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Review

ROLE OF OXIDATIVE STRESS IN BIOLOGICAL SYSTEMS

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Abstract: *Oxidative stress is a phenomenon wherein there is an imbalance between the rate of oxidant formation and its elimination from the body. It has been known to be a promoting factor of various acute and chronic diseases, some of which are lethal. Oxidative stress usually occurs when the generation of oxidants, as a byproduct of the metabolic processes is much higher than usual. However, several exogenous sources such as pollution and alcohol have been known to be major factors in oxidative stress. Although the human body produces several antioxidants their inadequacy can be combatted by the consumption of food rich in antioxidants. The following review briefly highlights the generation of free radicals in the body, their effect on biomolecules and the role of oxidative stress in the human body.*

Keywords: *antioxidants, glycoxidative damage, Oxidative stress, reactive oxygen species (ROS), reactive nitrogen species (RNS)*

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1. Introduction

Oxygen is the most vital element required for life. The process of oxidation-reduction during metabolism generates free radicals or oxidants. The balance between the rate of oxidant formation and their elimination is essential for the systematic functioning of biological processes [1]. An imbalance in this rate may be caused due to a certain disturbance in the endogenous system or exogenous factors such as unhealthy diet, smoking, medicinal side-effects, etc. This phenomenon of imbalance has been called oxidative stress [2].

Oxidants can be grouped as radicals and non-radicals. Both reactive oxygen species (ROS), as well as reactive nitrogen species (RNS), can exist in radical and non-radical form. Radicals can exist independently and contain one or more unpaired electron in the valence shell. Superoxide ($O_2^{\cdot-}$), Peroxyl radical ($ROO^{\cdot}$), Alkoxy radicals ($RO\cdot$), Nitric oxide (nitrogen monoxide) ($NO^{\cdot}$), Nitrogen dioxide ($NO\cdot_2$) and Hydroxyl (-OH) ions are some of the examples of radical oxidants [2, 3]. They are highly reactive and attain stability either by donating or accepting electrons, whereas non-radical oxidants are lesser reactive but participate in free radical reactions. Nonradical oxidants include Hydrogen peroxide (H_2O_2), Hypochlorous acid (HOCl), Ozone (O_3), Singlet oxygen ($^1O_2$), Nitrous acid (HNO_2), Organic peroxides (ROOH), Aldehydes (HCOR), Peroxynitrite (ONOOH), etc [1,3].

2. Generation of Free Radicals

Free radicals may be generated inside the body, i.e. endogenously as a by-product of aerobic metabolism while exogenous sources can be related to the individual's lifestyle and environment (Fig.1.). During normal metabolism, each cell produces approximately 20 billion oxidants per day. The insufficient reduction of oxygen in mitochondria during the electron transport chain (ETC) can lead to the formation of hydrogen peroxide and hydroxyl radicals. As a self-defense mechanism, white blood cells produce nitric oxide (NO), superoxides and H_2O_2 to combat with the pathogenic microorganisms. Moreover, during the degradation of fatty acids, peroxisomes may produce hydrogen peroxide as by-products. Usually, this hydrogen peroxide is degraded in the cell by catalase. However, under certain conditions, it might escape the catalysis and contribute to oxidative stress. Furthermore, cytochrome P450 enzymes produce oxidant as a defense against ingested toxic chemicals [4].

The exogenous sources may include inhalation of free radicals present in the environment from ionizing radiations (Ultraviolet light), automobile exhaust (mainly ozone and nitrous oxide), burning of certain substances, etc. These factors have been known to lower the level of antioxidants in the body thereby contributing to oxidative stress [4]. Exposure to air pollution or smoke generates oxygen radicals while breathing. Cigarette smoking (active or passive), consumption of alcohol and unsaturated fat may put at risk the natural antioxidant system in the body thereby contributing to oxidative stress [1, 4].

