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Decelerating aging process with physical activity - a review

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Abstract

Introduction: The process of aging is a progressive, patterned, and accumulative set of time-related changes resulting from a mix of genetic, epigenetic, and environmental factors, that are constantly evolving, and that lead the human body to be more prone to defects and susceptible to disease, and at last to death. On the molecular level, the accumulation of free radical reactions that constantly go on in every cell and tissue is thought to be the main culprit behind the process of aging [1]. These reactions amassed over time, hamper immune responses to external factors, cause homeostatic imbalance and lead to chronic pro-inflammatory status in body cells. This process has been dubbed "inflammaging" [2]. Physical activity, along with a balanced diet and a healthy lifestyle as a whole, has long been thought to be crucial in retaining health and good quality of life.

Aim of the study: A review of current knowledge about the process of aging, a summary of underlying pathologies, and current preventive protocols, with a focus on physical activity as a preventative measure in combating illness and age-related pathologies.

Methods and materials: A review of chosen literature in the PubMed database, MDPI database, and GoogleScholar was conducted using the following keywords: "aging pathophysiology", "physical exercise in the aging process", "aging process underlying conditions", "molecular biology of aging", "cell lifespan", "cell longevity".

Results and conclusions: Physical activity helps decelerate the process of aging, both physical and cognitive, through various pathways in the human body.

Keywords: "aging pathophysiology", "physical exercise in the aging process", "aging process underlying conditions", "molecular biology of aging", "cell lifespan", "cell longevity"

I. Introduction

The process of aging is a progressive, patterned, and accumulative set of time-related changes resulting from a mix of genetic, epigenetic, and environmental factors that are constantly evolving, which lead the human body to be more prone to defects and susceptible to disease, and at last to death. On the molecular level, the accumulation of free radical reactions that constantly go on in every cell and tissue is thought to be the main culprit behind the process of aging [1]. These reactions amassed over time, hamper immune responses to external factors, cause homeostatic imbalance and lead to chronic pro-inflammatory status in body cells. This process has been dubbed "inflammaging" [2]. Physical activity, along with a balanced diet and a healthy lifestyle as a whole, has long been thought to be crucial in retaining health and good quality of life.

II. Aim

A review of current knowledge about aging, a summary of underlying pathologies, and current preventive protocols, with a focus on physical activity as a preventative measure in combating illness and age-related pathologies.

III. Materials and methods

A review of chosen literature in the PubMed database, MDPI database, and GoogleScholar was conducted using the following keywords: "aging pathophysiology", "physical exercise in the aging process", "aging process underlying conditions", "molecular biology of aging", "cell lifespan", "cell longevity".

IV. Pathophysiology of aging

Aging is such an extensive mechanism, meaning it is a shared process affecting every cell and organ of the body just the same, but also very varied due to the diversity in human cell and tissue structure and function, that it is hard to propose a complete and exhaustive definition of underlying pathologies of the process as a whole. It is currently believed, that aging is a combination of different ongoing processes, the extent of exposure to adverse external factors, and individual genetic predispositions. Nonetheless, a constant decline in regenerative cell function, homeostatic imbalance, chronic pro-inflammation, and smoldering inflammation are common grounds for the aging process in all organs. Different aging models and theories have been proposed and studied throughout the years, and in this review, a few selected models are discussed in light of current knowledge.

- **Free radicals**

  The theory of free radicals, produced in cellular metabolic reactions, that lead to oxidative cell damage over time goes back to the 1950s. Reactive oxygen species (ROS) such as the superoxide anion, hydrogen peroxide, and hydroxyl radicals are constantly produced in human cells over their lifespan. When the balance between ROS production and gene-coded antioxidants, their countermeasures, is disturbed and shifts toward ROS, cells are eventually broken down. Orr et al. conducted a study comparing *Drosophila* flies with overexpression of the zinc superoxide dismutase (SOD) gene and *Drosophila* wild-type control flies and came to the conclusion that genetically modified flies lived one-third longer and displayed better physical performance in comparison with control flies [5]. Parkes et al. also conducted a study on *Drosophila* species, stimulating overexpression of the *SOD1* gene within motor neurons of the flies, and concluded that the lifespan of these flies increased by 40% in comparison to wild-type control flies [6]. Interestingly, results of experiments carried out on superoxide dismutase–deficient mice suggest that SODs may not be as crucial to regulating aging in more complex animals as they are to simple species [7][8]. However, later studies lead to conclusions, that reactive oxygen species have the most significant impact on the aging of cells that don't have regenerative abilities, such as cardiomyocytes and neurons, because of cumulative negative effects [9][10].

