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REVIEW ARTICLE

FREE RADICALS AND HUMAN HEALTH

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ABSTRACT

In recent years, there has been a large quantity of attention toward the field of free radical chemistry. Free radicals reactive oxygen species (ROS) and reactive nitrogen species(RNS) are generated by our body by different endogenous systems, exposure to various physiochemical conditions or pathological states. A balance between free radicals and antioxidants is needful for proper physiological action. If free radicals overwhelm the body's ability to regulate them, a condition known as oxidative stress ensues. Free radicals consequently adversely change lipids, proteins, and DNA and trigger a number of human diseases. Hence application of external source of antioxidants can assist in coping this oxidative stress. Thus, the search for effective, nontoxic natural compounds with antioxidative activity has been intensified in recent years. The attendant review provides a brief overview on oxidative stress mediated cellular damages and role of dietary antioxidants as functional foods in the management of human diseases.

Key Words: Free radicals, Oxidative stress, Antioxidant.

1- INTRODUCTION

A free radical can be defined as any molecular species capable of independent existence that contains an unpaired electron in an atomic orbital. The presence of an unpaired electron results in certain common properties that are shared by most radicals. Many radicals are unstable and highly reactive. They can either donate an electron to or accept an electron from other molecules, therefore behaving as oxidants or reductants (Cheeseman, 1993). The most important oxygen-containing free radicals in many disease states are hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet, hypochlorite, nitric oxide radical, and peroxynitrite radical. These are highly reactive species, capable in the nucleus, and in the membranes of cells of damaging biologically relevant molecules such as DNA, proteins, carbohydrates, and lipids (Young and Woodside, 2001). Free radicals attack important macromolecules leading to cell damage and homeostatic disruption. Targets of free radicals include all kinds of molecules in the body. Among them, lipids, nucleic acids, and proteins are the major targets.

2- Reactive Oxygen Species

Reactive oxygen species (ROS) is a term that encompasses all highly reactive, oxygencontaining molecules, including free radicals. Types of ROS include the hydroxyl radical,the superoxide anion radical, hydrogen peroxide, singlet oxygen, nitric oxide radical,hypochlorite radical, and various lipid peroxides. All are capable of reacting withmembrane lipids, nucleic acids, proteins and enzymes, and other small molecules, resultingin cellular damage. ROS are generated by a number of pathways. Most of the oxidantsproduced by cells occur as:

- A consequence of normal aerobic metabolism: approximately 90% of the oxygenutilized by the cell is consumed by the mitochondrial electron transport system.
- Oxidative burst from phagocytes (white blood cells) as part of the mechanism by whichbacteria and viruses are killed, and by which foreign proteins (antigens) are denatured.
- Xenobioticmetabolism, i.e., detoxification of toxic substances.

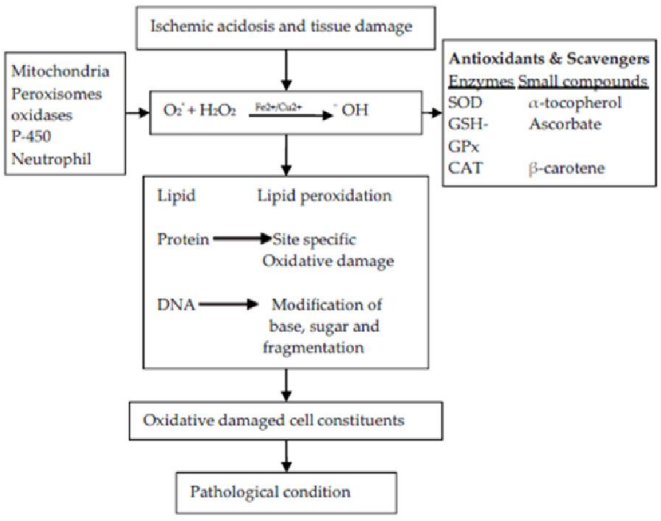

Figure 1. An overall picture of the metabolism of ROS and the mechanism of oxidative tissue damage leading to pathological conditions

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Consequently, things like vigorous exercise, which accelerates cellular metabolism; chronicinflammation, infections, and there illnesses; exposure to allergens and the presence ofsyndrome; and exposure to drugs or toxins such as cigarette smoke, pollution,pesticides, and insecticides may all contribute to an increase in the body's oxidant load (Uday Bandyopudya*et al.,* 1999; Chitra and Pillai, 2002)

3- Sources of reactive oxygen species and free radicals in an organism

All aerobic organisms produce ROS physiologically. The five most productive pathways are involved in regulating the production of ROS/RNS and the resulting effects on signalling cascades. The five mechanisms described produce ROS in a non-regulated mode. However, there are many sources within the cells that are only mentioned.

