Indian J Physiol Pharmacol 2002; 46(1) : 1–5

# *Guest Editorial*

## ANTIOXIDANTS IN HEALTH

Aerobic organisms exist in a perpetual catch-22 situation. Oxygen sustains them, but it also poisons them through reactive intermediates produced during respiration. The powerful oxidants produced in this process - including superoxide anions, hydroxyl radicals, and hydrogen peroxide - are known as free radicals. These highly reactive molecules are capable of independent existence with one or more unpaired electrons. The unpaired electrons are highly energetic and seek out other electrons to pair from another molecule, thus changing it and possibly damaging it and at least causing the second molecule to now be a reactive species resulting in damage to as yet third molecule, and so on. Only when a free radical pairs up with another free radical is the free radical terminated. Free radicals are unguided missiles that bounce around and attack healthy cells, tearing the cell membranes and spilling cytoplasm, and subjecting the cells to infection, genetic damage and mutations. They react with serum lipoprotein (LDL) and cause formation of atheromatous plaques or react with the cell membrane lipid and cause peroxidation of polyunsaturated fatty acids and cause generation of further free radicals. Some disorders in which free radicals are implicated are Alzheimer's, arthritis, hemorrhoids, Parkinson's, rheumatism, heart attack, AIDS, cataract, stroke, cancer, stress, jet lag, senility, varicose veins, phlebitis, immune system disorders, cancer, and a long list of degenerative diseases, including aging. Free radicals are also thought to contribute to heart disease.

Free radicals are not entirely bad— the macrophages and neutrophils use them to destroy bacteria and other foreign invaders. However, too much production or production in the wrong place can be harmful, both acutely and chronically. This is why the body needs antioxidant compounds. Antioxidants (also known as free radical scavengers) function by offering easy electron targets for free radicals. In absorbing a free radical, antioxidants "trap" (de-energize or stabilize) the lone free-radical electron and make it stable enough to be transported to an enzyme which combines two stabilized free radicals together to neutralize. The efforts of scientists to understand how free radicals cause destruction as well as how antioxidants protect cells from damage could provide clues to treat or prevent disease and perhaps even aging. Antioxidants are needed in the different compartments of the body such as the circulating system, the cell membranes, inside the cells and across the "blood-brain" barrier to the brain and the central nervous system. For these reasons, one must ingest a variety of different types of antioxidants, along with other important nutrients, to combat the damaging effects of free radicals in the body.

Antioxidants are of different types so that they might be available for action when and where they are needed. They are natural (enzyme antioxidants and metal carrier proteins in the body), scavenging or chain breaking (like vitamin A, C, beta-carotene, etc.), pharmacologic antioxidants and others. Antioxidant compounds must be constantly replenished since they are "used up" (converted) in the process of neutralizing free radicals. Therefore, one must continually produce more of the antioxidants in the body or ingest them either in diet or by supplementation. The repair enzymes that can regenerate some antioxidants are superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), catalase and the other metalloenzymes.

In 1967 biochemist Irwin Fridovitch of Duke University and Joe McCord (then a graduate student at Duke; now a professor at the University of Colorado School of Medicine in Denver) discovered the antioxidant enzyme superoxide dismutase (SOD), which provides an important means of cellular defense against free radical damage. This breakthrough caused medical scientists to begin to look seriously at free radicals. In most cases the process is automatically controlled and the number of free radicals does not become dangerously high. Fortunately, the body has, throughout the course of millions of years of evolution, become accustomed to coping with free radicals and has evolved various schemes for doing this. The enzyme SOD converts superoxide free radicals to the less reactive hydrogen peroxide. This is still fairly powerful and capable of damaging the tissues. The body produces another enzyme, called catalase, which immediately breaks down the hydrogen peroxide to water and oxygen. There is a third natural antioxidant enzyme called, glutathione peroxidase, which also reduces hydrogen peroxide to harmless water.

One of the most effective natural antioxidants is tocopherol (vitamin E). This fat-soluble vitamin is important because the most significant free radical damage in the body is damage to the membranes of cells and to low-density lipoproteins, and these are made of fat molecules. Vitamin C is also a powerful antioxidant, but it is soluble in water, not in fat. Therefore it gets distributed to all parts of the body. The two vitamins are both highly efficient at mopping up free radicals, and sometimes even mutually co-operate in doing so. Other natural body antioxidants include compounds such as cysteine, glutathione and D-penicillamine, and blood constituents such as the iron-containing molecule transferrin and the protein ceruloplasmin. These act either by preventing free radicals from being produced or by mopping them up. Selenium is a trace mineral, which enhances the properties of vitamin E and is also required by the body for the synthesis of the enzyme glutathione peroxidase. There is a strong correlation between low levels of selenium, and high occurrence of cancer and atherogenesis. Selenium also assists the immune system, by increasing the antibody response to infection. Beta-carotene which is a precursor to vitamin A (retinol) is another antioxidant and is present in liver, egg yolk, milk, butter, spinach, carrots, yams, tomato, peaches and fortified grain products. Since beta-carotene is converted to vitamin A by the body there is no set requirement. The hormone Melatonin is also an important antioxidant. It is able to permeate into any cell within the body. Melatonin is an efficient direct and indirect antioxidant. It detoxifies the highly reactive hydroxyl radical and neutralizes other toxic species, including singlet oxygen, hydrogen peroxide, nitric oxide, and peroxynitrite anion, and stimulates several antioxidative enzymes. The building block nutrients that the body requires for making SOD, catalase, and glutathione peroxidase include the minerals manganese, zinc, and copper.

