Review Article

Effect of Free Radicals & Antioxidants on Oxidative Stress: A Review

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Abstract

Recently free radicals have attracted tremendous importance in the field of medicine including dentistry and molecular biology. Free radicals can be either harmful or helpful to the body. When there is an imbalance between formation and removal of free radicals then a condition called as oxidative stress is developed in body. To counteract these free radicals body has protective antioxidant mechanisms which have abilities to lower incidence of various human morbidities and mortalities. Many research groups in the past have tried to study and confirm oxidative stress. Many authors also have studied role of antioxidants in reducing oxidative stress. They have come across with controversial results and furthermore it is not yet fully confirmed whether oxidative stress increases the need for dietary antioxidants. Recently, an association between periodontitis and cardiovascular disease has received considerable attention. Various forms of antioxidants have been introduced as an approach to fight dental diseases and improve general gingival health. The implication of oxidative stress in the etiology of many chronic and degenerative diseases suggests that antioxidant therapy represents a promising avenue for treatment. This study was conducted with the objective of reviewing articles relating to this subject. A Pub Med search of all articles containing key words free radicals, oxidative stress, and antioxidants was done. A review of these articles was undertaken.

Key words: Free radicals, Oxidative stress, Antioxidants, Superoxide dismutase

Introduction

In recent years there is an increasing awareness among people in prevention of disease especially the role of free radicals in health and disease. Free radicals are continuously produced by the body's normal use of oxygen.[1] Oxygen is an element indispensable for life. When cells use oxygen to generate energy free radicals are produced by the mitochondria. 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 and nucleic acid (DNA).[2]

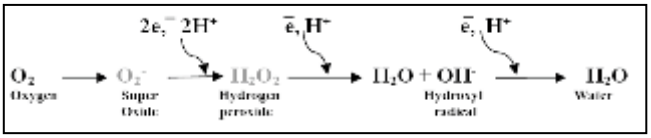
In a normal cell there is balance between formation and removal of free radicals. However this balance can be shifted towards more formation of free radicals or when levels of antioxidants are diminished. This state is called 'oxidative stress' & can result is serious cell damage if the stress is massive and prolonged. Oxidative stress plays a major role in the development of chronic and degenerative diseases such as cancer, arthritis, aging, autoimmune disorders, cardiovascular & neurodegenerative diseases.[3]

The human body has several mechanisms to counteract oxidative stress by producing antioxidants which are either naturally produced in body, or externally supplied through foods and /or supplements. Endogenous and exogenous antioxidants act as free radical scavengers & therefore can enhance the immune defense and lower the risk of cancer & degenerative diseases.[4] Recently it has been claimed that the imbalances in the levels of free radicals & antioxidants in saliva may play an important role in the onset of periodontal diseases, therefore measurement of oxidative stress in saliva represents major intraoral condition and this would provide a more accurate account of the oral environment. [5]

This article deals with the mechanism of formation of free radicals, the diseases caused by free radicals and understanding the disease process at molecular level and it discusses the advantages and inconveniences of the antioxidant supplementation in health maintenance.

Generation of free radicals

Most of the oxygen taken up by the cells is converted to water by the action of cell enzymes. However some of these enzymes leak electrons into the oxygen molecules and lead to the formation of free radicals. They are formed during normal biochemical reaction involving oxygen.



There are two important sources of free radical formation. One of the internal factors i.e. normal cellular metabolism like mitochondrial ETC, endoplasmic reticulum oxidation and many enzymatic activities.[6,7] Other external factors like radiation, oxidation of engine exhaust, carbon tetrachloride, cigarette smoke and oxygen itself. [8]

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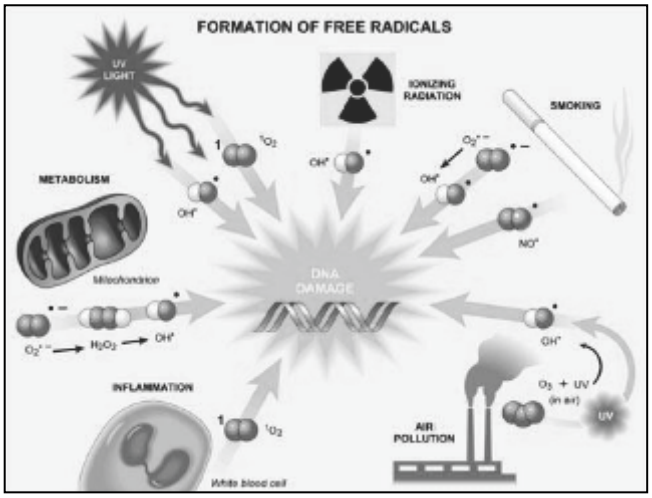

Fig. 1: Sources of free radical formation[9]

