The Role of Antioxidants in General Healthcare

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ABSTRACT

Antioxidants are intimately involved in the prevention of cellular damage. They protect the body against free radicals that cause pathological conditions such as cancer, ageing, diabetes, cardiovascular diseases and neurodegenerative diseases such as Alzheimer's disease. Athletes, in particular, have a keen interest in antioxidants because of the health concerns, the prospect of enhanced performance and recovery from exercise. The purpose of this article is to serve as a guide to what antioxidants are, briefly review their role in exercise and general health and to discuss how to obtain the optimal benefit from antioxidant therapy. There is no doubt that the health benefits of antioxidants are tremendous.

Keywords: antioxidants, free radicals, flavonoids, oxidative stress, lipid peroxidation.

INTRODUCTION

Antioxidants are a group of chemicals that oxidize preferentially and thereby prevent the oxidizing agent from oxidizing other compounds. They neutralize highly reactive destructive compounds called free radicals and are therefore known as "free radical scavengers".

Free radicals are atoms or group of atoms with an odd (unpaired) number of electrons. They are highly reactive as they try to steal electrons from other molecules, causing damage to the DNA and other molecules through a process known as oxidation. Once formed,. these highly reactive radicals can start a chain reaction resulting in cellular damage when they react with cellular components such as DNA or the cell membrane. Overtime, such damage may become irreversible and lead to diseased conditions including cancer[1-3]. Free radical production is actually a normal part of life as they are constantly being generated in the body as a result of the normal metabolic processes and immune system responses. The body has its own defence of antioxidants that render free radicals harmless. Many of these are enzymes such as gluthathione peroxidase, superoxide dismutase and catalase. Bilirubin, a breakdown product of blood has been identified as a possibly significant antioxidant. Excessive free radical formation sometimes occur in the body and the antioxidant systems in the body cannot cope. This situation is known as oxidative stress.

OXIDATIVE STRESS

Oxidative stress is a general term used to describe a state of potential oxidative damage caused by free radicals. Oxidative stress occur in various situations where there is a disturbance in the pro-oxidant / antioxidant balance in favour of the former, leading to potential damage. It can be caused when certain toxins enter the body, as during inhalation of cigarette smoke. Free radicals are generated as the body tries to detoxify these harmful chemicals. Localised oxidative stress can occur in areas of inflammation with the body where white blood cells such as neutrophils and macrophages gather. White blood cells attempt to kill invading bacteria by releasing bursts of free radicals. Much of the damage seen in inflammatory conditions such as arthritis and tuberculosis are thought to be oxidative destruction of tissues. Free radicals can cause damage to parts of cells such as proteins, DNA and cell membranes by stealing their electrons through oxidation. Hence, free radical damage is also called "oxidative damage". When free radicals oxidize important components of the cell, those components loose their ability to function normally and the accumulation of such damage may cause the cell to die.

Oxidation in itself is essential. Conversion of glycogen and fat to ATP occur by oxidation. It is now known that 20 times the oxygen of a couch potato is consumed during exercise, which pushes free radical production into the stratosphere[1]. It has been shown that there is a three-fold increase in muscle free radicals with moderate exercise in animal studies[4]. In the early 80s, Davies et al[5]. showed that free radicals generated by exercise caused extensive muscle damage.

SOME SITUATIONS WHEN FREE RADICALS ARE PRODUCED

- Energy production in mitochondria
- Phagocytosis during inflammation
- During reperfusion of ischemic tissues
- Cigarette smoking
- Disease conditions (hypertension, diabetes mellitus)

Oxidative stress has been linked to many human disease conditions. These include atherosclerosis, hypertension, diabetes and cancer. It has also been associated with the ageing process and ▶

cataract formation in the eye. There is increasing evidence that many of the other risk factors associated with atherosclerotic vascular disease (AVD) e.g. smoking, hyperhomocysteinemia are linked with oxidative stress and the resultant free radical-mediated damage. Moreover, oxidative stress leads to endothelial damage and dysfunction and impaired production of Endothelium Derived Relaxation Factor (EDRF) commonly known as nitric oxide (NO). Nitric Oxide is required to relax arterial smooth muscle and inadequate production of nitric oxide has been linked to hypertension.

