ANTIOXIDANT DEFENCE SYSTEM

Deepali Patekar Supriya Kheur Neeta Bagul Meena Kulkarni Aditi Mahalle Yashwant Ingle Varsha Dhas

Department of Oral Pathology & Microbiology,Dr. D.Y.Patil Dental College and Hospital, Pune, India

Corresponding Author: Deepali Patekar, Department of Oral Pathology,Dr. D.Y.Patil Dental College and Hospital, Pimpri, Pune-18,India.Ph- 09325311862. Email: drdypatekar@gmail.com

Abstract

Several types of reactive species are generated in the body as a result of metabolic reactions in the form of free radicals .These species may be either oxygen derived or nitrogen derived and called prooxidants. They attack macromolecules including protein, DNA and lipid etc. causing cellular/tissue damage. To counter their effect, the body is endowed with another category of compounds called antioxidants. These antioxidants are produced either endogenously or received from exogenous sources and include enzymes like superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase, minerals like Se, Mn, Cu and Zn, and vitamins like vitamin A, C and E. In a healthy body, prooxidants and antioxidants maintain a ratio and a shift in this ratio towards prooxidants gives rise to oxidative stress. Human antioxidant defenses have evolved to protect biological systems against oxidative stress, and a sophisticated cooperative array of antioxidant defense mechanisms is found in biological systems. The following article focuses on causes, role and conrol of oxidative stress in the development and progression of various human diseases.

Key Words: Antioxidants, Free radicals, Superoxide dismutase (SOD), Catalase

Introduction

A biological antioxidant may be defined as a substance(present in low concentrations compared to an oxidizable substrate) that significantly delays or inhibits oxidation of a substrate. Substances that neutralize potential ill effect of free radicals are generally grouped in so called a Antioxidant defense system(ADS).[1,2,3,4] Such a system encompasses many substances which are often called by the generic names such as Antioxidants , Free radical scavengers , Chain terminators or Reductants.[4,5] Currently, a large number of antioxidants(AO) are being investigated [6,7]

Antioxidant in biological system can be classified into:

1 Antioxidant in relation to lipid peroxidation:
2 Preventive AO : that will block the initial production of free radicals e.g. catalase(CAT), glutathione peroxidase(GSH Px)

Chain breaking antioxidants that inhibit the propagative phase of lipid peroxidation
eg superoxide dimutase(SOD),vitamin E, uric acid.

Antioxidants according to their location

1. Plasma AO e.g. b-carotene, ascorbic acid, bilirubin,uric acid, ceruloplasmin, transferring. 2. Cell membrane antioxidants e.g.a-tocopherol. 3. Intracellular antioxidants e,.g superoxide dimutase(SOD), catalase (CAT),glutathione peroxidase(GSH Px).

According to their nature and action

1.Enzymatic-e.g.SOD,GSH Px,CAT

2.Non enzymatic a) Nutrient AO e.g. carotenoids, alfa-tocopherol, ascorbic acid, selenium
b) Metabolic AO e.g. glutathione

ceruloplasmin albumin bilirubin transferring ferrin uric acid[34]

According to Davies[3,] ADS traditionally have be termed "primary" or "secondary".

Primary defenses includes antioxidant compounds-

A)Vitamin E,A,C and glutathione and uric acid,

B)AO scavenging enzymes such as SOD,CT and peroxidases.

For secondary defenses, he suggested lipolytic enzymes,phospholipases,proteolytic enzymes,proteases , peptidases, DNA repair enzymes , endonuclease and ligase.

Primary defenses interact with free radicals generated directly from O2(namely O2); secondary defenses scavenge radicals arising from dismutation of O2. AO are also classified as Extracellular AO and Intracellular AO. SOD,catalase(CT) and glutathione peroxidase(GSH-Px)are not only distributed in cytosol ,but are also localized in mitochondria, where most of intracellular free radicals are produced[8,9]

The most important biological extracellular antioxidant are glutathione, vitamine-E, ureat,GSH-Px,SOD,CT, ceruloplasmin, and transferring. Although considerable progress has been made in identifying and understanding the mode of action of ADS, complexity of intracellular network of various antioxidants has impeded understanding of overall protective efficacy of cytosolic defense system [10,11,12] Also various antioxidants in plasma is crucial for maximum suppression of free radical reaction in extracellular compartment.

