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DEPENDENCE OF AGEING ON REACTIVE OXYGEN SPECIES PRODUCTION AND THE CUSHIONING EFFECT OF ANTIOXDIANTS (REVIEW)

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Abstract

Ageing is a complex, unavoidable, universal, biological phenomenon affecting all multi-cellular organisms. From the biological perspective, genetic mutations, wear and tear, and cellular waste accumulation have been suggested as possible causes of ageing. The Oxidative Stress Theory of Ageing (OSTA) and Mitochondrial Free Radical Theory of Ageing (MFRTA) suggest that the accumulation of damages due to oxidative stress from free radicals generated from the mitochondria has negative impacts on the body and causes ageing and age-related diseases. Reactive oxygen species (ROS) are produced endogenously mainly in the mitochondria during aerobic respiration or generated from exposure to ultraviolet radiation, smoking and air pollution. They subsequently oxidize and damage macromolecules such as lipids, proteins and nucleic acids causing the disruption of cell membrane permeability, cellular dysfunction, mutagenesis, protein denaturation and inactivation. The body uses enzymatic and non-enzymatic antioxidant systems to scavenge and mop up free radicals. Differences in the incidence of many age-related diseases suggest that oxidative stress does significantly impact some aspects of the ageing process. Also, oxidative stress may affect ageing in diverse patterns among different tissues depending on extent of oxidation, environmental conditions and antioxidant status. Antioxidants are believed to slow down the process of ageing and prolong the lifespan, thus the interplay between ROS generation and antioxidant activity should modulate the incidence of age-related morbidity. The framework for integrating the implication of ROS in ageing and possible beneficial effects of antioxidants faces numerous challenges due to the conflicting results from longevity studies involving alterations of the expression of antioxidant enzymes. However, signaling pathways involving nuclear factor erythroid 2-related factor 2 (Nrf2) and tumor suppressor p53 have been linked to the control of response to oxidative stress by influencing the expression of genes coding for antioxidant enzymes. As a single theory cannot sufficiently explain the complex processes of ageing, healthy ageing therefore involves a positive balance in the interactions between genes, environment and lifestyle. Lifestyle modifications which focus on reduction of ROS generation are encouraged to ensure good health and healthy ageing.

Keywords: Ageing; Oxidative Stress; Free Radical; Reactive Oxygen Species; Antioxidants

Introduction

Man's physical body ages progressively. Ageing is a complex, unavoidable, universal, biological phenomenon affecting all multi-cellular organisms and probably common also among unicellular organisms, including protozoa, yeast, and bacteria [1, 2]. Our understanding on ageing is still quite limited but progressive. As a complex biological process, ageing involves a variety of factors such as genes, environment and eating habits [3]. This brings about the variations in lifespan across different geographical locations.

The process of ageing involves a progressive decline in the biological functions of cells and organs causing diseases and ultimately the death of most organisms over time [4, 5]. Age-related diseases such as cardiovascular diseases, cancer, stroke etc. and death are some inevitable events occurring during the ageing process and this gives the idea that ageing is undesirable and needs to be treated [6]. Recent advances in medical sciences, nutritional and hygiene improvements have profoundly increased life expectancy and lifespan [7]. Life expectancy is the average total number of years that a human expects to live, while life span is the maximum number of years that a human can live [6]. A gain in life expectancy could raise the population of elderly people and increase the incidence of age-related chronic diseases. The overall impact will be dependence, high social costs and pressures on healthcare systems [1].

Theories of Ageing

There are many biological theories proposed to describe the causes of ageing and all of them can be basically grouped genetic mutations, wear and tear, and cellular waste accumulation theories [8]. The Stochastic Theory of Ageing (STA) derived mainly from the wear and tear perspective suggests that ageing occurs due to accumulation of unrepaired damages to cells over time leading to age-related reduction in organ and system function. The damages could arise from constant exposure to infections, wounds and toxins [3]. The Free Radical Theory of Ageing (FRTA) or Oxidative Stress Theory of Ageing (OSTA), first proposed by Denham Harman in 1956, advances that an accumulation of damages due to oxidative stress from free radicals has negative impacts on the body and causes ageing and age-related diseases [3, 5, 9].

There is a strong relationship with FRTA and other theories, namely, the Mitochondrial Decline Theory of Ageing (MDTA) and the Mitochondrial Free Radical Theory of Ageing (MFRTA) because the age-related alterations in mitochondrial structure and function result in increased production of free radicals in the mitochondria [3, 10]. Protein misfolding and aggregation also contribute profoundly to the ageing process by increasing the accumulation of ubiquitinated proteins, development of neurodegenerative diseases and ultimately reducing the lifespan as put forward by the Decline Theory of Ubiquitin Proteasomal System (UPS) [3]. The Genetic Theory of Ageing (GTA) posits that longevity depends mainly on the genes as shown in the single gene mutation researches leading to elongated lifespan in Drosophila (fruit fly), Caenorhabditis elegans (roundworm) and rodents. As earlier stated, ageing is a complex process. A single theory may not completely explain the complicated interplay of genetic, environmental and nutritional factors involved in the process of ageing [3].

