Short Communication

Antioxidants: the defense mechanism against free radicals

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Abstract

Introduction: *Metabolism* refers to biochemical processes that occur within any living organism - including humans - to maintain life. It is sum of all anabolic (synthesis) and catabolic (break down) reactions occurring in our body. Metabolism can also be aerobic (O_2 dependent) or anaerobic (in absence of O_2). These biochemical processes allow us to grow, reproduce, repair damage, and respond to our environment. Oxidants are formed as a normal product of aerobic metabolism. This aerobic metabolism does not come without cost. "Free radicals" are formed as a by product of this metabolism which is capable of attacking the healthy cells of the body. They are responsible for causation and progress of many diseases like Atherosclerosis, Cataract, Cancer, degenerative diseases, inflammatory diseases, etc. Antioxidants are the first line of defense for these free radicals and are vital in maintaining optimum health and well being. These anti oxidants can be obtained from natural dietary sources or can be taken as nutritional supplements.
Keywords: Oxidants, Free Radicals, Antioxidants, Metabolism.

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INTRODUCTION

Human ecology requires both oxygen and water for generation of an immediate energy source, ATP, by oxidative phosphorylation. But as the saying goes "Too much of even best is bad", very high concentration of even Oxygen are toxic and can cause potential damage to human tissues and cells. Oxygen (in excess) can be toxic due to their potential to produce Reactive Oxygen Species (ROS). During metabolic processes molecular oxygen is completely reduced and converted to water. But, when oxygen reduction is incomplete then ROS are formed. Free radicals are electrically charged molecules, i.e., they have one or more unpaired electron, which are not only capable of independent existence but also causes them to seek out and capture electrons from other substances in order to neutralize themselves. Chemical compounds and reactions that can generate these free radicals are known as Pro-Oxidants. In contrast to this, compounds that remove/suppress the formation of free radicals are known as Antioxidants. In a normal healthy cell, a balance exists between the pro-oxidants and antioxidants. In case the level of pro-oxidants increases or level of anti-oxidants decreases leading to increased production of free radicals, this state is referred as "**Oxidative Stress**[1-2]". It results in serious cell damage which results in causation or progression of various diseases [3-5]

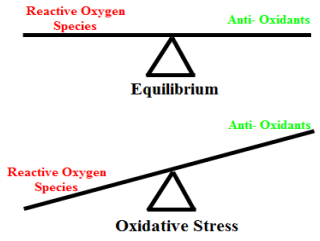

Figure 1: Oxidative Stress

Although the initial attack causes the free radical to become neutralized, another free radical is formed in the process, causing a chain reaction[6] to occur. When the chain reaction occurs in a cell, it can cause damage or death to the cell. Antioxidants terminate these chain

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reactions by removing ROS intermediates, and inhibit other oxidation reactions.

Reactive oxygen species (ROS) versus Free radicals

As stated above, ROS are produced in the cells due to incomplete reduction of molecular oxygen to water as shown below in Fig 2.

Figure 2: Formation of reactive intermediates from molecular oxygen[7].

Reactive oxygen species (ROS) is a collective term used for a group of oxidants, which are either free radicals or molecular species capable of generating free radicals[8] ROS are highly reactive having very short half life and potential to damage cells, bio-molecules and tissues. There is a common misconception that ROS and free radicals are synonyms. ROS is a super set consisting of free radicals and Non free radicals. Free radicals are ions that contain ≥ 1 unpaired electrons (O_2^-, OH^-, ROO^-, etc.). Non free radicals do not contain unpaired electrons (H_2O_2, [O], etc.)

