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Aging-physiological interpretation and adaptation to stressors

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Abstract
Aging is complex process characterized by numerous changes that take place at different levels of the biological hierarchy. It is presented as an ontogenic issue, the process of growing old and or the sum of all changes, physiological, genetic, molecular, that occur with the passage of time, from fertilization to death. The heterogenecity of the aging phenotype among individuals of the same species and differences in longevity among species underline the contribution of both genetic and environmental factors in shaping the life span. Aging is associated with a tissue degeneration phenotype marked by a loss of tissue regenerative capacity. Ageing is considered to weaken the body's ability to respond to stress. The age-associated changes in the ability of tissues to replace lost or damaged cells is partly the cause of many age-related diseases such as Alzheimer's disease (AD), cardiovascular disease, type II diabetes, and sarcopenia. Long time stress promotes the aging process, which is detrimental for all mammals well being.

Keywords: Aging, stress, exercise, Alzheimer's disease, degenerative changes, telomere

1. Introduction
Ageing is a physiological process that emerged as a side product of normal development and the metabolic processes involved in the reproductive potential of the species [1] It has been developed most likely as a non-adaptive phenomenon with no biological function [2] and allowed to evolve through a trade-off mechanism [3]. According to Orgel's[4] theory, ageing can also be linked to the attempt of the body to reduce energy expenditure when switching off from germ line to somatic cells, which is achieved by making protein production less accurate[5]. Therefore, ageing is a dysdifferentiation [6] a phenomenon that emerged from the byproducts of development (such as growth or sexual hormones), oxygen metabolism (active oxygen species) and also the by-products of stress (glucocorticoids: GC). Among these, development and oxygen metabolism are constant and necessary involuntary forces, and hence unchangeable, but the stress response in humans and other primates has changed over time, becoming more chronic and detrimental to the animal [7].

2. Aging-Physiological Interpretation
All animals have a definite life cycle which includes birth, a period of rapid growth, puberty, a gradual cessation of growth, senescence and finally death. The longevity of the different mammals is surprisingly difficult to ascertain, and is known reasonably well only for man, laboratory rats, mice, dogs and race horses. The most accurate measure of longevity is the median life span of a fairly large population of the animal in question; In general the large animals live longer than the small ones. The metabolism of a large number of animals and the total metabolism of an animal summed over his life span is about the same for all mammals. The large animals have a small surface to volume ratio so the metabolism per gram of tissue required to maintain body temperature is quite low. The shrew, for example, has the highest metabolism per gram body weight of all the mammals and by far the shortest life span. The average life span of each animal to a large extent is determined by its genetic background. However, there are several factors which alter this genetically programmed ageing considerably. It is thus important to understand something of the basic biological mechanism involved.

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1. Anatomical changes

In most animals, growth virtually stops after puberty and body weight remains relatively constant for most of the rest of the life span. An exception to this is rat, whose skeleton continues to grow at a slow rate throughout its lifespan, and whose weight increases accordingly. One of the most common observations with regard to ageing is the decline in muscular performance. At birth each muscle contains a definite number of muscle fibers or cells. As the animal grows the size and strength of the muscles increases. There is an increase in size of the individual fibers but not in their number. In senescence, the number of fibers decreases, although exact cell counts have not been made. The muscle mass tends to decrease quite variably.

Another factor is the accumulation of collagen. This protein is the chief constituent of scar tissue and is very important in maintaining the structural integrity of the soft tissues. Once it is deposited it is very insoluble and tends to remain in the tissues for years. Many of the connective tissue cells die and are replaced by collagen fibers, so that some organs such as skin become infiltrated with collagen fibers. These fibers tend to shrink and join together in the course of time, forming a dense network. This accounts for the wrinkled appearance of the skin in a old person. In lungs it interferes with the oxygenation of the blood and in muscles with the flow of oxygen and nutrients from the blood capillaries to the muscle cells. It can even shrink and restrict some of the blood capillaries to the muscle cells and other organs, thus causes further impairment of the bodily functions.

2. Physiological changes

Animals maintain a constant internal environment within quite narrow limits throughout their lifespan in comparison to extreme old age. This includes the body temperature (for warm blooded animals) and blood parameters like blood cell counts, blood composition, oxygenation capacity and various blood metabolites which are kept By the body within a normal range. Other bodily functions such as digestion, metabolism, and circulation of blood fall in the same category. It is thus evident that as many of body organs become deficient in functions with ageing because of loss of cells, a deficient circulation or other reasons will have to strive more to maintain homeostasis. Muscular performance declines most strikingly with age. The limiting factors are probably the cardiovascular and pulmonary functions and the decrement in the maximal functioning of these systems is approximately the same as that of the kidney. The control systems of the body likewise suffer a small linear decline with age. When placed in a cold environment, an old rat takes much longer to adjust its metabolism to the changed conditions than does a young one. In response to exercise, an older person takes longer to increase the heart rate and respiration.