3.1. Regulated production of reactive oxygen and nitrogen species

3.1.1. Nitric oxide synthase (NOS)

Nitric oxide ($NO^{\bullet}$) is produced from a guanidine nitrogen of L-arginine via electron transfer from NADPH in two successive steps.The enzyme responsible this exists in three isoforms:neuronal (nNOS, type I, NOS-I or NOS-1), endothelial (eNOS, type III, NOS-III or NOS-3) and inducible (iNOS, type II, NOS-II or NOS-2). nNOS and eNOS are constitutively expressed, but their activity is regulated by the intracellular Ca^{2+} concentration. nNOS exhibits NADPH-diaphorase (NADPH-d) activity (Miller, 2004).

3.1.2. NADPH oxidase

3.1.2.1. NADPH oxidase in phagocytic cells

Activated neutrophils and macrophages produce superoxide and its derivatives as cytotoxic agents forming part of the respiratory burst via the action of membrane bound NADPH oxidase on molecular oxygen.

3.1.2.2. NADPH oxidase in nonphagocytic cells

Fibroblasts, endothelial cells, vascular smooth muscle cells, cardiac monocytes and thyroid tissue nonphagocytic NAD(P)H oxidase (similar but not identical to phagocytic NADPH oxidase) produce $O_2^{\bullet-}$ and to regulate intracellular signalling cascades (Giese*et al.,* 2001; Zhao*et al.,* 2007). In most of these, rac1 is involved in the induction of NAD(P)H oxidase activity (Jones*et al.,* 1996; Zweier*et al.,* 1994). Muscle cells and fibroblasts account for the majority of $O_2^{\bullet-}$ produced in the normal vessel wall. The NAD(P)H oxidase isoforms of the cardiovascular system are membrane-associated enzyme that appear to utilize both NADH and NADPH (Giese*et al.,* 2001).

3.1.3. Arachidonate cascade enzymes

3.1.3.1. lipoxygenase (5-LOX)

The enzyme 5-LOX has been identified as an inducible source of ROS production inlymphocytes (Bonizzi*et al.,* 2000; McIntyre*et al.,* 1999), but the evidence for its physiological role in redox signalling isstill scarce.

3.1.3.2. Cyclooxygenase (COX-1)

Cyclooxygenase-1 has been implicated in ROS production through formation ofendoperoxides, which are susceptible to scavenging by some antioxidants in cells stimulated with TNF-α, interleukin-1, bacterial lipopolysaccharide, or the tumor promoter 4-Otetradecanoylphorbol-13-acetate (Dröge, 2002).

3.2. Non-regulated production of reactive oxygen species

3.2.1. Mitochondrial respiration

The four-electron reduction of oxygen occurs within the mitochondrial electron transport system of all cells undergoing aerobic respiration. It is estimated that 2-3% of O_2 consumed by mitochondria is incompletely reduced, yielding ROS (Turrens, 2003) and 1-5% leads to H_2O_2production.It is well documented that mitochondria are a source of H_2O_2; however, the release of $O_2^{\bullet-}$ from mitochondria into the cytosol has yet to be definitively established (Moller*et al*., 2007).

3.2.2. Chloroplasts

The ability of phototrophs to convert light into biological energy is critical for life andtherefore organisms capable of photosynthesis are especially at risk of oxidative damage,due to their bioenergetic lifestyle and the abundance of photosenzitizers and oxidablepolyunsaturated fatty acids in the chloroplast envelope.

3.2.3. Xanthine oxidoreductase (XOR)

XOR exists as either an oxidase (XO) which transfers reducing equivalents to oxygen, or as a dehydrogenase (XDH) that utilizes NAD or oxygen as the final electron acceptor. The enzyme is derived from xanthine dehydrogenase by proteolytic cleavage. It contains molybdenum in the form of molybdopterine, and two clusters with iron and sulfur compounds of FAD cofactor in both subunits. The enzyme catalyzes the production of uric acid with co-production of $O_2^{\bullet-}$. The physiological substrates, xanthine and hypoxanthine, bind with the oxidized enzyme and donate two electrons into the molybdenum cofactor reducing it from Mo^{6+} to Mo^{4+}. Substrates are hydroxylated by H_2O at the molybdenum site as the electrons travel via two iron-sulfide residues to flavine–adenine dinucleotide (FAD) (Hazell*et al*., 1994; Berry and Hare, 2004).