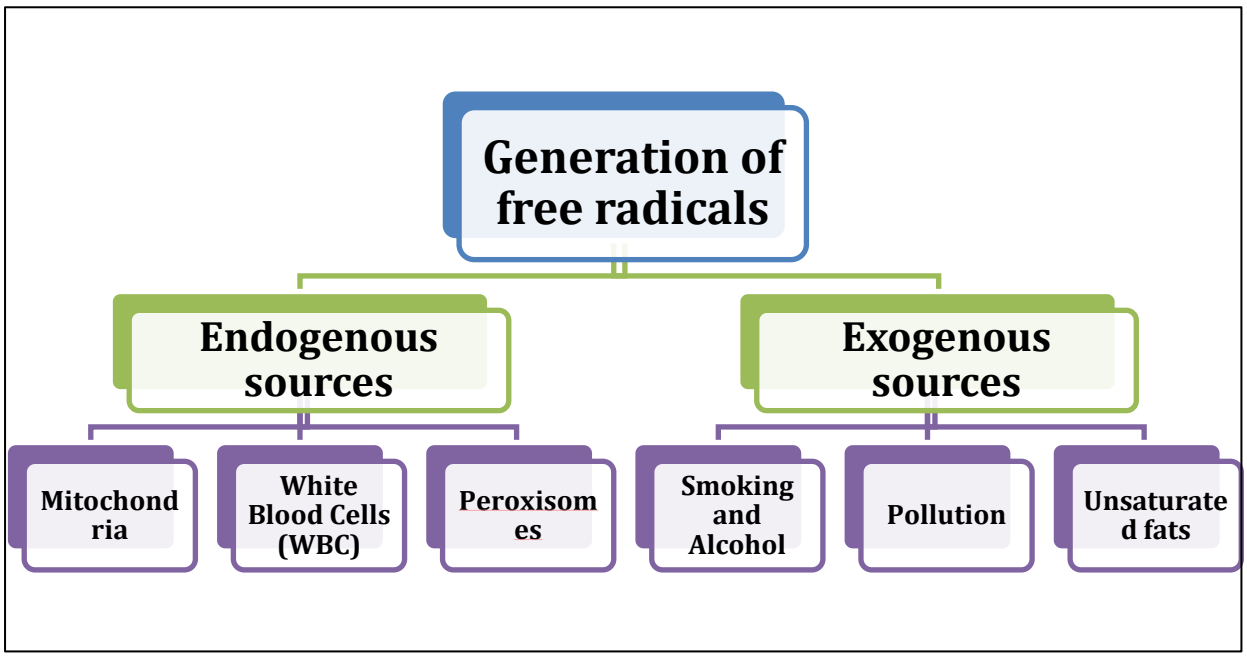

Figure 1. Sources for the generation of free radicals in the human body

3. Mechanism of action of free radicals

Most of the biomolecules and biochemical processes are affected by free radicals. However, the three major classes of biomolecules, i.e. nucleic acids, proteins, and lipids are severely affected by oxidative stress. These oxidized biomolecules may independently or simultaneously contribute to diseases affecting human health [5].

3.1. Nucleic acid

Since ROS is generated in mitochondria, the susceptibility of oxidative damage to the mitochondrial DNA is higher than nuclear DNA. Nitrogenous bases, as well as deoxyribose sugar, are adversely affected creating single and double-stranded breaks. Several adducts are formed by the attack of OH• radicals on purine and pyrimidine such as 5-hydroxy-6-hydro-cytosine, 8-hydroxydeoxy guanosine, 5-formyl uracil, etc. Of all the free radical-induced adducts, the presence of 8-hydroxydeoxy guanosine indicates oxidative DNA damage [3, 5].

Due to the single-stranded structure, RNA is more adversely affected by oxidative stress than DNA. The most studied adduct of RNA is the 7, 8-dihydro-8-oxo-guanosine (8-oxoG) and its linkage has been established with Alzheimer's, Parkinson's and other neurodegenerative diseases [2, 5].

3.2. Proteins

ROS mediated protein oxidation is usually determined by the presence of carbonyl groups. Different amino acids in the protein might get affected leading to conformational changes which may alter or decrease the function of the oxidized proteins [3, 4].

3.3. Lipids

Membrane lipid peroxidation is one of the conditions which may lead to a series of disorders. The decrease in membrane fluidity is observed during lipid peroxidation which further leads to the inactivation of membrane-bound proteins [4].

