Antioxidants in Health and Disease: Overview (43428)

JAMES A. OLSON*,[1] AND SHUHEI KOBAYASHI†
Department of Biochemistry and Biophysics, Iowa State University, Ames, Iowa 50011*
and National Institute of Health and Nutrition† 1-23-1 Toyama, Shinjuku, Tokyo 162, Japan

Abstract. **Molecular oxygen is an essential nutrient for higher forms of life. In addition to its normal physiological reactions, oxygen and its partially reduced forms can oxidize a variety of macromolecular and simpler compounds in cells and fluids of the body. Such oxidized and peroxidized compounds have been associated with, and may be causally related to, a variety of chronic diseases. As a protection against excessive oxidation, nature has developed a complex set of interactive antioxidant systems. Selected aspects of antioxidant actions are considered in this symposium.**

[P.S.E.B.M. 1992, Vol 200]

Molecular oxygen is an essential nutrient for nonfacultative aerobic organisms, including, of course, humans. Oxygen is used in many important ways, namely, as the terminal electron acceptor in oxidative phosphorylation, in many dioxygenase reactions, including the synthesis of prostaglandins and of vitamin A from carotenoids, in a host of hydroxylase reactions, including the formation and modification of steroid hormones, and in both the activation and the inactivation of xenobiotics, including carcinogens. The extensive P-450 system uses molecular oxygen in a host of important cellular reactions. Without oxygen, in short, we are dead. In a similar vein, nature employs free radicals in a large variety of enzymic reactions. Thus, the complete quenching of free radicals in cells also quenches life.

But if a little is good, more is not necessarily better. Excessive concentrations of various forms of oxygen and of free radicals can have serious adverse effects on living systems, including the peroxidation of membrane lipids, the hydroxylation of nucleic acid bases, and the oxidation of sulfhydryl groups and of other sensitive moieties in proteins. If uncontrolled, mutations and cellular death result. To offset such excesses, nature has devised a complex control system for minimizing the damage done by excessive oxygen and free radicals.

This symposium deals with selected aspects of the antioxidant control system, both in health and in probably related disease states. Because cancer and atherosclerosis are among the latter, the topic of oxidative stress and its prevention has recently received significant public health attention.

Types of Biological Antioxidants

In the first paper, Krinsky (1) proposes a broadening of the term biological antioxidant to include their protective effects against excessive (and consequently adverse) oxidative processes. Biological antioxidants include well-defined enzymes, such as superoxide dismutase, catalase, selenium glutathione peroxidase, and phospholipid hydroperoxide glutathione peroxidase. Nonenzymatic biological antioxidants include tocopherols and tocotrienols, carotenoids, quinones, bilirubin, ascorbic acid, uric acid, and metal-binding proteins. Various antioxidants, being both lipid and water soluble, are found in all parts of cells and tissues, although each specific antioxidant often shows a characteristic distribution pattern. The mechanism of lipid peroxidation is well defined, and the intervention of given antioxidants at various steps in the process has been amply studied. What is less clear is the manner in which these interactions occur physiologically.

Selenium, Sulfur, and Oxidative Stress on Malaria

Krinsky's excellent review of types and mechanisms of antioxidant action is followed by Levander's exposition (2) of the roles of selenium and sulfur in antioxidant defenses. From the outset, vitamin E and selenium have been closely linked. Although the discovery of glutathione peroxidase seemed to clarify the

[1] To whom requests for reprints should be addressed at Department of Biochemistry and Biophysics, Iowa State University, Ames, IA 50011.

0037-9727/92/2002-0245$3.00/0
Copyright © 1992 by the Society for Experimental Biology and Medicine

role of selenium, the physiological importance of the enzyme has now been questioned. More recently, other selenium-containing proteins have been discovered, and several low molecular weight selenium compounds show peroxidase-like activity. Thus, the physiological role of selenium seems to be more complex than originally thought.