Sources of Generation of ROS

Radicals can be generated in our body by exogenous source or endogenous source. The body is exposed to many exogenous or external sources of oxidants from the environment like smoking, alcohol, radiation, UV light, heat shock, strong sunlight, domestic chemicals like pesticides and air-fresheners, industrial and vehicular pollutants, certain drugs and deep fried and fatty foods. Modern food processing and preserving techniques produce free radicals and also destroy the antioxidants already present in the food item. Endogenous sources corresponds to cellular metabolism example leakage of electrons from ETC, production of NO from arginine, Peroxisomal O_2 and H_2O_2 formation, Auto-oxidation of metal ions, Oxidase enzymes, course of phagocytosis etc. Radicals have the capability to damage all types of Bio-molecules (protein, lipids, carbohydrates and nucleic acids). Some of the prominent diseases caused or promoted by free radicals are Cancer[9], CHD[10], atherosclerosis, Rheumatoid Arthritis, Diabetes, Cataract, Aging, Male infertility, etc. To protect the cells and organ systems of the body against reactive oxygen species, 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. Antioxidants are employed to protect biomolecules from the damaging effects of such ROS. There are various strategies[11] / lines of defenses applied by Antioxidants are:

PREVENTION

A first line of defense against reactive oxygen species is, of course, protection against their formation, i.e. prevention. Cell has several protective mechanisms that minimize the toxic potentials of radicals which includes some enzymes. Cytochrome Oxidase the terminal component of ETC although contains iron and copper ions but does not release superoxides and other radicals. Similarly, ribonucleotide reductase (RNR) that catalyses formation of deoxyribonucleotides from ribonucleotides. The tyrosyl radical of RNR is deeply buried inside the protein in a hydrophobic environment like a cage[12] preventing the radical from spreading to surrounding Furthermore; the initiation of chain reactions can be prevented by binding of metal ions (iron and copper ions). Specialized pigments, like melanin and carotenoids protect the cells from incident radiations like UV radiations and electronically excited states respectively. However, these and other strategies are not completely preventive, because they operate by decreasing the yield of a given challenging agent with less than 100 % efficiency.

INTERCEPTION

The basic problem is to intercept a damaging species, once formed, to prevent it from further deleterious reactions. This is the process of deactivation. Many enzymes perform antioxidant functions by scavenging the radicals or formation of non-radical and non-reactive end-products. These include superoxide dimutase (converts superoxide to H_2O_2 and O_2), catalase (H_2O_2 produced by above enzyme is converted to H_2O and O_2) and glutathione peroxidase (converts H_2O_2 to H_2O) Another way of intercepting the damage caused by radical is to transfer the radicals away from the sensitive target sites where the harmful effects will be more deleterious to compartments of cell where harmful effects will be of less strength. In general, this means transferring the radicals from the hydrophobic phases into the aqueous phases, e.g. from the membrane to the cytosol or from lipoproteins to the aqueous phase of the plasma.

Repair

Prevention and Interception alone are not able to remove all the ROS being continuously formed in our body and so may accumulate in our body. These ROS may cause DNA damage (in form of single/ double strand breaks, damage to bases), membrane damage, lipid peroxidation, damage to proteins, etc. To reverse these damages caused by ROS multiple enzyme systems are involved for these post damage repair. Protection from the effects of

oxidants can also be achieved by post damage repair. Since prevention and interception processes are not completely effective, reactive oxygen species are continuously formed in low concentrations and hence may accumulate. This causes DNA damage, in the form of damaged bases or as single-strand or double-strand breaks, membrane damage, in the form of a variety of phospholipid oxidation products, and damage to proteins and other compounds as well. Correspondingly, there are multiple enzyme systems involved in DNA repair and lipolytic as well as proteolytic enzymes capable of serving the functions of restitution or replenishment.

What if the defense is inadequate?

