World Journal of Nutrition and Health, 2014, Vol. 2, No. 3, 35-38
Available online at http://pubs.sciepub.com/jnh/2/3/2

DOI:10.12691/jnh-2-3-2

Free Radicals and Antioxidants: Role of Enzymes and Nutrition

Ahmed M Kabel[1,2,*]

[1]Department of Clinical Pharmacy, College of Pharmacy, Taif University, Taif, Saudi Arabia
[2]Department of Pharmacology, Faculty of Medicine, Tanta University, Tanta, Egypt
*Corresponding author: drakabel@gmail.com

Received September 12, 2014; Revised October 05, 2014; Accepted October 12, 2014

Abstract Free radicals are substances normally produced by the human body as one of the defense mechanisms against harmful substances. When the rate of their production exceeds the antioxidant capacity of the body, oxidative stress occurs. Oxidative stress carries harmful effects to all the body systems and is implicated in the pathogenesis of various diseases including hypertension, atherosclerosis, diabetes mellitus and cancer. Enzymatic and non-enzymatic antioxidants play an important role in protection of the body against the harmful effec ts of free radicals.

Keywords: *free radicals, antioxidants, enzymes, nutrition*

Cite This Article: Ahmed M Kabel, "Free Radicals and Antioxidants: Role of Enzymes and Nutrition." *World Journal of Nutrition and Health*, vol. 2, no. 3 (2014): 35-38. doi: 10.12691/jnh-2-3-2.

1. Introduction

Oxygen is an element indispensable for life. When cells use oxygen to generate energy, free radicals are created as a consequence of ATP production by the mitochondria. These products are called reactive oxygen species (ROS) that result from the cellular redox process and play a dual role as both toxic and beneficial compounds. At low or moderate levels, ROS exert beneficial effects on cellular responses and immune function. At high concentrations, they generate oxidative stress, a deleterious process that can damage all cellular structures [1].

Oxidative stress plays a major part in the development of chronic and degenerative diseases such as cancer, arthritis, aging, autoimmune disorders, cardiovascular and neurodegenerative diseases. The human body has several mechanisms to counteract oxidative stress by producing antioxidants, which are either naturally produced in situ, or externally supplied through foods and/or supplements. Endogenous and exogenous antioxidants act as free radical scavengers by preventing and repairing damages caused by ROS, and therefore can enhance the immune system and lower the risk of cancer and degenerative diseases [2].

2. Characteristics of Free Radicals and Oxidants

ROS are less stable than non-radical species, although their reactivity is generally stronger. A molecule with one or more unpaired electron in its outer shell is called a free radical [3]. Free radicals include hydroxyl (OH•), superoxide ($O_2^{\bullet-}$), nitric oxide (NO•), nitrogen dioxide (NO_2•), peroxyl (ROO•) and lipid peroxyl (LOO•). Also, hydrogen peroxide (H_2O_2), ozone (O_3), singlet oxygen, hypochlorous acid, nitrous acid (HNO_2), peroxynitrite, dinitrogen trioxide and lipid peroxide are not free radicals and generally called oxidants, but can easily lead to free radical reactions in living organisms [4].

3. Generation of Free Radicals and Oxidants

Free radicals are generated from either endogenous or exogenous sources. Endogenous free radicals are generated from immune cell activation, inflammation, mental stress, excessive exercise, ischemia, infection, cancer and aging. Exogenous free radicals result from air and water pollution, cigarette smoking, alcohol, heavy metals, certain drugs (cyclosporine, tacrolimus), industrial solvents, cooking and radiation. After penetration into the body, these exogenous compounds are decomposed into free radicals [2].

4. Oxidative Stress and Their Deleterious Activities

Oxidative stress results from an imbalance between formation and neutralization of free radicals. For example, hydroxyl radical and peroxynitrite in excess can damage cell membranes and lipoproteins by a process called lipid peroxidation. This reaction leads to the formation of malondialdehyde (MDA) and conjugated diene compounds, which are cytotoxic and mutagenic. Lipid peroxidation occurs by a radical chain reaction, i.e. Once started, it spreads rapidly and affects a great number of lipid molecules [1,2].