Glutathione participates both in enzymatic and nonenzyamtic antioxidant processes, as must also protein-bound cysteine residues. The so-called ovothiols, which are mercaptohistidine derivatives, also decompose peroxides nonenzymatically.

Although our current frame of thought tends to favor antioxidants as "good" and peroxidative processes as "bad," Levander (2) also discusses the effects of oxidant-antioxidant balance on the relationship between the malarial parasite and its host. Because the malarial parasite is more sensitive to oxidative stress than the host, antioxidants, such as vitamin E, tend to *favor* malarial infection, whereas oxidants, such as dietary highly unsaturated fish oils and the traditional Chinese medicine, ginghaosu, tend to *reduce* infections, particularly in vitamin E-depleted mice. Selenium states do not affect the parasite. Whether dietary manipulation can be used as one device for the control of malarial infection in humans remains to be seen.

Vitamin E Treatments in Children and Effects on Leukocyte Function

In a medical context, Mino (3) considers the utility of vitamin E supplementation in children with various clinical disorders. Treatment with vitamin E of children suffering from cholestasis and abetalipoproteinemia is well established. Although fat absorption and metabolism seem normal in patients with spinocerebellar degeneration, vitamin E therapy halts the progression of the disease by a yet unknown mechanism. The utility of vitamin E therapy in the anemia of premature infants, retrolental fibroplasia, bronchopulmonary dysplasia, and intraventricular hemorrhage is less clear. This situation has been complicated by the toxicity of some vitamin E preparations used to treat the above-cited disorders. This toxic syndrome, termed the E-Ferol syndrome after one such preparation, has been attributed to nonionic detergents in the preparation rather than to vitamin E itself.

Mino (3) also explores the effects of dosing with vitamin E on the production of superoxide ion by leukocytes. Superoxide ion is involved in the "oxygen burst" associated with the killing of bacteria. Because vitamin E can suppress the generation of superoxide ion, high doses of vitamin E might enhance bacterial infection. Although superoxide ion generation by leukocytes was suppressed by large doses of vitamin E in rats, no effect was seen in humans who ingested 900 IU (600 mg) of RRR α-tocopherol daily. Thus, vitamin E dosing, as commonly used therapeutically, does not apparently have adverse effects on leukocyte function. Nonetheless, vitamin E preparations with detergents or with high osmolarity should be used with caution.

Carotenoids and Their Metabolism

Among other antioxidants, carotenoids have also been implicated as protective agents against oxidative stress and chronic diseases. Canfield *et al.* (4) summarize reported relationships between carotenoids and various chronic diseases, including coronary heart disease, cataract, and cancer. Carotenoids dramatically reduce the incidence of certain premalignant conditions, such as leukoplakia, in some patients. In high doses, carotenoids also stimulate the immune response. The biological activity of carotenoids is complicated by the conversion of some of them into vitamin A. Vitamin A and its metabolite, retinoic acid, show their own set of physiological and pharmacological effects. The apparently beneficial actions of carotenoids in several chronic diseases, however, seem primarily to be due to their innate properties rather than to their conversion into vitamin A. Nonetheless, carotenoids are extensively metabolized, and little is known thus far of the possible biological activities of its metabolites, other than, of course, vitamin A.

After presenting possible molecular mechanisms of carotenoid action, Canfield *et al.* (4) discuss the inhibition of soybean lipoxygenase by β-carotene. Although the formation of linoleic acid peroxides is inhibited by β-carotene, the bleaching of β-carotene does not seem to be directly linked to hydroperoxide formation. Thus, the mechanism of this enzymatic process apparently is more complicated than originally thought. The products of β-carotene bleaching include an epoxide fraction and an as yet unidentified polar fraction.