Advantages of free radicals

Typically low concentration of ROS is essential for normal physiological functions like gene expression, cellular growth and defense against infection. Sometimes they also act as the stimulating agents for biochemical processes within the cells.[10] Apart from these; ROS also participate in the biosynthesis of molecules such as thyroxin, prostaglandin that stimulate developmental processes. ROS are also used by the immune system. Macrophages and neutrophils generate ROS in order to kill the bacteria that may engulf by phagocytosis.[11]

Disadvantages of free radicals

Free radicals are highly reactive and are capable of damaging almost all types of biomolecules (Proteins, lipids, carbohydrates & nucleic acid). The fact is that free radicals beget free radicals i.e. generate free radicals from normal compounds which continues as a chain reaction. Oxidative stress can arise when cell cannot adequately destroy the excess free radicals formed. These free radicals can damage cell membranes and lipoproteins by a process called as lipid peroxidation. Proteins may also be damaged by ROS/NOS, leading to structural changes and loss of enzyme activity.[12] Free radicals may cause DNA strand breaks which can cause cell mutation. The body has several mechanisms to counteract these attacks by using DNA repair enzymes and or antioxidants.[13] If not regulated properly; oxidative stress can induce a variety of chronic and degenerative diseases.

Free radicals and diseases

1) Periodontitis: Periodontitis is one of the most common oral infections induced by bacteria and bacterial products of dental plaque and is characterized by inflammatory destruction of tooth supporting connective tissues and alveolar bone.[14] Study revealed extensive increase in serum and salivary total lipid peroxide which was a resultant of concomitant increase in ROS production in periodontitis. Periodontitis is a Gram-negative bacterial infection. These bacteria have special enzymes and proteins that enable them to trigger host inflammation. As a result of stimulation by bacterial antigen PMN produces free radicals via respiratory burst as a part of host response to infection.[15] ROS cause periodontal tissue destruction either by degrading the ground substance or by release of collagenases or by release of various inflammatory mediators. Antioxidants remove harmful effects of these free radicals. A delicate balance exists between antioxidant repair systems and pro-oxidant mechanism of tissue destruction, which if tipped in favour of tissue damage, could lead to significant attachment loss.[16]

2) Cancer: Free radicals can damage DNA and cause mutagenicity and cytotoxicity and thus play a key role carcinogenesis. It is believed that ROS can induce mutations and inhibits DNA repair process that results in inactivation of certain tumor repressor genes, leading to cancer.[17]

Lipid Peroxidation plays an important role in control of cell division. The end product of lipid peroxidation, Malondialdehyde (MDA) due to its high cytotoxic and inhibitory action on protective enzymes is suggested to act as a tumor promoter and a co-carcinogenic agent.

3) Inflammatory diseases: Oxidants play a significant role in the pathogenesis of a number of disorders such as inflammation, rheumatoid arthritis, asthma, psoriasis and contact dermatitis leading to oxidative stress. The processes associated with inflammatory responses are complex and often involves ROS. There are many mediators, which initiate and amplify the inflammatory response such as histamine, serotonin, pro-inflammatory cytokines (interleukin-1B (IL-1b) and tumor necrosis factor (TNF-alpha), inflammatory cells (leukotrienes, macrophages), metabolic products of arachidonic acid (thromboxaneA_2, prostaglandins and leukotrienes).[18]

4) Cardiovascular diseases: ROS can stimulate oxidation of LDL, cholesterol, cholesterol derived species, protein modifications which can lead to foam cell formation and atherosclerotic plaques and vascular thrombosis (Heart attack and Stroke).[19]

5) Respiratory diseases: Direct exposure to the lungs to 100% oxygen for a long period is known to destroy endothelium and cause lung edema. This is mediated by free radicals. ROS are also responsible for ARDS, COPD, and asthma etc.[20] Cigarette smoke, as such contains free radicals and further it promotes the generation of more free radicals. The damages caused to lungs in the smokers are due to ROS.

6) Diabetes: Experimental evidence suggests that destruction of islets of pancreas due to accumulation of free radicals is one of the causes for the pathogenesis of insulin dependent diabetes mellitus. Excess generation of mitochondrial ROS due to hyperglycemia initiates a vicious circle by activating stress-sensitive pathways such as NF-κB, p38 MAPK and Jak/STAT, polyol (sorbitol) and hexosamine pathways, PKC and AGEs. Enhanced production of AGEs, sorbitol and proinflammatory cytokines exerts a positive feedback on ROS and RNS synthesis and potentiates PKC-mediated vascular dysfunction by altering gene expression as well as vascular function and structure.[21]

7) Male Infertility: Free radicals are known to reduce sperm motility and viability and thus may contribute to male infertility. The lipid composition of plasma membrane of mammalian spermatozoa is markedly different from mammalian somatic cells. They have very high levels of phospholipids, sterols, saturated and polyunsaturated fatty acids. Therefore sperm cells are particularly susceptible to the damage induced by excessive ROS release. Lipid peroxidation plays a major role in the etiology of defective sperm function. This may lead to the onset of male infertility via the mechanism involving the induction of peroxidative damage to plasma membrane.[22]