5. Free Radicals and Cancer

Free radicals act as second messengers in the intracellular signalling cascades, which induce and maintain the oncogenic phenotype of cancer cells. However, ROS can also induce cellular apoptosis and can therefore function as anti-tumourigenic species. Oxidative stress is common for many types of cancer cells that are linked with altered redox regulation of cellular signalling pathways. Oxidative stress was found in various cancer cells compared with normal cells; the redox imbalance thus may be related to oncogenic stimulation [5]. DNA mutation is a critical step in carcinogenesis and elevated levels of oxidative DNA lesions have been noted in various tumours, strongly implicating such damage in the etiology of cancer. It appears that the DNA damage is predominantly linked with the initiation process. ROS activate AP-1 (activator protein-1) and NF-kB (nuclear factor kappa B) signal transduction pathways, which in turn lead to the transcription of genes involved in cell growth regulatory pathways. The role of enzymatic and non-enzymatic antioxidants in the process of carcinogenesis as well as the antioxidant interactions with various regulatory factors, including NF-kB and AP-1 suggest a strong relationship between reactive oxygen species & the development of cancer [1,6].

6. Antioxidants

An Antioxidant is a molecule capable of slowing or preventing the oxidation of other molecules. Oxidation reactions can produce free radicals, which start chain reactions that damage cells. Antioxidants terminate these chain reactions by removing radical intermediates and inhibiting other oxidation reactions by being oxidized themselves. So, antioxidants are often reducing agents such as thiols or polyphenols [7].

Although oxidation reactions are crucial for life, they can also be damaging; hence, plants and animals contain various antioxidants, such as glutathione, vitamin C, and vitamin E as well as enzymes such as catalase, superoxide dismutase and peroxidases. Low levels of antioxidants or inhibition of the antioxidant enzymes causes oxidative stress and may damage or kill cells [2].

The antioxidant defense systems function through blocking the initial production of free radicals, scavengering the oxidants, converting the oxidants to less toxic compounds, blocking the secondary production of toxic metabolites or inflammatory mediators, blocking the chain propagation of the secondary oxidants, repairing the molecular injury induced by free radicals or enhancing the endogenous antioxidant defense system of the target. These defense mechanisms act cooperatively to protect the body from oxidative stress.The antioxidant defense system consists of powerful enzymatic and non-enzymatic antioxidants [1].

6.1. Enzymatic Antioxidants

All cells in the body contain powerful antioxidant enzymes. The three major classes of antioxidant enzymes are the superoxide dismutases, catalases and glutathione (GSH) peroxidases. In addition, there are numerous specialized antioxidant enzymes reacting with and detoxifying oxidants [2].

Superoxide dismutases (SODs)

They are a class of closely related enzymes that catalyse the breakdown of the superoxide anion into oxygen and hydrogen peroxide [8]. They are present in almost all aerobic cells and in the extracellular fluids. They contain metal ions that can be copper, zinc, manganese or iron. In humans, the copper/zinc superoxide dismutase is present in the cytosol, while manganese superoxide dismutase is present in the mitochondria. There also exists a third form of superoxide dismutase in extracellular fluids, which contains copper and zinc in its active sites [9]. Superoxide dismutase removes O_2. – by catalyzing a dismutation reaction. In the absence of superoxide dismutase, this reaction occurs non-enzymatically but at a very slow rate [10].

Catalase

Catalase (H_2O_2 oxidoreductase) is a tetramer of four polypeptide chains, each over 500 amino acids long, contains four porphyrin heme (iron) groups that allow the enzyme to react with the hydrogen peroxide. Catalase can decompose hydrogen peroxide (H_2O_2) in reactions catalyzed by two different modes of enzymatic activity : the catalatic mode of activity ($2H_2O_2 \rightarrow O_2 + 2H_2O$) and the peroxidatic mode of activity ($H_2O_2 + AH_2 \rightarrow A + 2H_2O$). Catalase has one of the highest turnover rates of all enzymes; one molecule of catalase can convert millions of molecules of hydrogen peroxide to water and oxygen per second. Decomposition of H_2O_2 by the catalatic activity of catalase follows the fashion of a first-order reaction and its rate is dependent on the concentration of H_2O_2 [2,11].

Catalase is an unusual enzyme since, although hydrogen peroxide is its only substrate, it follows a ping-pong mechanism. Here, its cofactor is oxidised by one molecule of hydrogen peroxide and then regenerated by transferring the bound oxygen to a second molecule of substrate [12].