3.2.4. Dopamine (DA)

As a neurotransmitter, DA is stable in the synaptic vesicle. When an excess of cytosolic DA exists outside of the synaptic vesicle, DA is easily metabolized via monoamino oxidase (MAO) or by autooxidation to produce ROS, subsequently leading to the formation of neuromelanin . During the oxidation of DA by MAO, H_2O_2 and dihydroxyphenylacetic acid are generated (Gill and Tuteja, 2010). Spontaneously oxidized cytosolic DA produces $O_2^{\bullet-}$ and reactive quinones such as DA quinones or DOPA quinones. DA quinones are also generated in the enzymatic oxidation of DA by COX in the form of prostaglandin H synthase, LOX, tyrosinase and XOR. These quinones are easily oxidized to the cyclized aminochromes: Dachrome and DOPA-chrome, and are then finally polymerized to form melanin, as reviewed in (Miyazaki and Asanuma, 2008). Although ROS from the autooxidation of DA show widespread toxicity not only in DA

neurons but also in other regions, highly reactive DA quinone or DOPA quinone exert cytotoxicity predominantly in DA neurons and surrounding neural cells. It is thought that DA acts as an endogenous neurotoxin, contributing to the pathology of neurodegenerative disorders and ischemia-induced damage in the striatum (Xia*et al.,* 2001; Maragos*et al.,* 2004).

3.2.5. Photosensitization reactions

Photosensitization reactions involve the oxidation of organic compounds by atmosphericoxygen upon exposure to visible light. The photoexcitated state, most often the triplet stateof the sensitizer, is the key photoreactive intermediate and exerts photodamage throughdirect reaction with substrate molecules (type I photosensitization) or activation ofmolecular oxygen by energy transfer reactions (type II photosensitization) (Wondrak*et al.,* 2006). $^1O_2$ is anexcited state molecule formed by direct energy tranfer between the excited sensitizer andground state $^3O_2$. Less than 1% of triplet oxygen is converted in parallel to superoxide anion(O^{2-}). The formation of O^{2-} as a precursor of H_2O_2 occurs via electron transfer via productionof a sensitizer radical cation, or after an intermediate reduction of the sensitizer with asubstrate followed by the single electron reduction of O_2 (Klotz*et al.,* 2003; Crofts*et a.,* 2008).

3.3. Other cellular ROS sources

The most studied producers of $O_2^{\cdot-}$ by oxidizing unsaturated fatty acids and xenobiotics are cytochrome P450 and the b5 family of enzymes (Thannickal and Fanburg, 2000). Electrons leaking from nuclear membrane cytochrome oxidases and electron transport systems may give rise to ROS. In addition to intracellular membrane-associated oxidases, aldehyde oxidase, dihydroorotate dehydrogenase, flavoprotein dehydrogenase and tryptofan dioxygenase can all generate ROS during catalytic cycling. pH-dependent cell wall peroxidases, germin-like oxalate oxidases and amine oxidases have been proposed as a source of H_2O_2 in the apoplast of plant cells (Bolwell andWoftastek, 1997). Glycolate oxidase, D-amino acid oxidase, urate oxidase, flavin oxidase, L-α-hydroxy acid oxidase, and fatty acyl-CoA oxidase are important sources of total cellular H_2O_2 production in peroxisomes (Foster and Stamler, 2004). Auto-oxidation of small molecules such as epinephrine, flavins, and hydroquinones can also be an important source of intracellular ROS production (Foster and Stamler, 2004).

4. Production route of free radicals

Production of free radicals in the body is continuous and inescapable. The basic causes include the following (Lippincott Williams and Wilkins Instructor's Resource, 2008):

4.1. The immune system

Immune system cells deliberately create oxy-radicals and ROS (Reactive oxygen species) as weapons.

4.2. Energy production

During energy-producing cell generates continuously and abundantly oxy-radicals and ROS as toxic waste. The cell includes a number of metabolic processes, each of which can produce different free radicals. Thus, even a single cell can produce many different kinds of free radicals.

