Review Article

Antioxidants - A mini Review

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ABSTRACT

Oxidative stress has become the etiology of various diseases and disorders. The role of antioxidants is emphasized to a great extent. This mini review focuses on the role of reactive oxygen species in triggering oxidative stress and quality of antioxidants with reference to what Total antioxidant status is. There is also a brief discussion of the antioxidants in various clinical conditions.

Keywords: Antioxidants, Reactive oxygen species, Total antioxidant status.

INTRODUCTION

Antioxidants

Reactive oxygen species (ROS) are produced as a consequence of normal aerobic metabolism. Unstable free radical species attack cellular components causing damage to lipids, proteins and DNA which can initiate a chain of events resulting in the onset of a variety of diseases. Living organisms have developed complex antioxidant systems to counter ROS and to reduce the consequent cellular damage. These antioxidant systems include enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, macromolecules such as albumin, cerruloplasmin and ferritin: and an array of small molecules including ascorbic acid, α tocopherol, β carotene, reduced glutathione, uric acid and bilirubin[1].

Antioxidants could be either Preventive or chain breaking antioxidants.

Preventive Antioxidants

Inhibit the initial production of free radicals. They are catalase, glutathione peroxidase and ethylene diamine tetra –actetate (EDTA).

Chain Breaking Antioxidants

Inhibit propagative phase. They include superoxide dismutase, uric acid and Vitamin E. They intercept the peroxyl free radical and inactivate it before a PUFA can be attacked.

Antioxidants fall into two categories

Exogenous Antioxidants

Antioxidants Vitamin A, C, E aid in defending against oxidative damage. They come under the group of exogenous antioxidants. These vitamins, principally Vitamin C (ascorbate) in the aqueous phase and Vitamin E (α and γ – tocpherol)[2] in the lipid phase act as chain breaking antioxidants. These vitamins are reducing agents: they donate a hydrogen atom (H) to radical intermediates formed by reaction of ROS with biomolecules. The vitamin C and E radicals produced in this reaction are resonance stabilized species: they do not propagate radical damage and are recycled by dehydroascorbate reductase.[2] Vitamin C reduces superoxide and lipid peroxyl radicals, but also has a special role in reduction and recycling of vitamin E. The antioxidants machinery works in harmony to inhibit lipid peroxidation reactions in plasma lipoproteins and membranes. In response to severe oxidative stress vitamin E is maintained at constant concentration in the lipid phase until all the vitamin C is consumed. Vitamin A is a lipophilic antioxidant. It is a potent singlet oxygen scavenger and protects against damage from sunlight in the retina and skin[1]. Although there are many antioxidants Vitamin E is receiving closer attention in people with diabetes. Alpha tocopherol is considered the major antioxidant for LDL-C and has been reported to increase the resistance of LDL to oxidation and improve non oxidative glucose metabolism in people with type 2 Diabetes mellitus[3,4].

Other exogenous antioxidants include α Lipoic acid, several bioflavanoids, antioxidant minerals(copper, zinc, manganese and selenium) and the cofactors (folic acid, vitamins B_1, B_2, B_6, B_{12})[2].

Endogenous antioxidants

Antioxidants synthesized in human include enzymes, certain other proteins and low molecular mass species.

Examples are superoxide dismutase, catalase, glutathione peroxidases, thiol specific antioxidants, metallothioneins, other metal ion binding and storage proteins, urates, glutathione and ubiquinol.[5-9]

Our first line of defense against oxidative damage is sequesteration or chelation of redox-active metal ions. These chelators include a number of metal–binding proteins that sequester iron and copper in inactive form

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such as transferin and ferritin. Hemopexin binds heme, a lipid soluble form of iron, which catalyzes ROS formation in lipid environments: it delivers the heme to the liver for catabolism. Haptoglobin binds to hemoglobin and decreases the pro oxidant activity of hemoglobin molecule. Haptoglobin later delivers hemoglobin to the liver for catabolism.[2]

Albumin, the major plasma protein, has a strong binding site for copper and effectively inhibits copper catalyzed oxidation reactions in plasma.[2]

Carnosine (β alanyl-L-histidine) is present in muscle and brain at millimolar concentration. They are potent copper chelators and play a role in intracellular antioxidant protection.