Examples of antioxidants used by the body in addition to the above mentioned ones are lipoic acid, albumin, uric acid, coenzyme-Q10, bilirubin, flavanoids, and thiols. Numerous other antioxidants have been suggested as preventive against heart disease and cancer: Oligomeric proanthocyanidin complexes OPCs) from grape seed and pine bark, turmeric, resveratrol from grapes, soy isoflavones and garlic are commonly mentioned. Lactate ions has been found to be a potential antioxidant for oxygen and hydroxyl radicals in *in-vitro* studies.

Lycopene is one of the latest entrants in the antioxidant group. As lycopene level in the blood goes up, the levels of oxidized lipoprotein, protein and DNA compounds come down. A human study conducted by the University of Toronto on dietary lycopene confirmed that it acts as an antioxidant (1). While fresh tomatoes are rich in lycopene, cooking them makes it even easier for the body to use their lycopene. Apparently, as the tomatoes break down when they are cooked, the lycopene is more easily absorbed. A study by Harvard Medical School estimated that consuming tomato products twice a week, as opposed to never, was associated with a reduced risk of prostate cancer of up to 34%. Of 46 fruits and vegetables evaluated, only tomato products showed a measurable relationship with reduced prostate cancer risk (2). Another study, the European study of antioxidants in myocardial infarction and cancer of the breast (EURAMIC study) conducted by the University of North Carolina, compared fat samples from 1,379 European men who had suffered a heart attack with those of healthy men. It found that those with high levels of lycopene were half as likely to have an attack as those with low levels. Low lycopene concentrations are found to be associated with early atherosclerosis (3).

The results from several animal studies suggest that increasing the intake of dietary antioxidants inhibit the progress of vascular diseases. Feeding of vitamin E reduces the atherogenic lesion in the arteries of rabbits, mice and monkeys which are either genetically susceptible to vascular disease or have been fed with atherosclerotic promoting diet (4). A study of 6035 women and 4903 men with no clinical history of atherosclerosis were given beta carotene and alpha tocopherol. In men carotene inversely correlated with carotid artery wall intima-media (WT) thickness. In older men alpha tocopherol intake was found to have inverse correlation with WT (5). The CHAOS study involving 2000 men and women with angiographically defined coronary artery disease resulted in marked reduction in non-fatal myocardial infarction in subjects taking vitamin E compared with the placebo group (6). A study on postmenopausal women showed an inverse relationship between vitamin E (but no association between vitamin A or vitamin C) and risk of death due to coronary heart diseases (7). In contrast the ATBC study showed increased risk of fatal heart disease in beta-carotene supplemented group when compared to the placebo group (8). Similarly the CARET study involving 18,000 smokers supplemented with beta-carotene and vitamin A showed an increased the incidence of cardiovascular disease and of lung cancer (9). In contrast other studies showed no effect on incidence of malignancies, neoplasms and cardiovascular diseases with long term supplementation of vitamin C and E and beta-carotene (10, 11). Epidemiological observations show lower cancer rates in people whose diets are rich in fruits and vegetables. This has lead to the theory that these diets contain substances, possibly antioxidants, which protect against the development of cancer (12).

Regular physical exercise enhances the antioxidant defense system and protects against exercise induced free radical damage. This is an important finding because it shows how smartly the body adapts to the demands of exercise. These changes occur slowly over time and appear to occur along with other adaptations to exercise. On the other hand intense exercise in untrained individuals overwhelms defenses resulting in increased free radicals damage. Endurance exercise can increase oxygen utilization from 10 to 20 times over the resting state. This greatly increases the generation of free radicals, prompting concern about enhanced damage to muscles and other tissues (13). Therefore a person who is sedentary during the week but engages in intense exercise would be doing more harm than good to his own self. Studies regarding supplementation of antioxidant vitamins to counteract exercise induced oxidative stress shows contradictory results.

Although free radicals are implicated in many diseases, it is not impossible that free radicals are not the cause but consequence of the disease at least in some situations. Whatever the case may be, it is difficult to give targetted therapy of antioxidants at the site of injury. Although antioxidants are necessary component for good health, we are becoming increasing aware of their potential toxicities. Many antioxidants can also act as pro-oxidants under a range of circumstances and it is possible that unforeseen metabolic disturbances may occur after prolonged use of highly bio-available pure compounds; such effects may not be apparent when antioxidants are obtained from natural foods. For this reason supplementation of antioxidants using natural sources seems to be a safe approach.

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