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Free Radicals, Oxidative Stress and Diseases An Overview

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ABSTRACT

Free Radicals are molecules with an unpaired electron. They are generated in our body by various endogenous systems, exposure to different physicochemical conditions or pathophysiological states. At low levels, free radicals exert beneficial effects while at high concentrations, they generate oxidative stress and damage all cell structures. This review deals with the sources of the free radicals, their beneficial and deleterious effects on cellular activities; it highlights the role of free radicals and oxidative stress in various physiological states like cancer, cardiovascular diseases, Alzheimer's disease, kidney disease, etc. The harmful effect of free radicals is neutralized by antioxidants, which prevents oxidative damage by reacting with free radicals. Therefore, the best remedy is to increase the intake of natural antioxidant.

Keywords: Free radicals, Oxidative stress, Disease, Reactive Oxygen Species.

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INTRODUCTION

Free Radicals are molecules having an unpaired electron. These molecules become highly reactive due to presence of free electron. Free radicals are continuously produced by the body's normal use of oxygen. Oxygen is an indispensable element for life. When cells use oxygen to generate energy, free radicals are produced by the mitochondria as the by-product. These by-products are generally reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) that result from the cellular redox process. The free radicals have a special affinity for lipids, proteins, carbohydrates and nucleic acids and have play important role in aging and various human diseases.

At low or moderate levels, ROS and RNS exert beneficial effects on cellular responses and immune function. At high concentrations, they generate oxidative stress, a deleterious process that can damage all cell structures. Oxidative stress plays an important role in the development of cancer, arthritis, aging, autoimmune disorders, cardiovascular and neurodegenerative diseases. The human body naturally produces antioxidants to counteract oxidative stress. Antioxidants are either naturally produced by body or externally supplied through foods or as supplements. Endogenous and exogenous antioxidants prevent and repair damages caused by ROS and RNS and act as “free radical scavengers”. Thus antioxidants can enhance the immune defense and lower the risk of cancer and degenerative diseases caused due to oxidative stress.

The theory of oxygen-free radicals has been known about fifty years ago. However, only within the last two decades, there has been an invention regarding their roles in the development of diseases and the health protective effects of antioxidants.

This review deals with the sources of the free radicals, it examines their beneficial and deleterious effects on cellular activities, defensive systems against free radicals, free radical diagnosis. It highlights the role of free radicals and oxidative stress in various physiological states like cancer, cardiovascular diseases, Alzheimer’s disease, cardiac reperfusion abnormalities, kidney disease etc.[1-4]

SOURCES OF FREE RADICALS

Free radicals and other reactive oxygen species (ROS) are generated either during metabolic processes in the human body or from external sources such as exposure to x-rays, ozone, cigarette smoking, air pollutants and industrial chemicals [5-6]. The sources include endogenous production from mitochondria [7], microsomes [8], enzymes or enzymatic reactions [8-10] phagocytes[11] and metal ions[12-13]. Exogenous sources of free radicals include cigarette smoking [8, 14], alcoholism [15] toxins and drugs[16-17] and ionizing radiation [8].

BENEFICIAL ROLE OF FREE RADICALS

- Free radicals control the flow of blood through our arteries, to fight infection, to keep our brain alert.
- Phagocytic cells involved in body defense, produce and mobilize oxygen free radicals to destroy the bacteria and other cells of foreign matter which they ingest.
- Similar to antioxidants, some free radicals at low levels are act as signaling molecules, i.e. they are responsible for turning on and off of genes.
- Free radicals such as nitric oxide and superoxide are produced in very high amount by immune cells to poison viruses and bacteria.
- Some free radicals kill cancer cells. Certain cancer drugs act by increasing the free radical amount in body.

DEFENSIVE SYSTEMS AGAINST FREE RADICALS

All aerobic forms of life maintain elaborate anti-free-radical defense systems, also known as antioxidant systems.

Enzymes

The defense enzyme, superoxide dismutase (SOD) changes superoxide molecule to a much less reactive form. SOD and another important antioxidant enzyme, set the glutathione system, work within the cell. Circulating biochemical's like uric acid and ceruloplasmin react with free radicals in the intercellular spaces and bloodstream.

Self repair

The body also has systems to repair or replace damaged building blocks of cells. Most protein constituents in the cell are completely replaced every few days. Scavenger enzymes break used and damaged proteins into their component parts for reuse by the cell.

Nutrients

Vitamins and other nutrients neutralize the oxide radicals and serves as second line of defense. Some nutrients used are Vitamins C and E, beta-carotene, and bioflavonoid [18].

FREE RADICAL DIAGNOSIS

Free radical can be diagnosed by following techniques:

i. Electron Spin resonance

ii. Nuclear magnetic resonance using a phenomenon called CIDNP

iii. Chemical labeling: This includes the use of X-ray photoelectron spectroscopy (XPS) or Absorption spectroscopy.

iv. Use of free radical markers: Stable, specific, or nonspecific derivatives of physiological substances can be measured. e.g. lipid peroxidation products (isoprostanes), amino acid oxidation products (meta-tyrosine, ortho tyrosine, hydroxyl-Leu dityrosine), peptide oxidation products (oxidized glutathione).

v. Indirect method: Measurement of the decrease in the amount of antioxidants (reduced glutathione-GSH) [19].