4. Effect of oxidative stress on human health

Oxidative stress has been known to promote the induction of several acute and chronic disorders some of which may be degenerative or fatal (Table.1).

4.1. Cancer

Oxidative stress can cause direct damage to various biomolecules. Oxidative DNA damage has now been proven to be a prerequisite in chromosomal abnormalities and oncogene activation thereby causing tumor genesis and/or carcinogenesis [6]. DNA-protein crosslinks, deformity in sugar and base structure are few of the structural changes induced by ROS. According to Hattori et al., 8-hydroxy-2-deoxyguanosine is a suitable biological marker for oxidative stress. Incessant oxidative stress may affect the proteome to cause an alteration in the protein structure [7]. This may generate abnormalities in the structure and function of the proteins such as phosphatases and kinases, Loss, gain or switch in function of these enzymes lead to uncontrolled cell growth [8]. Oxidative stress has been correlated with cancer mainly of the breast, colon and prostate [4].

4.2. Cardiovascular diseases

Oxidative stress acts as a triggering component for the formation of cholesterol plaque in the walls of arteries. This condition is called atherosclerosis and cause an obstruction in the blood flow [9]. Moreover, augmented levels of superoxide anions have been reported to have a direct effect on the pathogenesis of atherosclerosis. One of the theories suggests that these superoxide anions cause oxidative modifications in low-density lipoproteins (LDL) leading to atherosclerotic lesions and lipid accumulation [10].

4.3. Diabetes

High level of sugar in blood or hyperglycemia is known to elevate ROS levels leading to discrepancies in the normal functioning of metabolic pathways. One such example is the decrease in the activity of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) which is one of the key enzymes of

one of the major carbohydrate catabolism, i.e. Glycolysis, by modifying it with ADP-ribose polymers [11]. The islets β-cells of the pancreas get adversely affected when interacted with hydrogen peroxide and superoxide anions that cause lower or inefficient insulin activity [12].

4.4. Inflammation

Activation of transcription factors like NF-kappa B causes inflammation when stimulated by oxidants. Biswas has stated inflammation and oxidative stress to be a tightly linked pathophysiological process wherein one can act as the inducing factor for the other [13].

Endothelial dysfunction and tissue injury can occur at the site of inflammation with an increased number of ROS [14]. This can be exemplified with the pathogenesis of rheumatoid arthritis, the chronic inflammation of joints and the surrounding tissues, which is caused due to the formation of ROS and RNS at the inflammatory site [15].

4.5. Neurodegenerative disorders

The high lipid content, as well as a high level of oxygen consumption by the Central Nervous System (CNS), increases its susceptibility to oxidative stress. The decrease in membrane fluidity by lipid peroxidation increases the permeability of Ca^{2+} which affects the triggering of neurotransmitter release [16]. Huntington's, Alzheimer's, Parkinson's disease, amyotrophic lateral sclerosis (ALS), memory loss, depression, and multiple sclerosis are some of the few diseases resulting from oxidative stress [1, 5].

4.6. Obesity

A decrease in vasodilatory response to acetylcholine in obese patients has been observed as a result of the induction of oxidative stress [17]. Overweight leads to irregularity in the function of adipose tissue, which in turn facilitates hyperglycemia acting as a contributing factor in type-2 Diabetes mellitus [18]. Furukawa et al. propose that the chance of obesity-associated metabolic syndrome is proportional to the increase in the level of oxidative stress [19].

4.7. Respiratory diseases

Inflammation of the respiratory tract has been associated with periodic worsening of asthma**.** It has been observed that there has been an increase in hydrogen peroxide and isoprostanes levels in sputum and exhaled air during an allergic reaction [20].