4.3. Stress

The pressures common in industrial societies can trigger the body's stress response to mass produce free radicals. The stress response races the body's energy-creating apparatus, increasing the number of free radicals as a toxic by-product. Moreover, the hormones that mediate the stress reaction in the body - cortisol and catecholamine - themselves degenerate into particularly destructive free radicals.

4.4. Pollution and other external substances

Air pollutants such as asbestos, benzene, carbon monoxide, chlorine,formaldehyde, ozone, tobacco smoke, and toluene,Chemical solvents such as cleaning products, glue, paints, and paint thinners, Over-the-counter and prescribed medications, Perfumes, Pesticides, Water pollutants suchas chloroform and other trihalomethanes caused by chlorination,Cosmic radiation, Electromagnetic fields,Medical and dental x-rays, Radon gas, Solar radiation,the food containing farm chemicals, like fertilizers and pesticides, processed foods containing high levels of lipid peroxides, are all potent generator of free radicals.

4.5. General factors: Aging, Metabolism, Stress.

4.6. Dietary factors: Additives, alcohol, coffee, foods of animal origin, foods that have been barbecued, broiled,fried, grilled, or otherwise cooked at high, temperatures, foods that have been browned or burned, herbicides,hydrogenated vegetable oils, pesticides, sugar.

4.7. Toxins: Carbon tetrachloride, Paraquat, Benzo (a) pyrene, Aniline dyes, Toluene

4.8.Drugs: Adriamycin, Bleomycin, Mitomycin C, Nitrofurantoin, Chlorpromazine

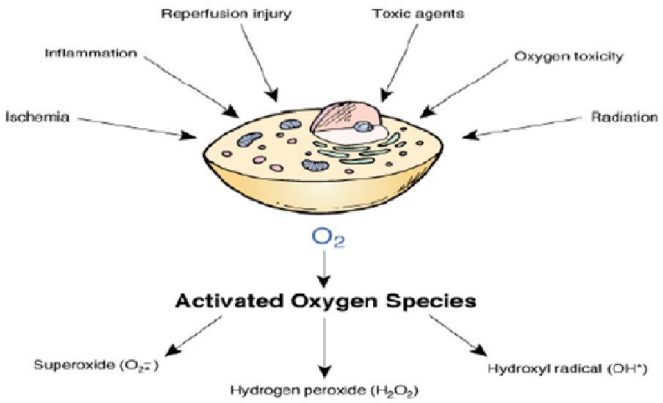

Figure 2. Free radical formation

5. Formation of radicals in biological systems and consequences ofoxidation of biological molecules

5.1. Oxidative damage to protein and DNA

Proteins can be oxidatively modified in three ways: oxidative modification of specific amino acid, free radical mediated peptide cleavage, and formation of protein cross-linkage due to reaction with lipid peroxidation products. Protein containing amino acids such as methionine, cystein, arginine,

and histidine seem to be the most vulnerable to oxidation (Freeman*et al.,* 1982). Free radical mediated protein modification increases susceptibility to enzyme proteolysis. Oxidative damage to protein products may affect the activity of enzymes, receptors, and membrane transport. Oxidatively damaged protein products may contain very reactive groups that may contribute to damage to membrane and many cellular functions. Peroxyl radical is usually considered to be free radical species for the oxidation of proteins. ROS can damage proteins and produce carbonyls and other amino acids modification including formation of methionine sulfoxide and protein carbonyls and other amino acids modification including formation of methionine sulfoxide and protein peroxide. Protein oxidation affects the alteration of signal transduction mechanism, enzyme activity, heat stability, and proteolysis susceptibility, which leads to aging.

5.2. Lipid peroxidation

Oxidative stress and oxidative modification of biomolecules are involved in a number of physiological and pathophysiological processes such as aging, artheroscleosis, inflammation and carcinogenesis, and drug toxicity. Lipid peroxidation is a free radical process involving a source of secondary free radical, which further can act as second messenger or can directly react with other biomolecule, enhancing biochemical lesions. Lipid peroxidation occurs on polysaturated fatty acid located on the cell membranes and it further proceeds with radical chain reaction. Hydroxyl radical is thought to initiate ROS and remove hydrogen atom, thus producing lipid radical and further converted into diene conjugate. Further, by addition of oxygen it forms peroxyl radical; this highly reactive radical attacks another fatty acid forming lipid hydroperoxide (LOOH) and a new radical. Thus lipid peroxidation is propagated. Due to lipid peroxidation, a number of compounds are formed, for example, alkanes, malanoaldehyde, and isoprotanes. These compounds are used as markers in lipid peroxidation assay and have been verified in many diseases such as neurogenerative diseases, ischemic reperfusion injury, and diabetes (Lovell*et al.,* 1995).