There is a major interest in understanding the biochemical principles and mechanisms involved in ageing in order to provide medical and dietary products which can afford safe, effective and practical methods for increasing longevity and quality of life during ageing [11, 12]. Research on free radicals and antioxidants can effectively contribute to understanding and possibly delay the ageing process. Consequently, there have been a significant number of studies within these areas. This paper describes the inevitable ageing process and possible elongation of lifespan by taking a fresh look at recent current research on the interplay of reactive oxygen species generation and antioxidant system in maintaining good health and vitality [12].

Reactive Oxygen Species

Reactive oxygen species (ROS) are group of very reactive molecules including free oxygen radicals such as superoxide anion, hydroxyl radical, and non-radical oxygen derivatives such as hydrogen peroxide [13, 14]. They are more abundant than other free radicals and could be beneficial in

defense response [3]. ROS are produced endogenously in the mitochondria during aerobic respiration and subsequently oxidize macromolecules such as lipids, proteins and nucleic acids [5, 9, 10]. The major exogenous sources of ROS include ultraviolet radiation, smoking and air pollution [15].

The negative impacts of ROS on these macromolecules include disruption of cell membrane permeability, cellular dysfunction, mutagenesis, protein denaturation and inactivation [3]. All aerobic organisms use oxygen as an oxidant, but oxidation of macromolecules and structures does not occur as molecular oxygen is less reactive. However, the generation of these free oxygen radicals and other non-radical oxygen agents which are highly reactive predisposes the body to harmful outcomes [2]. Cells and organisms are exposed to oxidative stress when there is increased ROS generation that overwhelms and alters the body's ability to cope [1].

Through the process of oxidative phosphorylation, the mitochondria produce and supply most cellular energy in the form of adenosine triphosphate (ATP). This involves the coupling of electron transfer with proton transport, giving rise to a proton gradient between the mitochondrial matrix and inner membrane. Most of the cell's oxygen is used in this process, with only a small fraction escaping from complex I and III of the electron transport chain in the form of the highly unstable superoxide anion. Hydrogen peroxide is produced from dismutation of superoxide by manganese superoxide dismutase (MnSOD). Hydroxyl radical is generated in the reduction of hydrogen peroxide [11, 16, 17]. Other important sources of ROS generation include plasma membrane, peroxisomes and endoplasmic reticulum through the actions of peroxidases, NADPH oxidase, xanthine oxidase, cytochrome P450 monooxygenases and lipoxygenase [1, 16].

Antioxidants and Antioxidant System

The term antioxidant refers to any molecule that can stabilize or deactivate free radicals from attacking cells. The body uses enzymatic and non-enzymatic antioxidant systems to scavenge and mop up free radicals. The enzymatic antioxidant system constitutes the mainline oxidative stress defense system in vivo and includes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GR) [1].

There are two major types of SOD. One is CuZnSOD (SOD1), which mainly exist in cytoplasm, with copper and zinc being present in the active site. The other one is MnSOD (SOD2), located in mitochondrial matrix, with manganese being present in the active site. They can catalyze the reaction to decompose superoxide anion radicals into hydrogen peroxide (H_2O_2), which will then be converted to water and oxygen by CAT or GPx. CAT is one of the most efficient redox enzymes, with iron being present in its active site, mainly found in peroxisome. It can catalyze the conversion of H_2O_2 into water and oxygen. Otherwise, H_2O_2 would be converted to hydroxyl radical, one of the most active and harmful radicals to living cells. GPx is a selenium-containing enzyme, protecting cells and tissues from oxidative damage by removing H_2O_2 with the oxidization of glutathione. On the other hand, GR can convert the oxidized glutathione (GSSG) to its reduced form (GSH) [1, 3].

Glutathione (GSH), thioredoxin, ascorbate, α-tocopherol, phenolics, flavonoids and carotenoids constitute the non-enzymatic antioxidant system [15].

Vitamin C (ascorbic acid) is the major hydrophilic antioxidant and a powerful inhibitor of lipid peroxidation. In membranes, this molecule rapidly reduces α-tocopheroxyl radicals and LDL to regenerate α-tocopherol and inhibit propagation of free radicals. Vitamin E (α-tocopherol) is the main hydrophobic antioxidant in cell membranes and circulating lipoproteins. Its antioxidant function is strongly supported by regeneration promoted by vitamin C. Resveratrol, curcumin, quercetin and other extracts are natural products from plants, known to possess antioxidant effects [1, 2].

Since nutrition has impact on overall mortality and morbidity, the concept of antioxidant supplementation in food has gained popularity. The Mediterranean diet approach emphasizes the consumption of fruits, vegetables and red wines which are all rich in antioxidants for protection

against oxidative damage [2]. Based on the free radical theory of ageing, antioxidants should slow down the process of ageing and prolong the lifespan. This apparently obvious conclusion has stimulated enormous number of studies aimed at finding a relationship between levels of endogenous antioxidants and lifespan of various organisms, and on the effects of adding of exogenous antioxidants on the course of ageing and lifespan of model organisms [2].

