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Battling the Balance: Oxidative Stress and the Power of Antioxidants

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Abstract

Background: Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidative defenses. ROS, derived from oxygen, are essential in cellular signaling but can also damage cellular macromolecules, including lipids, proteins, and DNA, when produced excessively. This imbalance is associated with aging and a range of diseases, including atherosclerosis, neurodegenerative disorders, diabetes, and cancer.

Aims: The aim of this article is to investigate the mechanisms of oxidative stress, its biological effects, and the role of antioxidants in mitigating oxidative damage. Additionally, the article explores the implications of oxidative stress in various diseases and potential therapeutic strategies.

Materials and Methods: The article involves a comprehensive review of existing literature to elucidate the sources and types of ROS, their mechanisms of action, and the body's enzymatic (e.g., superoxide dismutase, catalase) and non-enzymatic (e.g., vitamins C and E, glutathione) antioxidant defenses. Special attention is given to the biochemical pathways of ROS formation and detoxification.

Results: Findings indicate that ROS are naturally produced during cellular metabolism and play dual roles in physiological and pathological processes. Under stress conditions or exposure to environmental toxins, ROS production overwhelms antioxidant defenses, leading to lipid peroxidation, protein oxidation, and DNA damage. Antioxidants mitigate this damage by neutralizing ROS, maintaining cellular integrity, and reducing the risk of oxidative stress-related diseases.

Conclusion: Oxidative stress plays a pivotal role in aging and the development of chronic diseases. Antioxidants, both endogenous and exogenous, are crucial in managing oxidative damage. Enhancing antioxidant defenses through dietary intake or pharmacological interventions may provide therapeutic benefits and prevent oxidative stress-related pathologies. Further research into targeted antioxidant therapies is recommended to improve health outcomes.

Keywords: Oxidative Stress, Reactive Oxygen Species, Antioxidants, Chronic Diseases.

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INTRODUCTION

Oxidative stress is a multifaceted biological phenomenon characterized by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them through antioxidative systems. ROS, a collective term for chemically reactive molecules containing oxygen, play a dual role in human physiology. They are essential for normal cellular signaling and host defense mechanisms. On the other hand, their overproduction or insufficient detoxification can lead to cellular and molecular damage. This damage arises from the toxic effects of peroxides and free radicals, which attack essential cellular components such as lipids, proteins, and nucleic acids, thereby impairing cell function and viability.

Antioxidative systems encompass a range of enzymatic and non-enzymatic mechanisms that work to detoxify reactive intermediates or repair the damage caused by oxidative stress. These systems are critical in maintaining cellular homeostasis and preventing the harmful effects of ROS. Enzymatic antioxidants, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, play significant roles in converting harmful ROS into less reactive molecules. Non-enzymatic antioxidants, including vitamins C and E, glutathione, and carotenoids, further contribute to reducing oxidative damage by scavenging free radicals and terminating their chain reactions.

In humans, oxidative stress has been implicated in the pathogenesis of numerous diseases. For example, it contributes to the development of cardiovascular diseases such as atherosclerosis by promoting lipid peroxidation and endothelial dysfunction. Similarly, in neurodegenerative conditions like Alzheimer's and Parkinson's diseases, oxidative stress accelerates neuronal damage and death. Other chronic conditions, including diabetes mellitus, cancer, inflammatory disorders, and certain psychological diseases, have also been strongly linked to oxidative stress. Moreover, it is considered a key factor in the aging process, as the cumulative damage from ROS over time contributes to the decline in cellular and organ function associated with aging.[1]

Understanding the mechanisms of oxidative stress and its impact on health has become a critical area of research. Insights into how ROS production is regulated and how antioxidative defenses can be enhanced offer potential strategies for mitigating the detrimental effects of oxidative stress. These approaches may pave the way for novel therapeutic interventions to combat oxidative stress-associated diseases and promote healthy aging.

Free radicals and reactive oxygen species

Free radicals in an atom or group of atoms have one or more unpaired electrons. Free radicals can have positive, negative or neutral charge. They are formed as necessary intermediates in a variety of normal biochemical reactions but when generated in excess or not appropriately controlled, an extensive range of macromolecules. A well-known feature of free radicals is that they have extremely high chemical reactivity which is responsible for their biological activity as well as damaging effect on cells[2].

Oxygen radicals

There are many types of free radicals but those most concerned in the biological system are derived from O_2 and collectively known as ROS. Sequential reduction of molecular O_2 leads to the formation of a group of ROS:

- Super oxide anion (O_2^-)
- Peroxide (O_2^{2-})
- Hydroxyl radicals ($^{\bullet}OH$)

Another radicals derived from O_2 is singlet oxygen ($^{\bullet}O_2$).This is an excited form of O_2 in which one of the electrons jump to superior orbital following absorption of energy[2].

