POINT/COUNTERPOINT

Active Oxygen Intermediates—Beneficial or Deleterious? An Introduction (43885)

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Breathing oxygen is, it seems, hazardous to your health. Although life cannot go on without this element, many of the biochemical reactions in which oxygen participates generate oxygen-containing free radicals as byproducts. A free radical is any reactive molecule that contains one or more unpaired electrons (i.e., electrons present singly in atomic or molecular orbitals. An unpaired electron can be associated with almost any atom, and this review concentrates on oxygen-centered inorganic radicals, namely superoxide ($O_2^{\cdot -}$) and the hydroxyl radical (HO·), that are important agents in oxidative stress. The formation of highly reactive oxygen-containing molecular species is a normal consequence of a variety of essential biochemical reactions. The oxygen free radicals (i.e., superoxide anion, hydroxyl radical, singlet oxygen, and hydrogen peroxide) are capable of extensive tissue and endothelial damage. Superoxide anion is the best studied free radical species (1). This free radical may act as a reducing agent donating its electrons or as an oxidizing agent, in which case it is reduced to H_2O_2. The production of the superoxide radical is a double-edged sword. It is beneficial when produced by activated polymorphonuclear leukocytes and other phagocytes as an essential component of their bactericidal activities (2). Nevertheless, if allowed to proceed to excess, the same action may result in tissue damage associated with inflammation (3, 4).

Oxygen free radicals can injure lipids, proteins, and DNA, and thus may contribute to the development or exacerbation of many human diseases, including ischemia-reperfusion injury in heart attacks, organ transplantation, stroke, cancer, and emphysema, in various inflammatory-immune injuries and the disorders of aging, and in several neurodegenerative disorders (5–7). As a result of the potential for free radicals to damage cells and tissues, an intricate system consisting of both enzymes and small molecular weight molecules with antioxidant capabilities has evolved to protect against the adverse effects of free radical reactions. There exists ultimately a critical balance between free radical generation and antioxidant defenses. Some of the protective antioxidants are essential nutrients (e.g., vitamin C, vitamin E, and β-carotene). Some are nutritionally essential minerals incorporated into protective antioxidant enzymes (e.g., zinc, copper, and manganese are required for the activity of the two types of superoxide dismutases, the all important antioxidant enzymes). Selenium, an essential component of glutathione peroxidase, is important in the decomposition of hydrogen peroxide and lipid peroxides.

Intracellular detoxification of oxygen free radicals is mediated by the superoxide dismutases (SOD_S), catalases, and peroxidases. McCord and Fridovich (8) first described the function of SOD, which is found in most tissues, where it catalyzes the reduction of the superoxide anion to hydrogen peroxide, effectively detoxifying the superoxide anion. Similarly, the catalases and peroxidases detoxify hydrogen peroxide by catalyzing its reduction to water. Free radicals may play a significant role in tissue injury associated with toxic exogenous agents, such as ionizing radiation or chemotherapeutic agents, and circulatory shock. The delicate balance between beneficial and harmful effects of superoxide radicals is obviously influenced by

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several factors (e.g., the relative overproduction of superoxide radicals, the adequacy of free radical scavengers such as SOD or nitric oxide, or the blockade of free radical generation).

Oxidative stress can be defined as an increase over physiological values in the intracellular steady-state concentrations of active oxygen species. This can be evaluated in terms of oxidative stress indicators such as spontaneous chemiluminescence, H_2O_2 production, activities of antioxidant enzymes and serum tocopherol content, markers of cell and tissue damage (lactate dehydrogenase, alanine amino transferase, and creatine kinase activities in serum), and mitochondrial functions (mitochondrial respiratory activity and H_2O_2 production rate). Currently, a great deal of effort is being directed toward analyzing the effects of antioxidants on various disease entities. The National Cancer Institute conducted a study analyzing the cardiovascular effects of antioxidant supplements. A preliminary analysis of the data revealed some beneficial effects on the cardiovascular end points of ischemic heart disease and ischemic stroke. However, not all the effects studied showed reduced risk or improvement of outcome. Perhaps the most publicized result of the study was the failure of β-carotene to reduce the risk of lung cancer in heavy smokers (9, 10). The results of these studies were unexpected and demonstrate the fact that the toxicity or beneficial influence of antioxidants will only be elucidated when more studies are done, other kinds of trials are conducted, and a greater body of information is available for scrutiny.

The two minireviews following have been contributed by two very distinguished investigators in the area of superoxide radical physiology and pathophysiology. Dr. Hartmut Jaeschke provides a guide for the reader through the chemical background of free radicals and reactive oxygen species, and then leads into their potential functional significance in terms of pathophysiology. The excellent review by Dr. Joe M. McCord delves into the controversies, contradictions, and paradoxes surrounding the physiological and pathophysiological roles played by the superoxide radical. Through the efforts of these two eminent scientists and scholars, the reader should gain some understanding and appreciation for the difficulties as well as the challenges inherent in studying superoxide radicals. The study of free radical biology, which spans approximately 25 years, has always been multidisciplinary in nature. We can reasonably expect that future advances in this field will come about through the concerted efforts, contributions and multiple careful studies of chemists, biologists, and clinicians. Only collaborative research by scientists aware of the multifactorial nature of the role played by oxygen radicals and antioxidants will clarify the situation and lead to the development of new therapeutic advances.

1. Pryor WA. The role of free radical reactions in biological systems. In: Pryor WA. Ed. Free Radicals in Biology. New York: Academic Press, pp1–49, 1976.
2. Babior BM. Oxygen-dependent microbial killing by phagocytes. N Engl J Med **298**:659–668, 1978.
3. McCord JM. Oxygen-derived radicals: A link between reperfusion injury and inflammation. Fed Proc **46**:2402–2406, 1987.
4. Petrone WF, English DK, Wong K, McCord JM. Free radicals and inflammation: Superoxide-dependent activation of a neutrophil chemotactic factor in plasma. Proc Natl Acad Sci USA **77**:1159–1163, 1980.
5. Halliwell B. Oxidants and human disease: Some new concepts. FASEB J **1**:358–364, 1987.
6. Harman D. Aging: A theory based on free radical and radiation chemistry. J Gerontol **11**:298–300, 1956.
7. Coyle JT, Puttfarcken P. Oxidative stress, glutamate, and neurodegenerative disorders. Science **262**:689–695, 1993.
8. McCord JM, Fridovich I. Superoxide dismutase. An enzymatic function for erythrocuprein (hemocuprein). J Biol Chem. **244**:6049–6055, 1969.
9. The Alpha-Tocopheral, Beta Carotene Cancer Prevention Study Group (Principal Investigators: Heinonen OP, Albanes D, Huttunen JK). The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med **330**:1029–1035, 1994.
10. Hennekens CH, Buring JE, Peto R. Antioxidant vitamins—Benefits not yet proved. N Engl J Med **330**:1080–1081, 1994.