5.3. Oxidative damage to DNA

Many experiments clearly provide evidences that DNA and RNA are susceptible to oxidative damage. It has been reported that especially in aging and cancer, DNA is considered as a major target (Woo*et al.,* 1998). Oxidative nucleotide as glycol, dTG, and 8-hydroxy-2-deoxyguanosine is found to be increased during oxidative damage to DNA under UV radiation or free radical damage. It has been reported that mitochondrial DNA are more susceptible to oxidative damage that have role in many diseases including cancer. It has been suggested that 8-hydroxy-2-deoxyguanosine can be used as biological marker for oxidative stress (Hattori*et al.,* 1997).

6. The important beneficial role of free radicals

- Generation of ATP (universal energy currency) from ADP in the mitochondria: oxidative phosphorylation
- Detoxification of xenobiotics by Cytochrome P450 (oxidizing enzymes)
- Apoptosis of effete or defective cells
- Killing of micro-organisms and cancer cells by macrophages and cytotoxic lymphocytes
- Oxygenases (eg. COX: cyclo-oxygenases, LOX: lipoxygenase) for the generation of prostaglandins and leukotrienes, which have many regulatory functions (Yoshikawa*et al.,* 2000)

Table 1. Reactive oxygen and nitrogen species of biological interest

Reactive species	Symbol	Half life (in sec)	Reactivity / Remarks
Reactive oxygen species :			
Superoxide	$O2^{\bullet-}$	10^{-6} s	Generated in mitochondria, in cardiovascular system and others
Hydroxyl radical	$^{\bullet}OH$	10^{-9} s	Very highly reactive, generated during iron overload and such conditions in our body
Hydrogen peroxide	H_2O_2	stable	Formed in our body by large number of reactions and yields potent species like $^{\bullet}OH$
Peroxyl radical	$ROO^{\bullet}$	s	Reactive and formed from lipids, proteins, DNA, sugars etc. during oxidative damage
Organic hydroperoxide	ROOH	stable	Reacts with transient metal ions to yield reactive species
Singlet oxygen	$^1O_2$	10^{-6} s	Highly reactive, formed during photosensitization and chemical reactions
Ozone	O_3	s	Present as an atmospheric pollutant, can react with various molecules, yielding $^1O_2$
Reactive nitrogen species:			
Nitric oxide	$NO^{\bullet}$	s	Neurotransmitter and blood pressure regulator, can yield potent oxidants during pathological states
Peroxynitrite	$ONOO^-$	10^{-3} s	Formed from NO. and

7.Antioxidant protection system

To protect the cells and organ systems of the body against reactive oxygen species (ROS), humans have evolved a highly sophisticated and complex antioxidant protection system. It involves a variety of components, both endogenous and exogenous in origin, that function interactively and synergistically to neutralize free radicals (Table 1) (Mark Percival, 1998) these components include:

7.1.1. Endogenous Antioxidants

- Bilirubin
- Thiols, e.g., glutathione, lipoic acid, N-acetyl cysteine
- NADPH and NADH
- Ubiquinone (coenzyme Q10)
- Uric acid.

7.1.2. Enzymes

- copper/zinc and manganese-dependent superoxide dismutase
- iron-dependent catalase
- selenium-dependent glutathione peroxidase

7.2. Dietary Antioxidants

- Vitamin C
- Vitamin E
- Beta carotene and other carotenoids and oxycarotenoids, e.g., lycopene and lutein
- Polyphenols, e.g., flavonoids, flavones, flavonol's, and Proanthocyanidins

7.3. Metal Binding Proteins

- Albumin (copper)
- Ceruloplasmin (copper)
- Metallothionein (copper)
- Ferritin (iron)
- Myoglobin (iron)
- f.Transferrin (iron)

8. Conclusion

Oxidative processes are essential to life, particularly for obtaining the energy needed for various metabolic processes, but they also serve as a source of ROS. Oxidation and reduction processes are inseparable.

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