Formation of ROS by stress

O_2 derived radicals are derived constantly as part of normal aerobic life. They are formed in mitochondria as O_2 is reduced along the electron transport chain. ROS are also formed as necessary intermediates in a variety of reactions e.g. WBC like neutrophils constantly produce free radicals which are used in host defence to kill invading pathogen. Cell exposed to abnormal environments such as hypoxia generate abundant and often damaging ROS. A number of drugs have oxidising effects on cells and lead to production of O_2 radicals. Stress is well known to generate O_2 within biological system[1]. It generates ROS such as superoxide anions, hydrogen peroxide, and hydroxyl radicals, which show high reactivity to a variety of cellular macromolecules, including DNA, lipids and proteins. The damage caused by oxidative stress is either direct interaction with target molecules or indirectly by the formation of ROS, resulting from the radiolysis of water. As human tissues contain 80% water, the major radiation damage is due generation of ROS.

Biological effects of ROS

ROS are generated in a number of reactions, are essential to life. Evidence suggests that ROS are involved in cellular signaling and can function as mitogens. Yet, despite their beneficial effect, ROS can be toxic for cells. They damage all macromolecules including lipids, proteins and nucleic acids due to the presence of unpaired electrons (e^-).

Free radicals damage in 3 ways[2] :

- **By lipid peroxidation**: The free radicals attack the double bond of unsaturated fatty acids of membrane phospholipids and damage the cellular membranes.
- **By oxidative modification of protein**: The amino acids of protein get oxidized in contact with free radicals causing physical changes in the protein molecules including fragmentation and aggregation. This increases the susceptibility of the protein molecules to proteolytic degradation and thereby damaging functioning of the cell and its organelles.
- **By modification of genomic or cellular structure**: Free radicals cause the lesion of thymine and/or cytosine bases thereby breaking single or double stranded DNA and modify genomic DNA consequently cellular structure. (Figure 1)

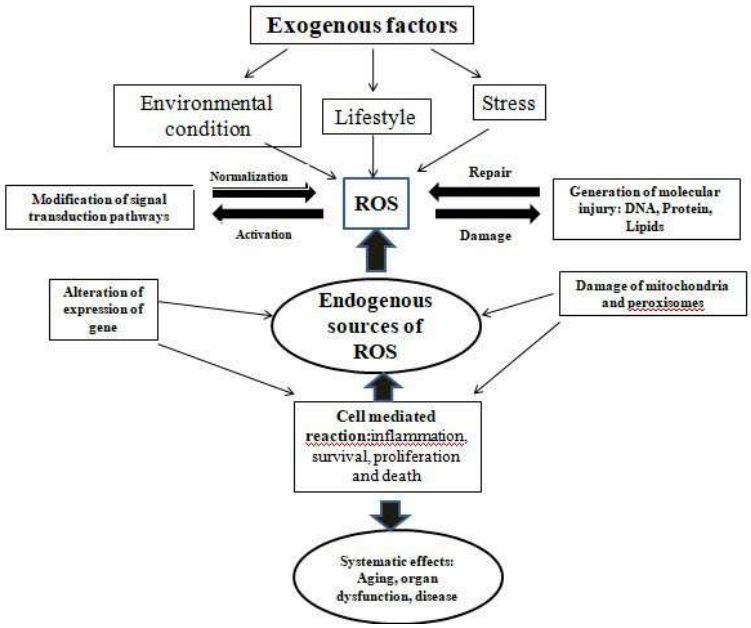

Fig. 1: Mechanism and effects of Reactive Oxygen Species (ROS) in cell

Mechanism of protection against free radicals

Life on earth evolved in the presence of free O_2 and necessarily adapted by evolution of large battery of the antioxidant system. Some of these antioxidants are present in all types of life forms; from bacteria to mammals, indicating their appearance early in the history of life.

Antioxidants

An antioxidant is a molecule capable of slowing or preventing oxidation of other molecules. Oxidation reactions can produce free radicals, which starts chain reactions that damage the cells. Antioxidants terminate these chain reactions by oxidising themselves.

Although oxidation reactions are crucial for life, they can also be damaging. Hence, plants and animals maintain complex systems of multiple types of antioxidants, such as glutathione, vitamin C, vitamin E as well as enzymes such as catalase, SOD and various peroxidases. Low level of antioxidants enzymes cause the oxidative stress and may damage to kill the cells.

a) Enzymatic antioxidants: These groups of enzymes play significant roles in protecting from oxidative stress.

Super oxide dismutase (SOD): These are enzymes that catalyze the conversion of two superoxides to H_2O_2 and O_2. The benefit here is that, H_2O_2 is substantially less toxic than super oxide (O_2^-). SOD accelerates this detoxifying reaction roughly 10,000 fold over non catalyzing reaction.