8) Ageing process: Mitochondrial ROS production and oxidative damage to mitochondrial DNA results in ageing. The most recent review on free radicals and ageing by Barja emphasizes that caloric restriction is the only known experimental manipulation that decreases rate of mammalian ageing.[23]

9) Neurological diseases: Oxidative stress has been implicated in neurological diseases including Alzheimer's disease, Parkinson's disease, multiple sclerosis, memory loss, depression. Although multiple factors can participate oxidative stress in cells, the neurotransmitter glutamate is the main effecter of this process in the brain, primarily through activation of its ionotrophic receptors. Free radical induced-damage can occur by stimulation of phospholipase A_2 and subsequent release of arachdonic acid. These substances and ROS enhances release of glutamate, thereby promoting a vicious cycle.[24]

10) Nephropathy: Oxidative stress can promote the production of vasoconstrictor molecules and primary salt retention by the kidney. Several hypertensive animal models showed increased activity of nicotine adenine dinucleotide phosphate (NADPH) oxidase, which is the chief source of O_2- in the vessel wall and kidneys. Evidence is presented that chronic renal failure (CRF) is a state of NO deficiency secondary to decreased kidney NO production and/or increased bioinactivation of NO by O_2-. Patients with CRF show decreased endothelium-dependent vasodilatation to acetylcholine.[25]

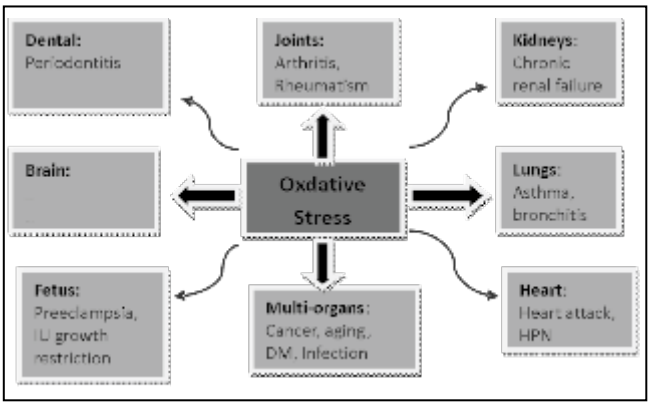

Fig 2: Oxidative stress induced diseases in humans[3]

Antioxidants

Antioxidants are the substances that may protect cells from the damage caused by free radicals. Antioxidants interact with and stabilize free radicals and may prevent some of the damage free radicals might otherwise cause. The antioxidants may be exogenous or endogenous in nature. The endogenous antioxidants can be classified as enzymatic and non-enzymatic. The antioxidant enzymes include Superoxide dismutase (SOD), Catalase (CAT), glutathione peroxidase (GPx), glutathione reducates (GRx).[26]

The non-enzymatic antioxidants are also divided into metabolic antioxidants and nutrient antioxidants. Metabolic includes lipoic acid, glutathione, L-arginine, uric acid, bilirubin etc.[27] While nutrient antioxidant belonging to exogenous antioxidants are compounds which can not be produced in the body and must be provided through foods such as vitamin E,vitamin C, caratenoids, trace elements (Se,Cu,Zn,Mn).[28]

Antioxidant Supplementation

Although cells are equipped with an impressive repertoire of antioxidant enzymes as well as small antioxidant molecules, these agents may not be sufficient enough to normalize the redox status during oxidative stress.[29] Before contemplating antioxidant supplementation, some questions needs to be answered. The most important aspect is to consider whether the patient really needs antioxidant supplementation and if so the rationale behind the decision.

Conclusion

Free radical formation is a continuous process in the human body and there is enough evidence for their involvement in many pathophysiological states, where antioxidant

counteracts the detrimental effect of free radicals. In the future, a therapeutic strategy may be formulated in such a way that where antioxidant capacity of the cells may be used for long term effective treatment. However, many questions about antioxidant supplementation in disease prevention remain unsolved. Further intensive research is needed before this supplementation can be recommended as an adjuvant therapy. As research reveals less antioxidant intake and lower antioxidant levels cause disease, it can be compensated with natural antioxidants in food. A plethora of antioxidant supplements are available over the counter. It is the view of the authors that availability of antioxidants must be regulated by prescription from certified health professionals. The public may however be advised about the advantages of antioxidants and they should be encouraged to take the foods containing fresh fruits, green leafy vegetables, seeds, nuts and vegetable oils which are rich sources of antioxidants. It is always one should remember that over dosage of supplements may cause harm as in large doses antioxidants may act as pro-oxidants.

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