- **Genetic pathways**

  Genetic programming is thought to be a more important factor in the regulation of aging in pre-mitotic cells than ROS damage. Tatar et al. argue, that growth factor pathways, in particular the insulin growth factor pathways (IGF), play an important role in human aging [11]. Holzenberger et al. concluded that IGF-1R heterozygous mice had a 26% longer lifespan than wild-type mice. Studies on *Caenorhabditis elegans*, a nematode that goes through four larval stages before reaching reproductive adulthood, observed genetic changes regulating aging under adverse external conditions, and extracted genes that encode for nematode IGF1 receptors [12] and subunits of phosphatidylinositol 3-kinase [13]. The phosphatidylinositol 3-kinase pathway has in humans been linked to various diseases such as diabetes mellitus and carcinoma and is thought to take part in regulating cell survival time. Genetic

regulatory pathways are of constant interest to molecular biologists. Studies have shown that stimulating the expression of cell survival factors increases cell longevity, but does not make it permanent, which suggests that other underlying processes also play a role in regulating cell lifespan.

- **Genomic instability**

  As mentioned above, upregulation of cell survival factors helps elongate cell lifespan, but cannot make it indefinite, which is blamed on genomic instability. Somatic gene mutations, which are accumulated with time, eventually lead to cell dysfunctions that are irreversible. Dolle et al. in a transgenic mice model study concluded that rapid spontaneous genome rearrangements in liver cells of mice increased rapidly after reaching a certain age threshold, but in brain cells, genome rearrangements were not as common and did not increase with age [15]. This suggests that random mutations may take part in regulating cell lifespan, but does not explain a typical aging pattern and predictable life duration of different species. Scientists have been on the trail of finding a more controlled molecular clock, which could help explain the predictability of aging in different species. One theory suggests, that cells have a limited amount of replications possible before reaching replicative senescence. Telomers are thought to be good indicators of cell lifespan. Harley et al. came to the conclusion that cells with lower telomerase activity, an enzyme that extends telomeric repeat sequences, have shortened telomeres and reach senescence [16]. Another study concluded that introducing telomerase to normal human cells increases their lifespan [17]. However, Blasco et al. did not observe rapid aging patterns in mice lacking telomerase RNA [18]. The direct role of telomeres in cell lifespan needs further studies and insight, but nonetheless, telomere shortening as a cause of genetic instability seems to be well-argued. It is worth noting, that an interesting study was conducted on mice lacking the *Xpd* gene that encodes a DNA helicase protein subunit of core transcription factor IIH, which unwinds DNA and is crucial for RNA polymerase II to initiate transcription, and to repair gene lesions. Mice lacking the *Xpd* gene showed clear signs of premature aging in comparison to control, such as cachexia, osteoporosis, osteosclerosis, and graying [19]. This study sheds light on the importance of DNA damage and molecular repair mechanisms in regulating cellular lifespan.

The theories on aging briefly overviewed above do not cover all possible mechanisms that constitute aging. Studies seem to confirm, that more complicated species have more complex aging mechanisms and are equipped with a large range of regulatory and repair tools. Further research on the topic is needed, although fully understanding the process of aging does not seem feasible.

V. Physical activity and aging

Physical activity affects both cognitive functions and bodily functions. In an attempt to confirm this thesis, at first, let's take a closer look at the process of bone formation.

During physical activity, bone tissue deforms and cellular mechanoreceptors such as ion channels and integrins change their original conformation, affecting several pathways including calcium activated pathways, mitogen-activated protein kinase (MAPK),Wnt and RhoA/ROCK [20]. The balance in the bone remodeling process is mainly regulated by the WNT-β-catenin pathway and the RANK-RANKL/OPG system.

The Wnt signaling pathway is known to be one of the important molecular cascades regulating cell fate throughout lifespan. Wnts are essential for skeletal formation and development and are involved in various processes, from limb modeling and formation to chondrogenesis, differentiation, proliferation and synthesis of bone matrix by osteoblasts, and osteoclast differentiation and function acquisition during development. In the early stages of reparation of bone fracture, β-catenin is required for pluripotent mesenchymal cells to differentiate into osteoblasts or chondrocytes, and for the later stages of repair, preosteoblasts to differentiate into osteoblasts. Agents known to activate the β-catenin pathway are used to accelerate bone healing. By regulating the expression of inhibitors of osteoprotegrin (OPG) and RANKL in osteoblasts, Wnt signaling also reduces osteoclastogenesis and osteoclast activity, thus, a decrease in β-catenin activity results in lower OPG expression and a decrease in bone mass due to increased osteoclast activity (Glass II, Bialek, 2005, Holmen, Zylstra, 2005)[21]. In order to better understand the problem, it is also worth quoting the study conducted by H.Blaine at al. on the impact of exercise frequency on bone mineral density (BMD) in the lumbar spine (LS) and hip. Seven studies with 17 exercise groups were included in the analysis. Significantly greater effect of high intensity (≥2 trainings/week) versus low intensity training (1–<2 trainings/week) was observed on Lumbar Spine- (SMD 0.55, 95%-CI: 0.20–0, 90), but not hip BMD (0.19,

-0.06 to 0.45). Study duration was found to be a significant moderator of the effect of training frequency on LS but still doesn't influence hip BMD. At the same time, the type of exercise moderately affects the effect of training frequency on LS, but not on hip BMD. In addition, researchers also observed a better effect of higher training frequency on BMD. Longer exposure to exercise escalates this effect [22].

