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ANTIOXIDANT, FREE RADICAL AND OXIDATIVE STRESS: A BRIEF OVERVIEW

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ABSTRACT

There has been a lot of attention toward the field of free radical chemistry in the recent years. Free radicals reactive oxygen species and reactive nitrogen species are generated by our body by various endogenous systems, exposure to different physiochemical conditions or pathological states. A proper balance between free radicals and antioxidants is necessary for proper physiological function. Antioxidants are capable of stabilizing, or deactivating, free radicals before they attack cells. Antioxidants are absolutely critical for maintaining optimal cellular and systemic health and well-being. Free radicals and oxidants play a dual role as both toxic and beneficial compounds, since they can be either harmful or helpful to the body. This process plays a major part in the development of chronic and degenerative illness such as cancer, autoimmune disorders, aging, cataract, rheumatoid arthritis, 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.

Introduction

Oxygen is an element indispensable for life. When cells use oxygen to generate energy, free radicals are created as a result of ATP production by the mitochondria. Antioxidants are capable of stabilizing, or deactivating, free radicals before they attack cells. Antioxidants are absolutely critical for maintaining optimal cellular and systemic health and well-being.[1,2] Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the by- products produced by the cellular redox process. These species play a dual role as both toxic and beneficial compounds. At low or moderate concentrations, ROS and RNS exert beneficial effects on cellular responses and immune function. At high levels, they generate oxidative stress, that can lead to cellular damage. Oxidative stress plays a major part in the development of chronic and degenerative ailments. 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 RNS, and therefore can enhance the immune defense and lower the risk of cancer and degenerative diseases.[3,4]

Free radicals

Free radical is a molecule with one or more unpaired electron in its outer shell. They are formed from molecules via the breakage of a chemical bond so that each fragment keeps one electron, by cleavage of a radical to give another radical and also via redox reactions. Free radicals include superoxide ($O2^-$), hydroxyl (OH), nitrogen dioxide (NO2), peroxyl (ROO) nitric oxide (NO), and lipid peroxyl (LOO). Also, hydrogen peroxide (H2O2), ozone (O3), nitrous acid (HNO2), singlet oxygen (1O2), hypochlorous acid (HOCl), peroxynitrite ($ONOO^-$), dinitrogen trioxide (N2O3), lipid peroxide (LOOH), are not free radicals and generally called oxidants, but can easily lead to free radical reactions in living organism.[5,6] Free radicals can be formed by enzymatic reactions which include those involved in the respiratory chain, the phagocytosis, the prostaglandin synthesis and the cytochrome P450 system and also by non enzymatic reactions which include processes that occur during oxidative phosphorylation (i.e. aerobic respiration) in the mitochondria. Some internal sources of free radicals are mitochondria, xanthine oxidase, peroxisomes, Inflammation, phagocytosis, arachidonate pathways, exercise and ischemia/reperfusion injury. Some external sources of free radicals are cigarette smoke, environmental pollutants, radiation, certain drugs, pesticides, ozone and industrial solvents.[7]

Oxidative stress

When the balance between free radicals generation and antioxidants defense is disturbed, a phenomenon is generated called oxidative stress that can seriously alter the cell membranes and other structures such as proteins, lipids, lipoproteins, and DNA. Lipoprotein damage can occur by the process lipid peroxidation when hydroxyl radical and peroxynitrite are produced in excess. Proteins may also be damaged by ROS/RNS, leading to structural changes and loss of enzyme activity. Different oxidative DNA lesions which causing mutations occur can due to oxidative damage to DNA. The body has several mechanisms to counteract these attacks by using DNA repair enzymes and/or antioxidants. If not regulated properly, oxidative stress can induce a variety of chronic and degenerative diseases as well as the aging process and some acute pathologies.[6,8]

Oxidative stress in disease

Cancer: Active oxygen may be involved in carcinogenesis through two possible mechanisms: the induction of gene mutations that result from cell injury and the effects on signal transduction and transcription factors. Which mechanism it follows depends on factors such as the type of active oxygen species involved and the intensity of stress. Oxidized and injured DNA has the potential to induce genetic mutation. That some telomere genes are highly susceptible to mutation in the presence of free radicals, is now apparent and it is known that tumor suppressor genes such as p53 and cell cycle-related genes may suffer DNA damage. In addition, oxidized lipids react with metals to produce active substances or synthesize malondialdehyde, which has the potential to induce mutation. Active oxygen species act directly or indirectly via DNA damage on gene expression and signaling at the cellular level. Some antioxidants play a role in such signal transduction. Two examples are glutathione and thioredoxin, working in the mechanisms of redox regulation. The aspect common to these substances is that thiol works as the major subject of redox control, implementing regulation of the activity of transcription factors and taking part in gene expression. It is also known that thioredoxin in the extracellular setting exerts a growth promoting action and a cytokine-like action on certain cells. This contributes to the activation of protein kinase, the oncogenes Fos and Jun, and the transcription factor NF-B.[9,10]

Cardiovascular disease: The oxidative stress has the potential to provide several benefits to the health and lifespan of an individual as heart disease continue to be the biggest killer. Poly unsaturated fatty acids occur as a major part of the low density lipoproteins (LDL) in blood and oxidation of these lipid components in LDL play an important role in atherosclerosis. Endothelial cells, smooth muscle cell and macrophage can release free radical, which affect lipid peroxidation and blood vessel damage can lead to generation

of foam cells and plaque the symptoms of atherosclerosis. Studies have also shown the role of oxidative stress in Ischemia, hypertension, cardiomyopathy, cardiac hypertrophy and congestive heart failure.[11,12]

Pulmonary disease: Oxidative stress plays an important role in inflammatory pulmonary diseases like asthma, chronic obstructive pulmonary diseases by activating different kinases and redox transcription factors such as NF-kappa B and AP-1.[13]