The Vitamin E Cycle

Biological antioxidants do not act in isolation, but as part of a complex system. Packer (5) summarizes the interactions among vitamin E, ascorbate, dihydrolipoate, and electron-transporting enzymes in protecting against oxidative damage. Packer's primary hypothesis is that vitamin E, although present in a relatively low concentration relative to lipids in membranes, acts catalytically in preventing peroxidative reactions by rapidly being reduced back from a free radical to a quinol-like state by interaction with other cellular antioxidants. Besides acting directly as an antioxidant, vitamin E also seems to modulate other signaling processes, such as the formation of prostanoids, hydroxyeicosatetraenoic acid, and sterols.

Packer (5) also points out that vitamin E is a family of substances with different degrees of unsaturation, e.g., tocopherols and tocotrienols, and of methylation, e.g., mono-, di-, and trimethyl analogs. All family mem-

bers do not possess the same biological activities in different situations, nor are they metabolized identically. Tocotrienols, for example, which are a major form of vitamin E in red palm oil, are better antioxidants than the tocopherols in certain contexts.

Packer (5) also summarizes the many clinical conditions that are reported to be ameliorated by treatment with vitamin E.

Final Comments

This symposium has considered only a few aspects of the antioxidant protection system, with a particular focus on lipid-soluble nonenzymatic factors. Broader and more detailed treatments might be found in recent treatises on this subject (6–12). Although vitamins have received particular attention in this regard, many other food components, which are *not* required nutrients, also have pro-oxidant and antioxidant activities (13).

Involvement in any field of endeavor induces an inherent bias, namely, that the investigator is convinced that his or her research activity is of crucial importance. The many actions of antioxidants in physiological processes and disease states fuel both further interest and enthusiasm. Such developments are both expected and laudable.

On the other hand, one must retain perspective. Panaceas don't exist, and too narrow a focus on a single subject can distort one's overall judgment. Antioxidants clearly are important in cellular regulation, but the appropriate balance between oxidative and antioxidative processes in cells under various conditions still needs to be defined. The investigator also must retain the proper balance between enthusiasm and constraint. But the subject is clearly fascinating, has many possible implications, and certainly will continue to be actively and intensively investigated in the foreseeable future.

Studies reported here were supported in part by the National Institutes of Health (CA 46406 and R13 DK 44225 to J. A. O.) and by the Japan-U.S. Cooperative Medical Sciences Program (to S. K.).

1. Krinsky NI. Mechanism of action of biological antioxidants. Proc Soc Exp Biol Med **200**:248–254, 1992.
2. Levander OA. Selenium and sulfur in antioxidant protective systems: Relationships with vitamin E and malaria. Proc Soc Exp Biol Med **200**:249–259, 1992.
3. Mino M. Uses and abuses of vitamin E in children. Proc Soc Exp Biol Med **200**:266–270, 1992.
4. Canfield LM, Forage JW, Valenzuela JG. Carotenoids as cellular antioxidants. Proc Soc Exp Biol Med **200**:260–265, 1992.
5. Packer L. Interactions among antioxidants in health and disease: Vitamin E and its redox cycle. Proc Soc Exp Biol Med **200**:271–276, 1992.
6. Halliwell B, Gutteridge JMC. Free Radicals in Biology and Medicine (2nd ed). Oxford: Clarendon Press, 1989.
7. Bendich A, Olson JA. Biological actions of carotenoids. FASEB J **3**:1927–1932, 1989.
8. Sies H (Ed). Oxidative Stress. New York: Academic Press, 1985.
9. Wendel A (Ed). Selenium in Biology and Medicine. Berlin: Springer-Verlag, 1989.
10. Dolphin D, Avramovic O, Poulson R (Eds). Glutathione: Chemical, Biochemical and Medical Aspects. New York: Wiley, 1989.
11. Bendich A, Phillips M, Tengerdy RP (Eds). Antioxidant Nutrients and Immune Functions. New York: Plenum Press, 1988.
12. Diplock AT, Machlin LJ, Packer L, Pryor WA (Eds). Vitamin E Biochemistry and Health Benefits. New York: New York Academy of Sciences, Vol **570**, 1989.
13. Ames BN. Dietary carcinogens and anticarcinogens. Science **221**:1256–1264, 1983.