Another example may be the effect of physical activity on changes in skeletal muscles during aging. Exercise may affect the remodeling of DNA methylation of significant genes in skeletal muscle[23].

In addition, exercise can modulate the expression of several miRNAs that mediate the beneficial process.

The elementary function of miRNAs is to downregulate protein by either inhibiting gene translation or promoting degradation of target mRNAs, the latter listed is responsible for most miRNA activity. Given their purported role in post-transcriptional regulation, miRNAs have emerged as a potential regulator of exercise-induced adaptations in skeletal muscle [24]. According to a study on mice, after voluntary strength training for 8 weeks, older mice show almost 8 weeks of younger epigenetic age in their muscles and a slight increase in lifespan [25].

In addition, voluntary running in treadmill has been observed to benefit older mice in terms of neurogenesis and learning ability and reduce abnormal changes in aging synapses [26].

Importantly, the rejuvenating effect of exercise is also observed in humans. There is a significant difference in the transcription profile between physically active and sedentary elderly people, and endurance exercise improves muscle function in the elderly. Resistance training reduces mitochondrial methylome levels in skeletal muscle of elderly people and partially restores aging-related changes in the nuclear gene methylome in muscle.

The age-protective effect of exercise in humans is intricately linked to epigenetic regulation. Exercise modifies DNA methylation patterns in aging human skeletal muscle and reduces stochastic epigenetic mutations in major pathways associated with carcinogenesis[27]. Of course, there are some risks/limitations. Above we mentioned the effect of ROS on aging. Physical activity, especially exercise, can modulate ROS. The effect of exercise on ROS ranges from harmful to beneficial and depends on the type of exercise, as it induces several types of ROS. Given that reactive oxygen species can be pathological or physiological, it is suggested that ROS have a biphasic

effect, beneficial up to a certain point and threatening as levels increase. An ischemia/reperfusion injury study showed that mitoPQ dosage increases ROS production. Low doses protect myocytes, but higher doses cause myocyte dysfunction and death [28]. Another study showed a biphasic effect of stimulating ROS production by treating damaged skeletal muscle with gelatin. A low dose of gelatin results in an increased antioxidant response, tissue adaptation to mild stress, myogenesis and muscle regeneration. High amounts of gelatin result in overproduction of ROS, leading to worse tissue damage. Therefore, ROS has a biphasic effect [29]. The production of reactive oxygen species can be regulated by physical activity. There are different effects of acute and chronic physical activity on oxidative stress. Very intense exercise induces reactive oxygen, nitrogen species and oxidative stress. However, regular physical training stimulates the endogenous antioxidant system and protects the body from the adverse effects of ROS-induced damages [30].

Nowadays, it seems obvious that lifestyle factors, such as physical activity and exercise, have a significant impact on preventing cardiovascular disease later in life and mitigating age-related decline in cardiovascular function in healthy individuals. Scientific studies show that physical activity can alleviate age-related changes in the cardiovascular system by improving cardiovascular fitness, cardiac function and metabolism. As for changes at the molecular level, physical activity increases the expression and activity of antioxidant enzymes and consequently reduces ROS, modifying oxidative stress-induced damage during cardiovascular aging.

VI. Conclusions

In view of the above, both endurance and resistance training in at least a moderate range are recommended for all individuals without contraindications throughout life. Exercise recommendations should be a multimodal approach to maximize the benefits of physical activity. According to accumulated evidence, starting physical activity early enough allows us to delay the aging of various areas of our body.

Given the potential importance of physical activity as a therapeutic tool, we need to better understand the basic molecular, biological and physiological processes that occur under the influence of physical activity to explain how it acts as a specific remedy.

Physical activity has been demonstrated able to reduce generation of oxidants during ischemia-reperfusion damage and to have a calcium-protective role via activation of the ROS

scavenger MnSOD. MnSOD is biologically significant to aerobic cells. Its role in protecting the cells against the deleterious effects of reactive oxygen species is evident.

This better oxidative status consequent to a correct program of physical activity is partially responsible for some benefits (such as decreased arterial stiffness, improved endothelial function and metabolic and clotting setting, and reduced body weight). [31]

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Author contribution:

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2. Ewa Uram: analysis & interpretation of data (18%)
3. Inga Magda: data research (16%)
4. Magdalena Gaik: concept & design (16%)
5. Rafał Bogacz: writting of manuscript (16%)
6. Dawid Gazda: intelectual content and data research (16%)

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