The various other non-enzymatic AO[13,14] are

Organosulfur compounds e.g-Allium, Allyl sulfide, indoles

Antioxidant cofactors e.g.- Coenzyme O10

Polyphenols –

Flavonoids-

Xanthones- e.g.- Mangostin

Flavonoids- e.g.- Quercein, Kaempferol

Flavanols- e.g.- Catechin, EGCG

Flavanones- e.g.- Hesperitin

Flavones- e.g.- Chrysin

Isoflavanoids- e.g.- Genistein

Anthocyanidins- e.g.-Cyanidin, Pelagonidin

Phenolic Acid-

Hydroxycinnamic acids- e.g.- Ferulic, p-coumaric

Hydroxybenzoic acid –e.g.- Gallic acid, Ellagic acid

_ Gingerol

_ Curcumin

Dietary sources of Antioxidants[13,14,1516,17,18]

Vitamin C : Fruits (especially citrus) and vegetables, including green and red peppers, tomatoes, potatoes, and green, leafy varieties (eg, spinach and collard greens).

Vitamin E : Vegetable oils (eg, soybean, corn, and safflower) and vegetable oil products (eg, margarine), whole grains, wheat germ, nuts and seeds, and green, leafy vegetables.

b-Carotene : Yellow-orange fruits (eg, cantaloupe) and vegetables (eg, carrots) and green, leafy vegetables.

Polyphenolic Antioxidants : Tea, coffee, soy, fruit, olive oil, chocolate, cinnamon, oregano and red wine[19.]

Mechanism Of Antioxidants

Free radicals are highly reactive molecules or chemical species containing one or more unpaired electrons in their outermost shell. They react quickly with nearest stable molecule to capture electron, in need to gain stability. They promote beneficial oxidation that produces energy and kill bacterial invaders. If free radicals are at reasonable levels, human body produces enzymes to combat them and is helpful in immune system and anti bacterial cell activity. A single free radical can cause damage to millions of other molecules in body from functioning properly.

This molecular destruction is continually occurring in our body. Although

antioxidants are a result of breathing but these free radicals attack us from many different sources every day. They are: Alcohol, Tobacco, Drugs, Smoked and Barbecued Foods, Harmful Chemicals and Pesticides, and Food Additives.

Antioxidant Defense

Antioxidant defense system (ADS) against oxidative stress is composed of several lines and antioxidants are classified into four categories based on their function[20]

First: - Preventive antioxidants which suppress formation of free radicals.

Second: - Radical scavenging antioxidants which suppress chain initiation and breaking chain propagation reactions.

Third: - Repair and de novo antioxidants.

Fourth: - Adaption where the signal for the production and actions of free radicals induces formation and transport of the appropriate antioxidant to the right site.

The Antioxidant Process

Antioxidants block process of oxidation by neutralizing free radicals. In doing so, antioxidants themselves become oxidized.

The two ways by which they act are-
Chain-breaking

When a free radical releases or steals an electron, a second radical is formed. This molecule then turns around and does same thing to a third molecule, continuing to generate more unstable products. The process continues until termination occurs - either radical is stabilized by a chain-breaking antioxidant such as beta carotene and vitamins C and E, or it simply decays into a harmless product.

Preventive

Antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase prevent oxidation by reducing rate of chain initiation. They can also prevent oxidation by stabilizing transition metal radicals such as copper and iron.

Role Of Enzymatic Antioxidants

1. Catalase:

Chemically it is tetramer of four polypeptide chains containing four porphyrin heme groups which allow the enzyme to react with hydrogen peroxide.Catalase is present in high amounts in the liver , kidney and red blood cells. In hepatocytes, peroxisomes exhibit high catalase activity as well as in microsomes and in the cytosol[21]. Catalase is a major primary antioxidant defense component which catalyze decomposition of hydrogen peroxide into water and oxygen.[22] Catalase the detoxify oxygen reactive radicals by catalyzing the formation of hydrogen peroxide which is derived from superoxide.

2. Superoxide Dismutase (SOD):-

Depending on metal ion content SOD is grouped as:-

Cu/Zn SOD
Mn SOD
Fe SOD

The Activity of SOD appears to be extracellular as well as intracellular seen in mitochondria and cytosolic compartment. SOD activity differs in various tissues, highest levels are seen in liver, adrenal gland and kidney and spleen. The SOD activity is regulated through biosynthesis, sensitive to tissue oxygenation[23]It is found that in rats and yeast , biosynthesis of SOD is elevated when subjected to high oxygen tension[24,25.] SOD is called primary defense as it removes the superoxide (O2-) radical ,repairs cell and reduces damage by catalyzing the reduction of superoxide anion to H2O2. Its catalytic function was discovered by Mc Cord and Fridovich [26]

3. Glutathione Peroxidase (GSH-Px):-

GSH-Px are classified as selenium dependent and selenium independent which catalyses the reduction of hydrogen peroxides and organic hydroperoxides. GSH-Px are

present intracellularly in the cytosol and mitochondrial matrix[27].GSH-Px protects against radical damage by reducing peroxides. The role of GSH-Px in the inhibition of lipid peroxidation were first reported by Mc Cay et al[28] Selenium dependent GSH-Px – associated with membranes was reported by urshi and colleagues[29,30] and is associated with degradation of phospholipids hydroperoxides.