The endocrine glands have been implicated in the ageing process for many years. These glands control both development and functions of many organ systems in the body. When the endocrine glands are examined anatomically or physiologically, they are found in general to be functioning quite normally. If the blood level of sex hormones, for example, is quite low in old age, it is not because the glands are incapable of maintaining higher levels, but because the functional state of the animal at that time requires those levels. Reaction time becomes progressively longer with age. There is apparently some slowing of the conduction velocity of peripheral nerves and some deficiency of function of peripheral sense organs but these are not nearly enough to account for the observed slowing. However, these may not be concrete findings and may have certain exceptions.

3. Degenerative changes

The decline in organ function is very important in relation to ageing, but the end result of ageing, death is related to this decline in only a very peripheral way. In general, the cause of death of the older domestic animals today is degenerative diseases.

3. Factors That Influence the Ageing

A. Genetic components of ageing

Every cell possesses a complex system for the reproduction and building of the molecules that allow it to develop. The information and the machinery to achieve it are codified in the nucleic acids (DNA and RNA) and in the proteins. In the cells the nucleic acids share an environment that contains numerous inorganic molecules, water and a great variety of reactive molecular species that can exist as excited molecules, ions or free radicals, and are later turned into chemically stable products [8].

B. Environmental components of ageing

Environmental damages that exceed the maintenance system of repair of the DNA can lead to premature ageing. For example, prolonged exhibition to the sun will lead to a premature ageing of the skin due to the high levels of ultraviolet radiation that damages the DNA [9, 10]. Animals live exposed to a diversity of magnetic fields, some of them generated by the magnetism of the earth, whereas others are generated by the solar storms and solar changes through time [11]. Electrical devices also create magnetic fields: engines, television sets, office furniture, computers, microwave ovens, electrical wires in the buildings.

4. Control Mechanism and Exercise

Ageing leads to the steady accumulation of detrimental cellular and molecular changes within tissues that reduce the body's ability to respond to stress [12]. In particular, advancing age causes progressive but significant losses in skeletal muscle mass and strength termed sarcopenia, which is believed to be the precipitating factor contributing to a decline in physical function, increased risk of frailty, disability and death observed in the elderly [13]. Currently, exercise is considered to have numerous health benefits that include maintaining muscle mass and function with age, but the underlying molecular details have yet to be fully elucidated [14].

a. Role of Exercise in upkeep of Telomere Length-Maintaining Proteins in Rodent Models

The role of exercise in altering the expression of telomere-related proteins has been studied by several trials in rodent tissues. Telomerase is a ribonucleoprotein that consists of two central components: a protein reverse transcriptase component (TERT) and an RNA template (TERC). Shelterin acts as both a positive and negative regulator of telomere length and as a negative regulator of telomerase enzyme activity. Shelterin consists of six proteins: telomere-repeat binding factors (TRF) 1 and 2. Werner [15] performed a thorough series of experiments to elucidate how exercise produced adaptations in cells that made them more resistant to environmental stressors, specifically investigating the functions of telomeres and telomere-related proteins in cardiovascular (left ventricle, aorta, blood vessels) and immune tissues. Investigating short-

term training effects (21 days of voluntary wheel running) in C57BL/6 mice, they observed that TERT protein and TRF2, Ku70, and Ku80 mRNA expression levels were increased compared to sedentary controls. Thus, short-term exercise training in rodents leads to enhancement of protective responses to ageing like increases in telomere length and greater expression of senescence protective expression profiles. To determine if the effects of exercise for 21 days were dependent upon TERT protein, TERT knockout animals were given access to a running wheel for three weeks. It was observed that the effects of exercise on TRF2, p16, Chk2, and p53 were not present in the exercised knockout animals compared to wild-type exercised animals [16]. Thus, in rodent tissues TERT seems to have extra-telomeric functions, acting as a transcription factor or part of a chromatin remodeling complex, which mediate the beneficial adaptations of exercise on telomere-related proteins [17]. Above study provides enough evidence on roles of exercise and physical activity to produce a protective environment, which protects against telomere shortening and subsequently producing protective phenotypes against ageing in heart, vascular, and immune cells.

b. Mechanisms associated with mitochondrial dysfunction in age-related muscle loss