TYPES OF FREE RADICALS

Free-radical generating substances can be found in the food we eat, the drugs and the medicines we take, the air we breathe and the water we drink. These substances include fried foods, alcohol, tobacco smoke, pesticides, air pollutants and many more. Environmental assaults on the body such as radiation, pollutants (e.g. tobacco smoke), and alcohol can overpower the body's ability to neutralize free radicals, allowing them to cause damage to the structure and function of the body's cells. There is good evidence that this damage contributes to ageing and leads to a host of illnesses including cancer and heart disease.

Free radicals of interest in biochemistry are often referred to as reactive oxygen species (ROS), because the most biologically significant free radicals are oxygen centered. Free radicals can live to exert their damaging influence for only fractions of a second, others last many hours. The semiquinone radical created by tobacco smoke, for example, can remain active for several days. The main types of free radicals are listed in the table below. Consumption of antioxidants help to provide the body with tools to neutralize harmful free radicals.

Table 1: COMMON REACTIVE OXYGEN SPECIES

REACTIVE OXYGEN SPECIES	CHEMICAL SYMBOL
Hydroxyl radical	HO.
Alkoxyl radical	RO.
Peroxyl radical	ROO.
Hydrogen Peroxide	H_2O_2
Superoxide anion radical	O_2-
Singlet oxygen	O_2
Nitric oxide radical	NO.
Peroxynitrite	ONOO-

Ultraviolet radiation from sunlight kills by multiple free radical damage[4], so does oxidation from polluted air. Breathing, though vital to life is toxic because of the wide range of free radicals generated by our not quite clean use of oxygen. Exercise or stress, anything that increases the heart rate and bodily use of oxygen simply increases damage.

TABLE 2: FREE RADICAL DAMAGE; AN OVERVIEW

SKIN	Aged skin "wrinkling" or "sagging"	Damage to collagen Damage to elastin
VISION	Blurred vision "cataracts", Loss of vision, "macular degeneration"	Damage to collagen in cornea Damage to macula in retina.
HEART	Clogged arteries, "Coronary artery disease"	Damage to collagen in blood vessels plus oxidation of LDL.
CELLS	Altered cells "Cancer"	Damage to membranes of cell and nucleus exposes genes to oxidative changes and possible mutation.

ENDOGENOUS ANTIOXIDANTS

Antioxidants often work by donating an electron to the free radical before it can oxidize other cell components. Once the electrons of the free radical are paired, the free radical is stabilized and becomes non-toxic to cells. Antioxidants that are produced by the body are referred to as endogenous antioxidants which are essentially enzymes. Enzymes are proteins that accelerates a specific chemical reaction within the body. The main ones are superoxide dismutase, catalase and glutathione.peroxidase. These function by "quenching" free radicals by receiving or donating an electron. This action converts the antioxidant itself into a free radical, but thanks to the brilliant chemistry designed into the human body, other antioxidants immediately step in to quench it, and still others quench them. Eventually, this chemical chain ends up as harmless waste products, such as water and carbon dioxide, for excretion from the body via urine, sweat and breath.

SUPEROXIDE DISMUTASE (SOD) - This enzyme converts the free radical superoxide into harmless oxygen and water. There are three isozymes of SOD, the manganese (Mn-SOD), the copper/zinc (Cu/Zn-SOD) and the iron (Fe-SOD) isozymes.

GLUTATHIONE PEROXIDASE - This enzyme eliminates the hydroxyl free radical and hydrogen peroxide by conversion into harmless water and oxygen. The enzyme requires selenium to do its work.

CATALASE - This enzyme converts the hydroxyl free radical into harmless water and oxygen.

In the high stress oxidative environment of modern life, endogenous antioxidants alone cannot protect us. The sheer volume of oxygen used easily overwhelms the body's production of antioxidants. It also exhausts the body's store of cytochrome C.

EXOGENOUS ANTIOXIDANTS

There is no shred of evidence that oral supplementation of cytochrome C can increase muscle cell cytochrome C by a molecule. The same goes for supplements of superoxide dismutase and catalase. Only glutathione has ►

been shown to be effective by mouth[6].

COENZYME Q10

Athletes learn to produce much higher levels of coenzyme Q10 (CoQ10) than muscles of sedentary folks[7]. Coenzyme Q10 helps in replenishing the body stores of cytochrome C. It is possible to achieve high levels by taking CoQ10 supplements[7]. In doubling up for cytochrome C, CoQ10 itself produces nasty types of free radicals called superoxide anion radicals, which unless quenched will create their own chain of damage. It is possible that the muscles of athletes put in place all the other antioxidants necessary to neutralize the superoxide radicals created by CoQ10, but taking CoQ10 by mouth puts nothing else in place to deal with its superoxide radicals which itself may increase free radical damage. It is therefore necessary to take CoQ10 with an antioxidant that quenches superoxide radicals such as Vitamin E.