Role Of Non-enzymatic Antioxidants

Vitamin-E : Vit E represents two groups of compounds called -Tocopherols and Tocotrienols Chemically tocopherols have a saturated long phytyl tail attached to a chromane ring, whereas tocotrienols have a unsaturated phytyl tail. Isomers of tocopherols and tocotrienels differ from each other based on the degree of methylation of the chromane ring. [31] There are eight structural isomers alfa, beta, gamma, delta etc., among these, alfa - tocopherol is with the most potent Antioxidant activity [32]. High levels of tocopherol are found in selected mammalian tissues such as liver, heart, testes and adrenal glands. Intracellurlarly, Vitamin E is associated with lipid rich membranes such as mitochondria and ER and therefore antioxidation property of tocopherol must be high in protecting against membrane lipid peroxidation .[33]

Thus, as Vitamin E in Lipophilic in character, it protects the unsaturated fatty acids (PUFAS from peroxide, reacts and acts as a scavenger and gets itself oxidized to quinone formed by free radicals [34] Vitamin E is Essential for the membrane structure and integrity of Cell.

Selenium

Selenium is thought to be as essential micronutrient and it exerts benefial effects on health through is selenoproteins. The enzyme GPX is one of the most important selenoproteins in which contribution to the oxidatitive defence animal tissue by catalyzing reduction of hydrogen and lipid peroxidation. The biological antioxidant fuction of the selenium was confined to its interaction enzyme GSH – PX [35 36]. The amino acid selenocysteine is involved in the synthesis of diverse selenoenzyme such as glutathione peroxidase (reducing peroxides) [37,38] iodothyronine deiodinases (regulating thyroid hormone activity), and thioredoxin reductase. (regenerating antioxidant systems) [39,40,41].

Selenium play important role to replace sulphur in urethionine to form selenomethionine, and gets incorporated into proteins[42] selenium contributes to its anticariogenic activity[43, 44] selenium concentration is found to be highest in nucleus, followed by cytosol, mitochondria and microsome. It has been hypothesized that selenium may act at the cellular level to prevent the enzymatic conversion of precarcinogens to carcinogens.

An alternate possibility is that selenium enhances the detoxification process of carcinogens substances and protects against carcinogen induced chromosomal damage [45]

Selenium deficiency alters antioxidant defense systems by depressing GSH Px [8] in both liver and skeletal muscle and affects SOD & CAT activity

Vitamin C (Ascorbic acid):-

It is hydrophilic scavenger of free radicals and act as reducing and antioxidant agent. It is essential for collagen, carnitine and neuro transmitters' biosynthesis vit C works synergistically with vit E and restores the antioxidant properties of oxidized vit E [46]

Ascorbic acid reserves both antioxidant and prooxidant[47,48,49]. In the presence of transition metals like Fe3+ or Cu2+, vit C/ascorbic acid generates oxygen free radicals thus induce lipid peroxidation [50,51,52]. Synergistic action of Vit C and E helps in inhibition of nitrosation from nitrite i.e. inhibits N-nitro compound formation in heterogenous mixture of water and lipid phase[53].

Vitamin A

Beta-carotene is a fat soluble member of the carotenoid which are considerd pro vitamins therefore they can be converted to active vitamin A. Beta carotene is converted to retinol, which is essential for vision. Carotenoids acts as antioxidant because of its property to scavenge free radicals [54,55]. It protects lipid against peroxidation by quenching free radicals and other reactive oxygen species, mostly singlet oxygen[56,57,58]. Same as vit C, beta carotene function as both antioxidant and pro-oxidant at higher oxygen partial pressure its free radical tracking capacity shows autocatalytic pro-oxidant effect with concomitant loss of its antioxidant activity[59].

Conclusion

The new direction in combacting any disease is prevention. The challenge now is to determine which combination of nutrients supplied as an adjunct can prevent or cure various diseases including cancer. The implication and varied consequences of mounting stress in the etiology of various chronic and degenerative diseases suggest antioxidant therapy can be need for the treatment. Further research is needed before this supplementation could be officially recommended as an adjuvant therapy. Additionally avoiding oxidant sources (cigarette,alcohol,stress etc) must be considered as important as taking diet rich in antioxidants.

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