Ageing leads to mitochondria dysfunctions, which become incapable to adapt to higher levels of oxidative stress and ultimately succumb to, increased systemic losses of muscle mass and function leading to sarcopenia. Mitochondria are central mediators of muscle health and are highly sought-after targets of physiological and pharmacological interventions.
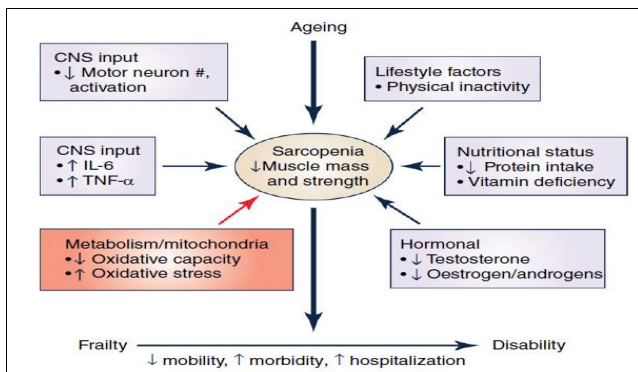

Fig 1: Factors contributing to age-related muscle mass loss

Exercise is the only known strategy to combat sarcopenia and this is largely mediated through improvements in mitochondrial plasticity. More recently a critical role for mitochondrial turnover in preserving muscle has been postulated. A disturbance in cellular pathways which regulate mitochondrial turnover, by processes of biogenesis, dynamics and autophagy, lead To a reduction in the clearance and enhanced accumulation of damaged organelles within the cells, which further accelerates the ageing process. When mitochondrial quality is compromised and homeostasis is not re-established, myonuclear cell death is activated and muscle atrophy ensues. Exercise both in acute and chronic form attenuates these deficits in the muscle, and helps to restore mitochondrial turnover thus, promoting a healthier mitochondrial pool and preservation of muscle. The overall aetiology of sarcopenia is multifactorial and includes alterations in variables such as nutritional status, physical activity levels and hormone concentrations (Fig. 1). At a

cellular level, impaired mitochondrial function and metabolic capacity contributes to reduced muscle health. A variety of muscles wasting conditions have been shown to be the result of deregulation at various levels in this intricate mitochondrial biogenesis pathway [18]. The most prominent age-associated mitochondrial profile alterations include reduced overall volume density, ATP production and protein synthesis, and these decrements are strongly linked to impaired skeletal muscle function, aerobic capacity and walking speed [19] (Fig. 2).
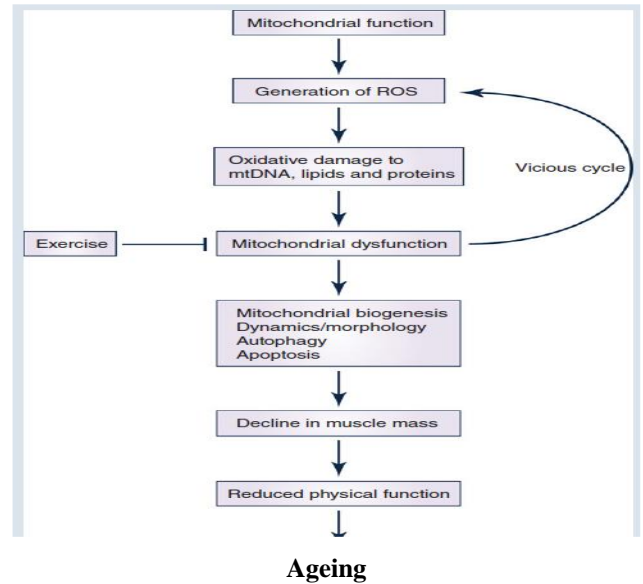

Ageing

Fig 2: Role of exercise in prevention of Aging process

c. Age-induced mitochondrial oxidative stress

Mitochondria are an important source of reactive oxygen species (ROS) in the cell and are produced via inappropriate electron leakage at ETC complexes I and III during normal respiration [20].
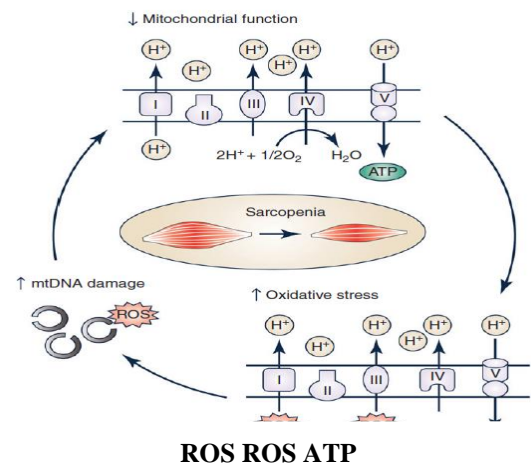

ROS ROS ATP

Fig 2: Proposed role of age-induced oxidative stress and mtDNA mutations in sarcopenia