Interplay of ROS and Antioxidants in Ageing

The oxidative stress theory of aging has provided a plausible framework that integrates numerous observations on the production, toxic nature and the detoxification of ROS, as well as the variations of these processes with the physiological conditions of cells and organisms and with chronological age. The theory proposes that ageing is caused by the toxic effects of ROS through a vicious cycle in which ROS cause damage to the constituents of mitochondria leading to the generation of more ROS. Many features involved in mitochondrial free radical production include: a strong correlation between chronological age and the level of ROS generation and oxidative damage; loss of mitochondrial function during ageing; enhanced ROS production when mitochondrial function is inhibited; and a strong link between age-dependent diseases and severe oxidative stress [10].

Despite the support for this theory, data from longevity studies on long-lived species and transgenic animal models are not always compatible with the predictions of the theory. This raises a concern for a separation of effects, conclusions and validation of acceptance of the theory. For instance, in transgenic Drosophila and C. elegans, there is a correlation between increased lifespan and resistance to oxidative stress when antioxidant enzymes are over-expressed. But over-expression of antioxidant enzymes in transgenic mice is not enough to elongate the lifespan [15]. Similarly, there are other results that are incompatible with MFRTA. Mutations in SOD-2 of C. elegans increase oxidative stress and surprisingly prolong the lifespan while mice lacking SOD2 and GPx1 did not show a shortened lifespan [10]. Many studies have focused on the possibility of using antioxidant agents such as vitamins, especially vitamins C and E, and synthetic compounds as therapies to reduce oxidative stress and prolong the lifespan of test organisms [2, 16]. In vitro and in vivo studies on the consumption of nutraceuticals (food substances with health benefits), especially the ones containing high concentrations of antioxidants, show that they can reduce the incidence of cardiovascular diseases, various cancers, and diabetes, though their anti-ageing activity is unknown [3].

It has also been observed that the over-consumption of antioxidant multivitamin supplements has not shown the expected efficiency in reducing oxidative stress-mediated diseases, rather they have been implicated in increasing mortality rates [5, 15]. This could result from lack of effectiveness of antioxidants, inadequate dose and/or timing of antioxidant supplementation, poor bioavailability, heterogeneous nature of internal environments, antioxidant status of the study population, and untargeted delivery of the antioxidant compound [15, 16].

According to Edrey and Salmon (2014) and Salmon et al., (2010), these possible conclusions could be drawn on the impact of oxidative stress on ageing:

1. Reduced antioxidant expression may not accelerate ageing
2. Increased antioxidant expression may not slow ageing
3. Altering the expression of multiple antioxidants may not affect ageing
4. Altering expression of antioxidant genes in mice may affect the ageing process, but has limited effects on ageing
5. Reduced antioxidant expression may accelerate age-related diseases
6. Increased antioxidant expression may delay age-related diseases

Organisms have developed specific stress response pathways for the protection of cells from oxidative stress by detecting ROS and activating transcription factors that control the expression of genes for oxidative stress defense. It has been observed in long-lived species that there is a higher level of cytoprotection and resistance to oxidative

and chemical stress. Some signaling systems for cellular defense have been linked to the relationship between oxidative stress and antioxidants in the longevity observed in these organisms. One is mediated by the transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2), which in the presence of endogenous and exogenous stressors, links with antioxidant response elements (AREs) and controls the transcription of many cytoprotective genes coding for proteins that detoxify internal and external toxins [11, 19]. Another signaling activity involves the context-dependent roles of tumor suppressor p53, which is involved in apoptosis and senescence in response to different stressors including oxidative stress. In response to low levels of oxidative stress, p53 shows antioxidant activities and ensures cell survival. Alternatively, when there is high oxidative stress, it exhibits prooxidative activities which further leads to cell death. p53 plays these roles by regulating the expression of many genes involved in response to oxidative stress, although the exact mechanism controlling both activities remains unclear [20, 21]. Further elucidation of the mechanisms of these pathways and their influence on the ageing process could give more insight in designing intervention efforts for extending lifespan.

Prevention of free radical generation should precede the costly approach of neutralizing with synthetic antioxidants. Certain interventions and lifestyle changes targeted at modulating mitochondrial function and thus decrease an organism's oxidative stress have been suggested. They include: induction of adaptive responses to stress conditions through hormesis (beneficial actions due to an organism's response to mild stressors); caloric restriction (reduced food intake, without micronutrient malnutrition leading to more efficient electron transport in mitochondria); moderate exercise to increase oxygen consumption, upregulate the free radical defense system and improve insulin sensitivity; and mitochondrial uncoupling to dissipate the chemiosmotic gradient and increase electron transport in the mitochondria so that ROS formation is reduced [15, 20].

Conclusion

The relationship between reactive oxygen species generation and the antioxidant system has been shown to have considerable impact on the ageing process. A perfect balance in these factors will be beneficial in the maintenance of good health and also help in healthy ageing.

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