Superoxide dismutase

Superoxide dismutases (SOD) are a class of closely related enzymes present in almost all aerobic cells and in extracellular fluid catalyzing the breakdown of superoxide anion into oxygen and hydrogen peroxide. SOD present in the cytosol has copper/zinc, while the mitochondrial SOD has manganese. The third form in the extracellular fluid has copper and zinc in its active sites.[2]

Catalase

Catalyzes the conversion of hydrogen peroxide to water and oxygen, using iron or manganese as cofactor. This enzyme is localized in peroxisomes. Catalase has a peculiar ping pong mechanism of action on its only substrate whereby its cofactor is oxidized by one molecule of hydrogen peroxide and then regenerated by transferring the bound oxygen to a second molecule of substrate[10].

Peroxidases

Glutathione peroxidase is widely distributed in the cytosol, in the mitochondria and in the nucleus. It reduces both hydrogen peroxide and lipid hydroperoxides to water and a lipid alcohol. It requires Glutathione as a co substrate.

Glutathione

Glutathione functions as a direct free radical scavenger as a co substrate for glutathione peroxidase activity and as a cofactor for many enzymes, and forms conjugates in endo and xenobiotic reactions.

Glutathione Peroxidase and reductase are two enzymes that are present in cytoplasm, mitochondria and nucleus. Glutathione Peroxidase metabolizes hydrogen peroxide to water by using reduced glutathione as a hydrogen donor. Glutathione disulfide is recycled back to glutathione by glutathione reductase, using NADPH generated by glucose 6 phosphate dehydrogenase of the Hexose Monophosphate Shunt Pathway[11,12].

Melatonin: Melatonin is an endogenously produced powerful antioxidant that can cross blood brain barrier. Melatonin once oxidized, cannot be reduced to its former state because it forms several stable end products on reacting with free radicals. It is a terminal antioxidant.[13]

Uric Acid

The ability of urate to scavenge oxygen radicals and protect the erythrocyte membrane from Lipid oxidation was originally described by Kellogg and Fridovich[14] and was characterized further by Amesl.[15] In the above studies the effects of uric acid was shown under specific conditions where exogenously added uric acid protected cells from oxidants, which were also added exogenously to aqueous incubation media. This kind of condition is relevant to a variety of physiological situations when circulating uric acid can scavenge reactive radicals released into the blood by deleterious reactions, such as autoxidation of hemoglobin or peroxide production by macrophages.[15] According to a popular hypothesis in the early eighties by Ames[15] the silencing of the uricase gene with an increase in the blood level of uric acid provided an evolutionary advantage for ancestors of Humans. This hypothesis was based on in vitro experiments which showed that uric acid is a powerful scavenger of singlet oxygen, peroxyl radicals (RO_2) and hydroxyl radicals (OH). Urate circulating in elevated concentrations was proposed to be one of the major antioxidants of the plasma that protects cells from oxidative damage, thereby contributing to an increase in life span of our species and decreasing the risk for cancer. In the plasma urate can prevent lipid peroxidation only as long as Vitamin C is present.[16] Uric acid is an antioxidant only in the hydrophilic environment, which is probably a major limitation of the antioxidant function of uric acid. On the other hand, a vast literature on the epidemiology of cardiovascular disease, hypertension, and metabolic syndrome overwhelmingly shows that, at least among modern Humans, a high level of uric acid is strongly related and in many cases alarms development of hypertension[17-19] visceral obesity,[20-22] insulin resistance,[23] dyslipidemia,[20,23,24,25] type II diabetes,[24] kidney disease,[18] and cardiovascular and cerebrovascular events.[18,26]

Coenzyme Q_{10} is a potent antioxidant. Antioxidant Co Q_{10} has proven to have protective function especially in heart.[27]

Apart from the above broad spectrum of antioxidants, there is also a HDL associated PON 1 enzyme with antioxidant properties. Studies across the globe show evidence of the prevention of LDL and HDL oxidation by PON 1.[28] In fact, previous studies have shown that PON1 is able to hydrolyze preformed lipid hydroperoxides and to delay or inhibit the initiation of oxidation induced by metal ions on lipoproteins.[29,30]

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