The association of free radicals and ageing was introduced by Harman [21] and later extended to become the mitochondrial theory of ageing, which postulates that the steady accumulation of mitochondrial ROS with age leads to irreversible cell and tissue damage. Furthermore, ROS-induced oxidative damage to macro molecules, particularly within mitochondria (i.e. mt DNA, ETC components) can

lead to additional mitochondrial dysfunction and further elevations in ROS to create a 'vicious cycle' scenario that contributes to cell death and sarcopenia [22,23] (Fig. 3). Pioneering work by Holloszy [24] demonstrated that exercise can improve mitochondrial function and content in muscle to meet the increasing energy demands of active cells. Since then, there is definitive evidence that endurance exercise improves muscle health by increasing oxidative phosphorylation (OXPHOS), oxidative enzyme activities, and mitochondrial content in both young and elderly individuals [25,26].

d. Exercise enhances memory consolidation in the ageing brain

Observational studies have identified physical activity (exercise) as one of the three main modifiable risk factors for developing alzimer disease (AD) and dementia [27] Exercise is known to promote brain health and delay the onset of cognitive decline in ageing and AD. Exercise has been reported to increase synaptic plasticity and long-term potentiation; upregulate brains derived neurotrophic factor (BDNF) expression, and reduce accumulation of reactive oxygen species. Thus, exercises has profound affects on brain function and improves cognitive abilities by modulating underlying and reduce the detrimental effects of molecular and synaptic changes associated with ageing [28].

5. Gerontology and Adaptation To Stressors

Ageing weakens the ability of the body to respond to stressors, also stress affecting the organisms in a similar manner as ageing and thus accelerating the ageing [29] It has been suggested that one of the factors contributing to this exacerbated effect of stress in the aged organisms is their inability to terminate the production of GC in response to stress [30]. According to the GC cascade hypothesis, the age-induced degeneration of the region of the brain leads to failure of control mechanisms which are, responsible for communication with the endocrine system cascade and stop the production of GC after the effect of the stressor has ended [30]. In that way, excessive amounts of GC further damage the target brain region, starting a positive feedback cascade [30].

There is a functional connection between the immune and neuroendocrine systems, which stems from the interplay between their components, cytokines and hormones, at various levels in the body [31], thus, the response of GC to stress and ageing significantly affects the immune function. The simultaneous effects of ageing and stress on immune response, are both influenced by the way of ageing and various early life experiences of the animal [32]. Further, it has been suggested that the immune system has been developed as a response to pathogens which are a specific type of stressors (i.e. antigenic stressors) [31]. In that way, immunosenescence in more complex organisms such as vertebrates will be the product of the continuous accumulation of damage due to lifelong exposure to antigenic stress [33]. Chronic stress, ageing and the immune system The main danger to immunity, however, occurs with synergy of ageing and chronic stress, which plays as the main threat to an already compromised immune-compromised older rats. As mentioned above, severe stressors with a long-term effect such as a loss after death of a close family member or friend have been shown to relate to changes in the ability of aged neutrophils to produce reactive oxygen species through which they kill rapidly dividing pathogens.

A) The link between stress resistance and ageing: an early geroscience topic

Geroscience is an interdisciplinary field emerging at the interface of the basic biology of ageing and chronic diseases. Many laboratories are now adapting their research strategy to take account of ageing as a vital factor in the etiology of old age diseases. Various studies indicate towards cellular ageing being the underlying cause of various disease mechanisms and the ability of body to respond to age related damage being the critical link in the interventions. Ageing biology and stress biology is in turn share a critical association with each other. Chronological ageing is evident and obligatory for all organisms, but the rate of biological ageing is "elastic" in nature and modulated by interactions between genes and their environment. For example, in invertebrates, mutations in single genes can dramatically extend lifespan in the laboratory. However, the magnitude of lifespan extension is highly dependent on the environment in which the animals are maintained. Most organisms are sensitive to the type and severity of threats to physical or social survival, naturally embedded in life experiences. The relationship between rate of ageing and an animal's response to stress is extremely complex.

6. Conclusion

Aging is physiological process in all mammals, which is increases with age and it is accelerated by various factors. Stress promotes the aging process. Stress and the ageing process prove detrimental to an organism's well-being. Both aging and stress affects the body is through shared mechanisms, with particular regard to the neuroendocrine and immune systems from the level of the tissues, cells and even intracellular components. The mechanisms of deterioration are principally related to the generation of Reactive Oxygen Species (ROS) and to the glycosylation of proteins; both processes narrowly relate to environmental factors. Regular exercise prevent from damaging effect of aging it regulate the all system properly. Aging is determined by shortening of telomeres. Telomere-protective phenotype induced by moderate levels of physical activity, indicating an important cellular adaptation that may slow the onset of symptoms or prevent certain age-related diseases. Antioxidant capacity induced by the exercise of the individual tissues. Exercise prevent from detrimental effects of exercise.

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