VITAMIN E

Inside the protective fatty membrane that surrounds each muscle cell, just climbing a flight of stairs looses a flood of free radical, including singlet oxygen, hydrogen peroxide, and superoxide radicals like those produced by CoQ10. These oxidize the fats of the membrane turning it rancid, a form of damage known as lipid peroxidation. The rancid fat then continues the chain of damage as peroxyl radicals and over a period of days, they inflame and this often kill affected cells. Peroxyl radicals are one big reason the muscles of athletes are often more painful the second day, rather than the first day after an intense workout. Food sources of vitamin E include wheat germ, nuts, seeds, whole grains, green leafy vegetables, vegetable oil and fish-liver oil.

Fat-soluble antioxidant vitamin E quenches a lot of the lipid peroxidation that starts this chain of damage, but in doing so becomes a pro-oxidant, producing damaging tocopherol and tocopheroxyl radicals. Vitamin C has to step in to quench these nasties and regenerate the vitamin E[8]. Hence, supplementary vitamin C is needed along with vitamin E supplements. Vitamin C is a water-soluble vitamin antioxidant and cannot be stored in the body, so it is important to get some regularly. Important sources of vitamin C include citrus fruits (such as oranges, tangerines, sweet lime etc) green peppers, tomatoes, broccoli, grean leafy vegetables, raw cabbage, and potatoes.

SELENIUM

Vitamin E works in synergy with endogenous antioxidant glutathione to quench lipid peroxidation. Glutathione needs mineral selenium to hold the lipid radicals so that glutathione can get a crack at them[9]. Selenium is also required for Vitamin E to function properly[10]. Intense exercise can deplete glutathione by 40% and liver glutathione (from which the muscles get their refills) by 80%. If selenium is being taken as a supplement in such a case, then the preformed glutathione or its precursor, n-acetylcysteine, both of which work in different ways to increase body glutathione levels, is required. Good food sources include fish, shellfish, redmeat, grains, eggs, sunflower seeds, chicken, garlic and brazil nuts. Vegetables can also be a good source if they are grown in selenium-rich soils

VITAMIN A AND CAROTENOIDS

Doses of vitamin A can accumulate over time to toxic levels. The body can make vitamin A easily from beta-carotene which because it is virtually non-toxic has become the preferred supplement source of vitamin A. The antioxidant function of beta-carotene is however independent of its role as a precursor of vitamin A. Therefore, you can receive both vitamin A and beta-carotene benefits from one nutrient. Carrots, squash, broccoli, sweet potatoes, tomatoes, peaches, apricots are particularly rich sources of beta-carotene

Beta-carotene neutralizes singlet oxygen radicals and does so better than vitamin C or vitamin E[11]. This warrants its inclusion in sports antioxidant supplement. Lycopene, the analogue of beta-carotene, found plentifully in tomatoes is even better. It is the best known major protector of the human eye from oxidation by ultra-violet light. It also has a greater capacity than other carotenoids to quench singlet oxygen radicals. The oxy-carotenoids, notably lutein and zeaxanthin also protect the eyes, and other tissues from oxidation by a variety of mechanisms. Carotenoids also work with vitamin E, selenium and glutathione to inhibit peroxyl radicals, thus helping to prevent lipid peroxidation of cell membranes.

MINERAL ANTIOXIDANTS

The antioxidant selenium which is a mineral works at the cell membrane as discussed above. In the body of the cell, the endogenous antioxidant, superoxide dismutase (SOD) is the major antioxidant. It sucks the extra electron from supeoxide radicals, thereby producing hydrogen peroxide. Glutathione or the other main endogenous antioxidant, catalase then converts the hydrogen peroxide into harmless oxygen and water. SOD is made of copper and also requires the mineral zinc to keep it stable. Glutathione requires selenium and the amino acid cysteine as discussed above. Catalase requires both iron and copper to be active. Hence, the minerals iron, copper, zinc and selenium are needed in the antioxidant mix.