FREE RADICALS AND DISEASES

Cancer

Like radiation and carcinogens, oxidation of free-radical breaks strands of DNA. Some mistakes occurs during oxidation, leading mutations in genes. These genetic mutations can cause cancers. The age-related increase in cancer rates might have something to do with an age-related rise in oxidative damage to DNA [20].

Neurodegenerative disease

Oxidative stress leads to neurological diseases like Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS), memory loss, and depression. In Alzheimer's disease, numerous experimental and clinical studies have demonstrated that oxidative damage plays a key role in the loss of neurons and the progression to dementia. A toxic peptide ß-amyloid present in Alzheimer's patients' brain is due to oxidative stress and plays an important role in the neurodegenerative processes [21-24].

Kidney

Mitochondrial free radical production induces lipid peroxidation during myohemoglobinuria. Iron catalyzed free radical formation and lipid peroxidation are accepted mechanisms of heme protein-induced acute renal failure. However, the sources of those free radicals which trigger lipid peroxidation in proximal tubular cells remain unknown [20].

Oxidative stress plays an important role in different renal diseases such as glomerulonephritis, tubulointerstitial nephritis, chronic renal failure, proteinuria, uremia etc. Certain drugs like cyclosporine, tacrolimus (FK506), gentamycin, bleomycin, vinblastine, causes the nephrotoxicity, is mainly due to oxidative stress via lipid peroxidation [25- 29]. Heavy metals (Cd, Hg, Pb, As) and transition metals (Fe, Cu, Co, Cr)-induced different forms of nephropathy and carcinogenicity are strong free radical inducers in the body [30- 31].

Ageing

The "Free Radical Theory of Aging" is the most popular theory of aging. This theory was first

proposed by Dr. Denham Harman, and postulates that aging results from an accumulation of changes caused by reactions in the body initiated by highly reactive molecules known as "free radicals." The major cause of aging, disease development or death is the changes induced by free radicals in our body [32].

Diabetes mellitus

During diabetes, persistent hyperglycemia causes increased production of free radicals, especially reactive oxygen species (ROS), for all tissues from glucose auto-oxidation and protein glycosylation. The increased production or /and decreased destruction by nonenzymic and enzymic catalase (CAT), reduced glutathione (GSH), and superoxide dismutase (SOD) antioxidants leads to increase in the level of ROS, in diabetes. The level of these antioxidant enzymes critically influences the susceptibility of various tissues to oxidative stress and is associated with the development of complications in diabetes [33].

Cardiovascular Diseases

Etiology of Cardiovascular disease (CVD) is associated with a variety of risk factors for its development including hypercholesterolaemia, hypertension, smoking, diabetes, poor diet, stress and physical inactivity. Further the in vivo and ex vivo studies have revealed the role of oxidative stress in a number of cardiovascular diseases such as atherosclerosis, ischemia, hypertension, cardiomyopathy, cardiac hypertrophy and congestive heart failure [34- 37].

Recently, research data has raised a passionate debate as to whether oxidative stress is a primary or secondary cause of many cardiovascular diseases [16].

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease characterized by chronic inflammation of the joints and tissue around the joints with infiltration of macrophages and activated T cells. The pathogenesis of this disease is due to the generation of the ROS and RNS at the inflammation site. Oxidative damage and inflammation in various rheumatic diseases were proved by increased levels of isoprostanes and prostaglandins in serum and synovial fluid compared to controls [38-40].

Cataract

Oxidation of lens protein and lipid leads to oxidative stress is an initiating factor for the development of maturity onset cataract. H2O2 is one of the oxidant involved in cataract formation. The young lens has substantial reserves of antioxidants to prevent lens damage and proteolytic enzymes, proteases that selectively remove damaged proteins. The function of the lens with aging is related to depleted antioxidant reserves, diminished antioxidant enzyme capabilities and decreased proteases [41-42].

Pulmonary disease and oxidative stress

Inflammatory lung diseases such as chronic obstructive pulmonary disease (COPD) and asthma are characterized by systemic and local chronic inflammation and oxidative stress. Oxidants may cause the activation of different kinases and redox transcription factors such as NF-kappa B and AP-1 and enhances the inflammation [43-46].

Atherosclerosis

High levels of ROS (e.g. the highly reactive hydroxyl radical) exert antiangiogenic effects and promote arteriosclerosis and endothelial cell death. The oxidative modification hypothesis of atherosclerosis centres on the well-known association between low-density lipoprotein (LDL) cholesterol and atherosclerosis and, in particular, on the uptake of oxidized LDL by macrophages within the arterial wall to form foam cells, the earliest stage in atherogenesis. Oxygen free radicals increases plasma levels of MDA and nitrite in patients of myocardial infarction that results into endothelial damage, and elevated superoxide dismutase levels in these patients may indicate that the body attempts to combat this oxidative stress by raising level of anti-oxidants. Antioxidant compounds found in fruits and vegetables are vitamin C, carotenoids, and flavonoids, may influence the risk of CVD by preventing the oxidation of cholesterol in arteries [47-50].

CONCLUSION

Monitoring and rapid detection of free radical is necessary to prevent the spread of various diseases. So the detailed knowledge regarding the hazards and benefits of free radicals must be known so that we can easily combat against the hazardous effect of free radicals and can live a healthy life.

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