Neurological disease: Oxidative stress play a vital role in various neurological disorders including Alzheimer's disease, Parkinson's disease, memory loss, amyotrophic lateral sclerosis (ALS), multiple sclerosis and depression. Oxidative damage plays a key role in the loss of neurons and the progression to dementia.[14]

Nephrological diseases: Renal sources for ROS are activated macrophages, vascular cells and various glomerular cells. The balance between formation of ROS and antioxidative defence mechanisms depends on the activity of enzymes such as superoxide dismutases (SOD), catalase, NO-synthase, and glutathione peroxidase. This balance, however, is rather fragile, difficult to predict, and strongly dependent on environmental conditions. Loss of renal energy and uremia result in an imbalance between free radical production and antioxidant defenses. Chronic kidney disease patients usually have multiple cardiovascular risk factors like diabetes mellitus, dyslipidemia, and hypertension. These conditions are associated with oxidative stress, which can trigger the inflammatory process and accelerate renal injury progression. There are some clinical biomarkers to detect oxidative stress and antioxidant status in CKD patients. Antioxidant therapies may be beneficial in reducing oxidative stress, lowering uremic cardiovascular toxicity, and improving survival.[15,16]

Rheumatoid arthritis: Rheumatoid arthritis is an autoimmune disease of unknown etiology, characterized by articular inflammation. Oxidative damage induced by reactive oxygen species has been related to the pathophysiology of rheumatoid arthritis. Antioxidant enzyme activities, glutathione concentration,increased levels of isoprostanes and prostaglandins in serum and synovial fluid, reduced glutathione/oxidized glutathione ratio were higher in rheumatoid arthritis patients as compare to controls. Enhanced ROS production, lipid peroxidation, protein oxidation, DNA damage and failure of antioxidant defence system indicates that there occurs an imbalance between ROS production and elimination leading to the oxidative stress in RA patients which in turn contributes to tissue damage and hence to the chronicity of the disease.[17,18]

Ocular diseases: The eye is an organ particularly sensitive to oxidative stress because it is formed by different highly susceptible tissues that play different related roles aimed at preserving the visual function. This sensitivity due to the variety of tissues leads to a large number of extraocular and ocular mechanisms that produce an oxidative imbalance affecting the ocular apparatus. A change in either one or several of these tissues can produce an alteration in the visual function. In addition, the eyes are under a particular risk of oxidative stress due to their high exposure to different extraocular agents, such as oxygen the high content of polyunsaturated fatty acids in the retina, their high exposure to light and environmental contaminants and their exposure to ultraviolet radiation. Under the action of free radicals, the crystalline proteins in the lens can cross-link and aggregate, leading to the formation of cataracts. In the retina, long-term exposure to radiation can inhibit mitosis in the retinal pigment epithelium and choroids, damage the photoreceptor outer segments, and have been associated with lipid peroxidation. [19,20]

Antioxidant and ageing : Ageing is a universal phenomenon and it is a accumulation of changes responsible for sequential alteration that accompany advancing age and associated progressive increases in the chances of death. The ageing process is now considered to the major cause of disease and death after about the age 28. The free radical theory of ageing arose in 1954 from a consideration of ageing phenomenon and a premise that a single common process modifiable genetic and environmental factors was responsible for ageing and death of all living being.

Antioxidant and their sources in food

Type of antioxidant	Major food sources
Flavonoids	
Flavones	• Parsley • Celery • Lemon and orange zest (peel)
Isoflavones	• Soy beans • Soy beverages • Tofu • Miso
Flavanols (including catechins and proanthocyanidins)	*Catechins* • Green and black tea • Dark chocolate • Black grapes • Red wine *Proanthocyanidins* • Grapes • Peaches • Apples • Pears • Berries • Chocolate
Flavanones	• Citrus fruits • Mint
Flavonols	• Apples • Onions • Blueberries • Leeks • Kale • Broccoli • Cherry tomatoes
Anthocyanins	• Purple and dark red foods such as prunes, blueberries, blackberries, black grapes, cranberries, cherries, eggplant and radishes. • Red wine • Wholegrains
Isothiocyanates	
Sulphoraphane	• Broccoli • Cabbage • Cauliflower • Horseradish
Phenolic acids	
Caffeic acid, ferrulic acid	• Blueberries • Kiwi fruit • Plums • Cherries • Apples • Pears • Coffee • Wheatgerm • Bran
Sulphides	
Various allyl sulphides	• Garlic • Onions • Leeks
Vitamins	
Vitamin C	• Fruits • Vegetables
Folate	• Green leafy vegetables • Avocado • Salmon • Fortified cereals and breads
Beta carotene	• Orange and green fruits and vegetables
Vitamin E	• Wheat germ • Sunflower and other seeds • Nuts • Vegetable oils

Minerals	
Selenium	• Brazil nuts • Wholegrains • Seafood

Conclusion

Although much of the research to date focuses on the potential benefit of single antioxidant nutrients, it has become clear that the best protection against oxidative stress comes from a wide assortment of interrelated antioxidants and antioxidant cofactors. The reducing potential of each individual member of the antioxidant defense team is enhanced when a full complement of players is available. For example, some evidence suggests a poor concentration of any one of the antioxidants vitamin C, vitamin E, or beta carotene, appears to increase the risk of cardiovascular disease. Additionally, the combination of several suboptimal concentrations may have an additive or even synergistic affect on increasing risk. Conversely, it has been suggested that, under certain conditions, an excess of any one type of antioxidant in the absence of balance with the others may actually be counter-protective. Moreover, the relative importance of a given antioxidant may vary with different disease conditions because the type or types of ROS generated are likely to differ, and because varying levels of specific antioxidants exist within the different tissues of the body.

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