SOD are the metal containing enzyme that depends on the Mn, Cu, or Zn for their antioxidant

activity. In mammals, Mn containing enzyme is most abundant in the mitochondria, while Zn and Cu containing enzyme forms predominate in the cytoplasm. Interestingly SOD is an inducible enzyme. Exposure of bacteria or vertebrate cells to higher concentration of O_2 results in rapid increase in concentration of SOD[3].

Catalase: This is formed in peroxisomes of eukaryotic cells. It degrades H_2O_2 and O_2 and hence finishes the detoxification reaction started by SOD[3].

Glutathione peroxidase: This is a group of enzymes the most abundant of which contain Se. These enzymes like catalase degrade H_2O_2. They also reduce organic peroxidase to alcohol providing another route for eliminating toxic O_2[4].

Nitric oxide synthase (NOS): NOS is an enzyme in the body that contributes to transmission from one neuron to another, to the immune system and dilating blood vessels. It does so by the synthesis of nitric oxide (NO) from terminal N_2 atom of L-Arginine in the presence of NADPH and dioxygen. NOS is the only known enzyme that binds FAD, FMN, heme, and calmodulin. NOS activates cyclic GMP, which induce smooth muscle relaxation by multiple mechanisms[5]. There are 3 types of NOS; neuronal NOS (nNOS),which was originally identified in nervous system tissues and is present all the time in the cells, endothelial NOS (eNOS) which is also expressed constitutively in the endothelial cells and synthesizes NO needed for the regulation of blood pressure, and inducible NOS (iNOS) which is found at the site of chronic inflammation.

b) Non enzymatic antioxidant:

The non enzymatic antioxidants having particular importance are:

Vitamin E: This is the major lipid soluble antioxidant and plays a vital role in protecting membranes from oxidative damage. Its primary activity is to trap peroxyradicals in cellular membranes.

Vitamin C: Also called Ascorbic acid, is a water soluble antioxidant that can reduce free radicals from a variety of sources. It also appears to participate in recycling vitamin E radicals.

Glutathione: It may be the most important intracellular defence against damage by ROS. It is tri-peptide (glutamyl-cysteinyl-glycine). These cystein provides protection against exposed free radicals i.e. very reactive, providing an abundant target for free radical attacks. Reaction with radicals oxidise glutathione, but the reduced form is regenerated in a redox cycle involving glutathione reductase and electron acceptor NADPH[6].

Carotenoids (β-Carotene)

These are mainly colored pigments present in plants and microorganisms. Epidemiological studies have revealed that a diet rich in carotenoids is correlated with a lower risk of age-related diseases[7]. Primarily, β-carotene has been found to react with peroxyl (ROO.) to prevent damage in lipophilic compartments hydroxyl (.OH), and superoxide radicals[8]. The antioxidant activity of carotenoids arises due to their ability to delocalize unpaired electrons, and thus quench singlet oxygen without degradation. The efficacy of carotenoids with respect to physical quenching is related to the number of conjugated double bonds present in the molecule. Both β-Carotene and retinoic acid are capable of regulating different transcription factors, β-Carotene inhibits the oxidant-induced NF-κB activation and interleukin (IL)-6 and tumor necrosis factor-α production. On the other hand, retinoic acid can affect cell, arrest cell cycle, or both[9-13].

Melatonin

This is a neurohormone that is derived from tryptophan mainly in the pineal gland. One of the major functions of melatonin is scavenging free radicals in oxygen metabolism, thereby potentially protecting against free radical-induced damage to DNA, proteins and membranes. Owing to these properties, it has the potential to play an important role in the reduction of free radical-mediated diseases[10].

In addition to these big three, there are numerous other small molecules that act as antioxidant eg. bilirubin, uric acid etc.

CONCLUSIONS

Present research has led to a universal agreement that oxidative damage to proteins, lipids, and DNA occurs as a result of ROS overproduction. These are highly reactive due to the unpaired electrons in their structure that allow them to react with several biological macromolecules in cell, thus altering their functions. ROS are produced by cellular metabolic reactions that use oxygen and shift the balance in oxidant/antioxidant status in favour of the oxidants. A variety of environmental factors, such as air pollutants or cigarette smoke, can result in the production of ROS, which can also affect

the expression of several genes by upregulation of redox-sensitive transcription factors and chromatin remodelling through alteration in histone acetylation/deacetylation. The human body deals with the pathological effects of ROS by utilizing the endogenous antioxidant enzymatic system and by the ingestion of exogenous antioxidants in the diet. If the oxidative stress exceeds the protection afforded by antioxidants, the aging process and some of the diseases associated with it such as cardiovascular diseases, neurodegenerative diseases, diabetes and cancer can accelerate. Regulation of redox state is critical for cell viability, activation, and proliferation, as well as organ function.

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