In the cell mitochondria a lot of fuel is burned to produce energy along with which the bulk of free radicals, especially those caused by exercise, are produced. It is known that free radical damage to the mitochondria especially by superoxide radicals causes most of the decline in human performance that occurs with age, and likely even determines human lifespan[12]. Thus, the mitochondria needs potent antioxidant protection. SOD is the major antioxidant for the mitochondria, but mitochondrial SOD uses the essential mineral manganese to suck the unstable electron from superoxide radicals. Therefore manganese is another important mineral addition to sports antioxidants. Food sources of manganese include nuts, whole grains, legumes, fruits and vegetables, food sources of zinc include seafood, legumes, meat eggs and whole grain and souces of copper include shell fish and nuts.

ALPHA-LIPOIC ACID

Alpha-lipoic acid is often referred to in popular articles as the "newest", the "best", the "master", the "universal" antioxidant, but it is not more important than the rest.
Alpha-lipoic acid was discovered in the human body in 1951 and for many years it was thought to be a simple co-enzyme in the energy cycle.
Meanwhile, some researchers found it could prevent scurvy in guinea pigs ▶

deliberately made deficient in Vitamin C. (Like humans, guinea pigs are one of the few mammals that lack the liver enzyme necessary for their bodies to make vitamin C). Alpha-lipoic acid also corrected vitamin E deficiency in rats. These findings suggested that it might have widespread antioxidant acitivity in both water (vitamin C) and lipid (vitamin E) environments[13]. In the mid 80s, a rapid and ongoing series of studies spearheaded by Dr. Lester Packer, showed that alpha-lipoic acid can directly neutralize singlet oxygen, hydroxyl and some peroxyl radicals. Its metabolite, dihydrolipoic acid, also neutralizes peroxynitrite radicals [14]. Moreover, alpha-lipoic acid helps to regenerate vitamin C, vitamin E, glutathione and probably CoQ10. However, it cannot neutralize hydrogen peroxide and most superoxide radicals[14]. The body does not produce enough alpha-lipoic acid for stressful situations such as exercise. The body's ability to make it declines rapidly with usual ageing, so athletes can benefit from a higher intake than couch potatoes.

The only potent dietary source of alpha-lipoic acid is red meat and since it is not advisable to eat too much of this due to their high saturated fat content and their high content of pro-inflammatory arachidonic acid[15], the only sensible way is to take it as a supplement. In addition to its antioxidant effect, it is important to note that alpha-lipoic acid also prevents protein degradation, chelates the toxic metals mercury and cadmium, improves learning and memory and enhances insulin metabolism[14]. It is recommended that an athlete whose insulin is stable should take 100-400mg of alpha-lipoic acid per day. This is half the dose recommended in diabetic neuropathy. An overdose of alpha-lipoic acid can lead to hypoglycaemia, therefore it is contraindicated in patients with hypoglycaemic tendencies.

FLAVONOID ANTIOXIDANTS

Flavonoids are a sub-class of the plant chemicals (phytochemicals) called polyphenols. They form a vast new source of potent antioxidants, some of which are probably essential substances for health which are not synthesized in the body but can be obtained from food. Gyorgi, the first man to isolate vitamin C in 1928 found that citrus bioflavonoids protected vitamin C from oxidation[16]. They also appeared to be direct protectors of the membranes of blood vessels and connective tissue, preventing free radicals "burning" holes in them. He proposed that bioflavonoids should be classified as vitamin P for "permeability factor", but at that time, a nutrient was regarded as essential only if you could produce an obvious deficiency disease in animals by depriving them of it. It is now known that deficiency of citrus bioflavonoids allows oxidative processes to weaken membranes and connective tissue, thereby causing widespread bodily injury and inflammation. However, because this is not a clear disease entity, Gyorgi was ignored and interest in flavonoids lapsed for nearly half a century.

Over 400 years later, Masquelier isolated a rich source of mixed antioxidant flavonoids from the bark of Pinus maritime, a local French coastal pine similar to the Anneda pine. He named the mix "pycnogenol"[17]. In 1969, he assigned his patent to the Swiss company Horphag who promptly tradmarked the name Pycnogenol. Fortunately the same flavonoids occur in a wide variety of much cheaper sources than the patented pine bark extract. They are the procyanidins, a sub-class of the proanthocyanidins, the class of phytochemicals responsible for the deep reds, blues and purples of many plants. Of the 5000 flavonoids so far chemically identified, some 250 are proanthocyanidins. Most of them are potent antioxidants. They occur widely in fruits and vegetables, including many types of beans, grapes, cranberries, blackcurrants, green tea and the inner skins of nuts.