Catalase is present in all prokaryotes and eukaryotes. With the exception of erythrocytes, it is predominantly located in peroxisomes of all types of mammalian cells where H_2O_2 is generated by various oxidases. Since H_2O_2 serves as a substrate for certain reaction that generate the highly reactive hydroxyl radical, catalase is believed to play a role in cellular antioxidant defense mechanisms by limiting the accumulation of H_2O_2 [13].

The role of catalase in defending cells and tissues against oxidative stress has been studied extensively. Overexpression of catalase renders cells more resistant to toxicity of H_2O_2 and oxidant-mediated injury. In addition, transgenic mice overexpressing catalase are protected against myocardial injury following administration of adriamycin and development of hypertension from treatment with norepinephrine or angiotensin. Catalase-deficient patients are phenotypically normal with the exception of an increased tendency to development of progressive oral gangrene as a result of tissue damage from H_2O_2 produced by peroxide-generating bacteria such as streptococci and pneumococci as well as by the phagocytic cells at the sites of bacterial infection [14].

Thioredoxin and glutathione systems

The thioredoxin system contains thioredoxin protein and thioredoxin reductase [15]. Proteins related to thioredoxin are present in all organisms. The active site of thioredoxin consists of two neighboring cysteines that can cycle between an active dithiol form (reduced) and an oxidized disulfide form. In its active state, thioredoxin acts as an efficient reducing agent that scavengers reactive oxygen species [16].

The glutathione system includes glutathione, glutathione reductase, glutathione peroxidases and glutathione S-transferases. Glutathione peroxidase is an enzyme that catalyzes the breakdown of hydrogen peroxide and organic hydroperoxides. Glutathione S-transferases are another class of glutathione-dependent antioxidant enzymes that show high activity with lipid peroxides [17]. These enzymes are at high levels in the liver and also help in detoxification metabolism [18].

Glutathione reductase (GR) is a crucial enzyme that reduces glutathione disulfide (GSSG) to the sulfhydryl form (GSH) by the NADPH-dependent mechanism, an important cellular antioxidant system. Due to its significance, the enzyme has been purified from a number of animals, plants and microbial sources and studied in an effort to identify and explain its structure, kinetic mechanism and molecular properties [19]. Its kinetic mechanism is known to be a ping-pong/sequential ordered model. GR is a flavoprotein that contains two FAD molecules as a prosthetic group, which is reducible by NADPH. GR is one of the thermostable enzymes. GR belongs to the defense system protecting the organism against chemical and oxidative stress. Deficiency of GR is characterized by hemolysis due to increased sensitivity of erythrocyte membranes to H_2O_2 and contributes to oxidative stress which plays a key role in the pathogenesis of many diseases [20].

6.2. Non- Enzymatic antioxidants

Ascorbic acid

Ascorbic acid or vitamin C is a monosaccharide antioxidant found in both animals and plants but cannot be synthesised in humans and must be obtained from the diet. In cells, it is maintained in its reduced form by reaction with glutathione. Ascorbic acid is a reducing agent that can reduce and thereby neutralize reactive oxygen species such as hydrogen peroxide [19].

Glutathione

Glutathione is a cysteine-containing peptide found in most forms of aerobic life. It is not required in the diet and is synthesized in cells. Glutathione has antioxidant properties since the thiol group in its cysteine is a reducing agent and can be reversibly oxidized and reduced. In cells, glutathione is maintained in the reduced form by glutathione reductase and in turn reduces other metabolites and enzymes as well as reacting directly with oxidants. Due to its high concentration and its central role in maintaining the cell's redox state, glutathione is one of the most important cellular antioxidants [20].

Tocopherols and tocotrienols (vitamin E)

Vitamin E (α-tocopherol) is the most important lipid-soluble antioxidant and protects cell membranes against oxidation by reacting with the lipid radicals produced in the lipid peroxidation chain reaction and removing the free radical intermediates. Tocotrienols may have a specialised role in neuroprotection [21].

Beta-carotene

Carotenoids are compounds with lipophilic properties that have antioxidant functions in lipid phases. Beta-carotene besides being a precursor to vitamin A has potent antioxidant properties as it removes singlet oxygen thus protects against free radical attack. They are present in liver, egg yolk, milk, butter, spinach, carrots, tomato and grains [19].

