in the organism inducing stress-dependent signals that activate kinases, deacetylases and transcription factors such as Nrf-2 or NF-kB that increase the amount of protective and antioxidant proteins and the activity of reparation systems all kind of biomolecules including DNA and proteins. Long-term exercise training induces manganese-SOD (MnSOD) in heart of senescent rats[68]. The effect of exercise is not only focused on muscle but also can affect other organs such as kidney where exercise increase antioxidant defenses and decreases oxidative stress by activating Nrf-2-dependent mechanisms[69]. Or in the case of vascular system where the practice of exercise increases SOD activity, downregulates NADPH oxidase activity and reduces oxidative stress[70] improving endothelial function in the whole organism and cardiovascular system. This effect also involved protein turnover that removes and replaces damaged proteins avoiding one of the main causes of physiological impairment found in aging[71].

Concluding remarks

Several evidences indicate that maintaining physical activity at older ages would produce beneficial effects in the whole organism reducing the deleterious effects of physiological decline associated with aging and improving healthy aging. The practice of exercise is able to maintain cell physiology at higher levels improving the capacity of cells to eliminate damage in lipids, proteins and DNA. Maintenance of a balanced turnover of biomolecular components of cells would permit a higher capacity of cells, tissues and organs. Furthermore, mitochondria are also a key component in the improvement of body capacity induced by exercise or by caloric restriction that has demonstrated its positive effect on life-span. As the key component in cell bioenergetics, the maintenance of a balanced activity of mitochondria at older ages would be a key component in the increase of organs and systems activity during aging. The discovery of the molecular mechanisms involved in the effect of exercise or dietary restriction on healthy aging would permit us to design new therapies based on nutrition, pharmacology and exercise to increase the capacity of people during last years of the life. These therapies not only will affect humans as individuals but also will produce a higher social impact reducing the considerable cost of the treatments of chronic aging-related diseases.

Acknowledgements

This work was supported by DEP2005-00238-C04-04 and DEP2009-12019 grants of the Ministerio de Ciencia e Innovación and by the IMD2010SC0002 grant of the Consejería de Turismo, Comercio y Deporte de la Junta de Andalucía.

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