PROCYANIDINS

It is known that procyanidins protect vitamin C and potentiate its action. It is also known that they directly neutralize superoxide, hydroxyl and hydrogen peroxide radicals[18]. They are also directly anti-inflammatory, both by antioxidant actions and because they inhibit production of inflammatory prostaglandins[19]. Procyanidins also have specific antioxidant action of special relevance to athletes and to those who wish to inhibit aging. Those from grape seed and green tea, in particular, selectively bind with connective tissue- that network of elastic fibers that holds the skin together. There, in combination with vitamin C, they directly protect the collagen and elastin that keep the skin supple and flexible.

OTHER FLAVONOIDS

Those flavonoids with the best researched antioxidant action can be divided into nine categories depending on their chemical characteristics (Table3).

Table 3: ANTIOXIDANT FLAVONOIDS

FLAVONOID	CLASS	PLANT SOURCES
Flavonols	Catechins	Green tea, grape seeds, pine bark
Proanthocyanidins	Oligomeric catechins	Pine bark, grape seeds, leaves of bilberry, birch, ginkgo biloba.
Flavones & Flavonols	Quercetin kaempferol	Apples, green tea, ginkgo leaves, grape skins, milk thistle fruits
Biflavones	Amentoflavone, bilobein	Ginkgo leaves
Flavanones	Hesperidin, naringin	Citrus peels
Flavononoles	Taxifolin	Milk thistle fruits, pine bark
Anthocyanins, anthocyanidins, anthocyanosides	Cyanidin, delphinidin, malvidin, petunidin.	Red and black grapes, red wine, bilberries.
Flavonolignans	Silymarin	Milk thistle fruits, artichokes.
Isoflavones	Genestein, diadzein	Soy beans

The isoflavone genestein has proved to be a potent inhibitor of both superoxide anion radical and hydrogen peroxide radical, but diadzein only showed moderate effects[20].

MELATONIN

Most scientist think of melatonin solely as a hormone produced by the pineal gland of the brain, which acts as controller of the circadian rhythm of hormones, sleep, immune function and cognition. It is true that melatonin has important hormonal functions, but it is a lot more than that[21-24]. It is primarily a nutrient which occurs throughout our food chain. The first clear evidence of melatonin as an antioxidant was reported in 1993 by Dr Russel Reiter, at the University of Texas Health Science Centre in San Antonio. His team showed that melatonin is more effective than glutathione in quenching one of the deadliest of all radicals, the hydroxyl radical. Other studies since show that melatonin is also a more potent quencher of the peroxyl radical than vitamin C, vitamin E or glutathione[22-24].

Whole brown rice, whole oats and whole sweet corn contain up to 1mg of melatonin per pound, tomatoes and bananas contain half as much. Melatonin supplements are non-toxic in physiological amounts i.e 0.25mg to 3.0mg per day. Usual requirement is 1mg per day under age 30 and 1-3mg per day over the age of 30yrs. Higher doses have been shown to be no more effective than physiological doses.

CARING FOR FOOD ANTIOXIDANTS AT HOME

- Avoid browning: fruits and vegetables can turn brown without their protective skin. The enzymes within food react with oxygen to create the brown colour, an indication of oxidation and destruction of antioxidants. This loss can be stopped by adding an acid (lemon, vinegar or citrus) to the food once peeled or cut. The acid will decrease the browning action of the enzyme.

- Fruits and vegetables should be cut in large pieces and not cut any earlier than necessary. The outer covering of fruits and vegetables protects against free radicals.

- Keep fruits and vegetables in the refrigerator or freezer. Oxygen works best at room temperature.

- Like all water-soluble vitamins and minerals, those important nutrients can float away in cooking water. If the food is not intended to be served as a soup, stew or gravy mixture, waterless cooking should be used such as, steaming, stir-fry, microwave, oven-broil, barbeque, grill or baking.

- The longer the food is cooked, the greater the loss of antioxidants. Lengthy cooking time should be avoided. Antioxidant-containing food should be cooked in a hot, covered pan and only until crisp.

It is very clear that endogenous antioxidants alone cannot protect us in the high stress oxidation environment of modern life so there is need for members of the public to be aware of the food sources of antioxidants. Antioxidants from food sources provide better insurance that the antioxidant is being obtained in the right form and in the right amount. If supplementation is required, a knowledge of the complementary antioxidant necessary to support its use is needed in order not to create a pro-oxidant situation. There is no doubt about the role of antioxidants in maintaining a state of general well-being

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