7. Conclusion

There are numerous sources of free radicals that, in excess, may have deleterious effects on the human body. Enzymatic and non-enzymatic antioxidants protect the body from these effects. Further studies are needed to explore the molecular mechanisms by which antioxidants prevent the harmful effects of oxidative stress.

Competing Interests

The author has no competing interests.

References

[1] Halliwell B (2007): Biochemistry of oxidative stress. Biochem Soc Trans; 35: 1147-50.

[2] Valko M, Leibfritz D, Moncol J, Cronin M, Mazur M et al. (2007): Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol; 39 (1): 44-84.

[3] Bahorun T, Soobrarree MA, Luximon-Ramma V, Aruoma OI (2006): Free radicals and antioxidants in cardiovascular health and disease. Internet J Med Update; 1: 1-17.

[4] Genestra M (2007): Oxyl radicals, redox-sensetive signaling cascades and antioxidants. Cell Signal; 19: 1807-1819.

[5] Miranda-Vilelaa AL, Portilhoa FA, de Araujoa V, Estevanatoa L, Mezzomoa B, Santosb M, Lacavaa Z (2011): The protective effects of nutritional antioxidant therapy on Ehrlich solid tumorbearing mice depend on the type of antioxidant therapy chosen: histology, genotoxicity and hematology evaluations. J Nutr Biochem; 22 (11): 1091-1098.

[6] Jomova K, Valko M (2011): Advances in metal-induced oxidative stress and human disease. Toxicol; 283 (2-3): 65-87.

[7] Duarte TL, Lunec J (2005): When is an antioxidant not an antioxidant? A review of novel actions and reactions of vitamin C. Free Radic Res; 39 (7): 671-86.

[8] Zelko I, Mariani T, Folz R (2002): Superoxide dismutase multigene family: a comparison of the CuZn-SOD (SOD1), Mn-SOD (SOD2), and EC-SOD (SOD3) gene structures, evolution, and expression. Free Radic Biol Med; 33 (3): 337-49.

[9] Johnson F, Giulivi C (2005): Superoxide dismutases and their impact upon human health. Mol Aspects Med 26 (4-5): 340-52.

[10] Nozik-Grayck E, Suliman H, Piantadosi C (2005): Extracellular superoxide dismutase. Int J Biochem Cell Biol; 37 (12): 2466-71.

[11] Berg JM, Tymoczko JL, Stryer L (2002): Biochemistry, 5th ed., Freeman WH and Co., New York; pp: 205-206.

[12] Kabel AM, Abdel-Rahman MN, El-Sisi Ael-D, Haleem MS, Ezzat NM, El Rashidy MA (2013): Effect of atorvastatin and methotrexate on solid Ehrlich tumor. Eur J Pharmacol; 713 (1-3): 47-53.

[13] Ho YS, Xiong Y, Ma W, Spector A and Ho DS (2004): Mice lacking catalase develop normally but show differential sensitivity to oxidant tissue injury. J Biol Chem; 279: 32804-32812.

[14] Yang H, Shi MJ, Van Remmen H, Chen XL, Vijg J et al. (2003): Reduction of pressor response to vasoconstrictor agents by overexpression of catalase in mice Am J Hypertens; 16 (1): 1-5.

[15] Nordberg J, Arner ES (2001): Reactive oxygen species, antioxidants, and the mammalian thioredoxin system. Free Radic Biol Med; 31 (11): 1287-1312.

[16] Mustacich D, Powis G (2000): Thioredoxin reductase. Biochem J; 346(1): 1-8.

[17] Sharma R, Yang Y, Sharma A, Awasthi S, Awasthi Y (2004): Antioxidant role of glutathione S-transferases: protection against oxidant toxicity and regulation of stress-mediated apoptosis. Antioxid Redox Signal; 6 (2): 289-300.

[18] Hayes J, Flanagan J, Jowsey I (2005): Glutathione transferases. Annu Rev Pharmacol Toxicol; 45: 51-88.

[19] Linster CL, Van Schaftingen E (2007): Vitamin C: Biosynthesis, recycling and degradation in mammals. FEBS J; 274 (1): 1-22.

[20] Ulusu NN, Tandoğan B (2007): Purification and kinetic properties of glutathione reductase from bovine liver. Mol Cell Biochem; 303(1-2): 45-51.

[21] Sen C, Khanna S, Roy S (2006): Tocotrienols: Vitamin E beyond tocopherols. Life Sci; 78 (18): 2088-2098.