Today's modern lifestyle encourages quick meals such as fries, bagels, burgers, pizzas, pastries, ice-creams, chocolate bars, etc that are derived from single or few food sources. Additionally, they not only lack antioxidants but are also loaded with oxidants. This does not allow someone to have a balanced platter of vegetables, fruits, cereals, nuts and lentils, lean meats and / or fish. The good-old "food pyramid" and "balanced diet" dictums are all but extinct. However, the ideal level of oxidants is never achieved and a portion of the oxidants go on a rampage damaging cell membranes, lipids, DNA etc. causing significant cell defects or destruction. Physiological and psychological stress also adds to pool of endogenous radicals. As already mentioned, much of this damage is repaired by naturally occurring antioxidant systems that scavenge oxidants, but not all of them When the body's antioxidative defenses are inadequate, or when the supply of nutritional antioxidants is unreliable, or when the oxidant attacks are consistently alarming, the state of balance is tilted from a state of health to a state of slow degeneration. Over the years of evolution the human body has developed a whole arsenal of antioxidative enzyme systems and vitamins for its protection. What are these exogenous and endogenous antioxidants and where are they found? The antioxidants are broadly classified as enzymatic and non enzymatic antioxidants. The endogenous enzymatic antioxidants include superoxide dismutase, catalase, Glutathione Peroxidase, Glutathione Reductase. There interceptive actions have been defined above. Non enzymatic group of antioxidants consists of nutrient and metabolic antioxidants. Nutrient antioxidants are the various vitamins and minerals that we get from exogenous dietary sources. Vitamins like vitamin A, vitamin C[13] and Vitamin E[14- 15] function as independently active natural antioxidants. The active forms of vitamins are vitamin A in the form of beta-carotene, vitamin C as ascorbic acid, and vitamin E as tocopherols and tocotrienols. Besides these many minerals like selenium, zinc, copper and manganese also act as dietary antioxidants. They cary out the activation of antioxidant enzyme systems in the body Beside these naturally occurring nutrient oxidants many metabolic compounds formed in our body also function as antioxidants. They function either by binding to metal ions or by protecting molecules from lipid peroxidation. These include Uric acid, ceruloplasmin, transferring, albumin, bilirubin and haptoglobluin.

Table 1: Sources of antioxidants[16]

Antioxidants	Some Rich Sources
Vitamin A	Carrots, Cheese, kale, Sweet Potatoes,etc.
Vitamin C	Lime, Indian Gooseberry, Strawberries, Kiwi, etc
Vitamin E	Broccoli, Corn, Nuts and seeds, Whole grain, etc.
Selenium	Fish, red meat, chicken, etc.
Lycopene	Tomato, Papaya, Guava, Apricot, etc.
Lutein	Spinach, Kale, Broccoli, Kiwi, etc.
Curcuminoids	Turmeric
Quercetin	Onion, red wine, green tea
Catechin	Green Tea

Limitations of antioxidants

As stress has become a part and parcel of today's life, so in order to counteract the stress induced ill health people have started overdosing themselves with antioxidants. The term antioxidants have become so popular in general public that they have linked it to elixir of optimum health[17]. They focus only on the beneficial effects of antioxidants, ignoring the toxicity. There's a general belief that antioxidants are always safe. Researchers have revealed that antioxidants may also have pro-oxidant actions in certain conditions. Vitamin C in presence of high ferric ion concentrations enhances lipid peroxidation. Similarly, β-carotene in smokers increases the incidence of lung cancer[18-20]. In addition, impairment in blood coagulation has been observed with increased levels of Vitamin E. In large doses these exogenous antioxidants also disrupt the proper functioning of endogenous antioxidants. So, proper doses depending upon the individual's needs, bioavailability, and their interactions with other micronutrients/drugs taken by the person, should be taken into consideration before taking nutritional/pharmaceutical supplements of antioxidants. The primary concern regarding antioxidant supplementation is prooxidant action as precise modulation of ROS levels are needed to allow normal cell function. In fact, some negative effects of antioxidants when used in dietary supplements (flavanoids, in as, natural antioxidant compounds have relatively poor bioavailability. It is therefore necessary to consider the bio-availability and activities of natural and synthetic antioxidant compounds before taking them as therapeutic or pharmacological agents.

CONCLUSION

Supplementation of these dietary antioxidants in the correct doses is important for protection and prevention of disease and premature ageing. Nutrition, like all sciences is constantly changing. Vitamins, minerals and other nutrients are no more 'boring' or old fashioned in the public consciousness. They have now been proven to act as antioxidants and protect against illnesses, repair tissues, and safeguard against the daily stresses of pollution and lifestyle. leading a healthy lifestyle by avoiding intake of junk foods, exercising regularly and consuming a well balanced diet rich in natural antioxidants like fresh fruits and vegetables, nuts whole grains, fish etc. will help to retard the ageing process and increase life span, preventing and/or decreasing intensities of diseases like diabetes, artherosclerotic heart disease, cancer, arthritis, skin diseases, eye disorders, degenerative diseases and many other ailments.

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