Table 1. Diseases caused due to Oxidative stress

Disease/ Disorder	Particulars	References
Cancer	Colorectal, breast, prostate	[5, 6]
Cardiovascular diseases	Atherosclerotic lesions and lipid accumulation	[9, 10]
Diabetes	Lower or inefficient insulin activity	[11, 12]
Inflammation	Endothelial dysfunction and tissue injury, Rheumatoid arthritis	[13, 14]
Neurodegenerative disorders	Huntington's, Alzheimer's, Parkinson's disease, ALS, memory loss, depression, multiple sclerosis	[4, 16]
Obesity	Obesity-associated metabolic syndrome	[17, 18]
Respiratory diseases	Asthma	[20]

5. Antioxidants

Antioxidants are the substances that help to maintain the stability in oxidative stress by preventing oxidation [21]. The human body produces a wide range of antioxidants which can be grouped into enzymatic and non-enzymatic antioxidants (Figure 2).

Superoxide dismutase or SODs (EC 1.15.1.11), catalases (EC 1.11.1.6) and glutathione peroxidase or GSH-Px (EC 1.11.1.9) are the major enzymatic antioxidants in the body. SODs are widely expressed in the lungs and help in the dismutation of superoxides. Of the three types of SODs, MnSOD and CuZn-SOD are expressed in mitochondrial and extracellular matrix respectively, while certain SODs are expressed extracellularly and hence called EC-SOD. Catalases and GSH-Px help in the reduction of H_2O_2 produced during the action of SODs or during ETC [21, 22].

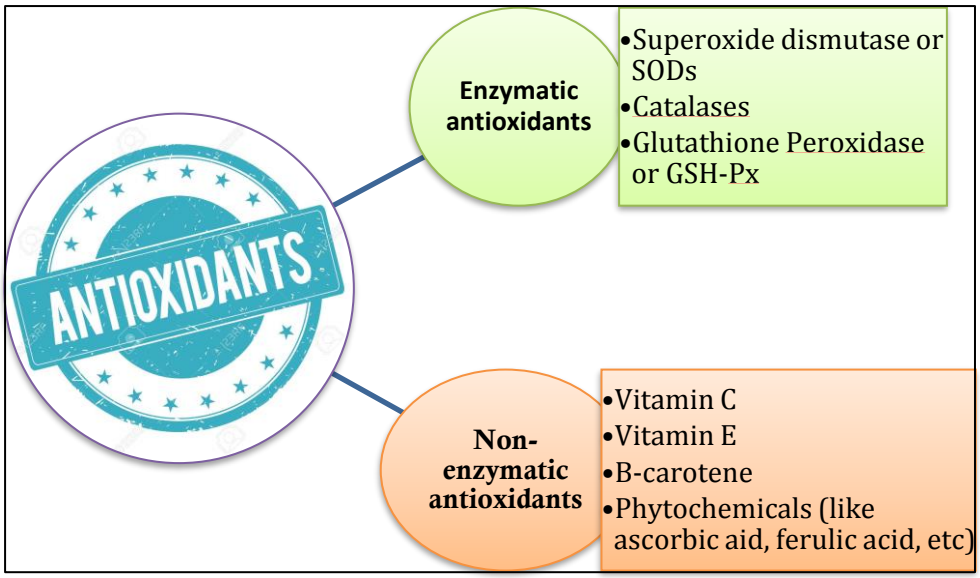

Figure 2. Types of antioxidants

Vitamin C is one of the important non-enzymatic antioxidants in the body. Being water-soluble, it provides an aqueous phase for free radical scavenging. α-Tocopherol OR Vitamin E is a membrane-bound active form of vitamin E antioxidant which inhibits free radical formation. Phytochemicals in the plant have been proven to show antioxidant activity. B-carotene acts as an effective antioxidant against peroxyl (ROO•), hydroxyl (•OH), and superoxide (O_2^{-}) radicals [22, 23]. The phytochemicals are being tested for suitability as it appears to be a promising candidate for antioxidant supplements [23].

6. Conclusion

Over-production of oxidants or unavailability of antioxidants can cause an imbalance in the free radical generation and their detoxification leading to oxidative stress. Oxidative stress seems to be playing a major role in inflammation that further acts as a contributing factor to a plethora of diseases. The human body can combat oxidative stress by maximizing the availability of natural antioxidants. However, antioxidants can be supplemented to the human body from a wide range of drugs synthesized from chemical as well as natural sources. However, being environmentally friendly, natural antioxidants like phytochemicals are considered to be more convenient and safer for consumption.

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