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Oxidative stress and antioxidants: *Distress* or *eustress*?

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ABSTRACT

There is a growing consensus that reactive oxygen species (ROS) are not just associated with various pathologies, but that they act as physiological redox signaling messenger with important regulatory functions. It is sometimes stated that "if ROS is a physiological signaling messenger, then removal of ROS by antioxidants such as vitamins E and C may not be good for human health." However, it should be noted that ROS acting as physiological signaling messenger and ROS removed by antioxidants are not the same. The lipid peroxidation products of polyunsaturated fatty acids and cholesterol induce adaptive response and enhance defense capacity against subsequent oxidative insults, but it is unlikely that these lipid peroxidation products are physiological signaling messenger produced on purpose. The removal of ROS and inhibition of lipid peroxidation by antioxidants should be beneficial for human health, although it has to be noted also that they may not be an effective inhibitor of oxidative damage mediated by non-radical oxidants. The term ROS is vague and, as there are many ROS and antioxidants which are different in chemistry, it is imperative to explicitly specify ROS and antioxidant to understand the effects and role of oxidative stress and antioxidants properly.

1. Introduction

Dr. Helmut Sies, recognized as a Redox Pioneer [1], has contributed enormously to the development of science and technology of oxidative stress. Sies has performed numerous pioneering work in this area, including the biochemistry and quantitation of hydrogen peroxide, hydroperoxide metabolism, physiology of glutathione, selenium nutrition, singlet oxygen biochemistry, and health benefits of dietary antioxidants such as carotenoids and flavonoids. He has received many awards including the one from the Vitamin Society of Japan (Fig. 1). It is a privilege for me to have a chance to acknowledge his outstanding achievement and contribution in the field of oxidative stress at this special occasion.

2. Oxidative stress, reactive oxygen species, free radicals, and antioxidants

In 1985, Sies defined oxidative stress as "a disturbance in the prooxidant-antioxidant balance in favor of the former" in an introductory chapter of a book entitled "Oxidative Stress" [2]. This was a time when reactive oxygen species (ROS) and oxygen radicals in biology and medicine attracted much attention from the scientists in the field of chemistry, biochemistry, pharmacology, biology, nutrition, and medicine. The first Gordon Research Conference on Oxygen Radicals in Biology and Medicine was organized by Krinsky and Packer in 1981. Many international meetings on related subjects were organized. Two new journals were launched in 1985, *Journal of Free Radicals in Biology & Medicine* (now *Free Radical Biology & Medicine*) and *Free Radical Research Communications* (now *Free Radical Research*). Sies served as Co-Editor-in-Chief of *Free Radical Research* for many years. The International Society for Free Radical Research (SFRRI) was founded in 1982, reorganized in 1985, and has held biennial general meetings since then. Sies served as the President of SFRRI and organized the biennial meeting of SFRRI in 1986 at Dusseldorf.

It was generally accepted in 1980's that oxidative stress played a causative role in the pathogenesis of various disorders and diseases [3,4]. For example, it was proposed that the oxidative modification of low density lipoprotein is a pivotal initial event in the progression of atherosclerosis [5]. It was accepted that reactive oxygen species (ROS) produced in the ischemia-reperfusion played a causative role in the subsequent oxidative injury [6]. In fact, many in vitro, animal, and human studies have suggested that oxidative

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HNE, hydroxy-2-nonenal; HPETE, hydroperoxyeicosatetraenoic aicd; H(P)ODE, hydro(-pero)xyoctadecadienoic acid; MPO, myeloperoxidase; MPTP, 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine; PC, phosphatidylcholine; RNS, reactive nitrogen species; ROS, reactive oxygen species; SIN-1, 3-morpholinosydnonimine.

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Fig. 1. Award was presented to Dr. Helmut Sies from the Vitamin Society of Japan at the First International Congress on Vitamins and Biofactors in Life Science held at Kobe, Japan, in September, 1991. The commendation certificate was given from Niki, the chairman of his commemorative lecture.

stress is involved in the pathogenesis and progression of various diseases.

It has been realized and demonstrated later that ROS, reactive nitrogen species (RNS), and related reactive species are used in physiological settings as redox signaling messenger with important regulatory functions [7–12]. The basic premise of redox signaling is that reactive species regulate specific and reversible post-translational modifications to thiol moieties on target proteins implicated in cell signaling. The modifications include disulphide formation, sulfenic acid formation, S-nitrosylation, S-glutathionylation, and sulfoxide formation. This was an important paradigm shift and the concept of oxidative stress was updated to include the role of redox signaling and adaptation [13–15]. There are multiple definitions of oxidative stress; one may be that oxidative stress is a signal which induces oxidative reaction and/or affects redox balance, resulting in either stimulation of defense capacity or induction of deleterious damage [16].

It is now clear that ROS and related species are capable of exerting positive stress, *eustress*, as well as deleterious effects, *distress*. The stress-response hormesis has received much attention [17]. This corresponds to the induction by stressors of an adaptive, defensive response through alteration of gene expression. Many studies confirmed that low level of oxidative stress enhances defense capacity by enhancing the expression of antioxidant compounds, proteins, and enzymes, resulting in beneficial health effects [16,18–21].

The adaptive response is one of the important defense functions to cope with oxidative stress. The aerobic organisms respond to low levels of stressors including ionizing radiation and toxins by enhancing antioxidant enzyme expression and repair capacity. It has been found that the low level of endogenous ROS such as hydrogen peroxide induces adaptive response and enhances defense capacity against subsequent oxidative insult [18–21]. Furthermore, even the lipid peroxidation products produced by non-regulated free radical mediated mechanisms were confirmed to induce adaptive response [22]. It was claimed that ROS act as essential signaling molecules to promote metabolic health and longevity [23].

It has been argued that, if ROS and RNS act as a beneficial signaling messenger, then the removal of such ROS/RNS by antioxidants may result in deleterious effect [24–26]. However, it should be noted that, in general, ROS that act as physiological signaling messenger and ROS that are removed by antioxidants such as vitamin E and vitamin C are not the same. The main obstacles in the proper and sound perception of the effects of ROS/RNS and antioxidants are the lack of definition of ROS/RNS and antioxidants. The terms ROS, RNS, and antioxidants are vague. There are many ROS/RNS and antioxidants which are different in chemistry. Some ROS/RNS are free radicals, but others are not. Some free radicals are reactive, but others are not. It is essential to explicitly specify the ROS and antioxidant to properly interpret and discuss the role and effects of ROS and antioxidants in oxidative stress [26,27]. Unless the oxidants are defined, the effect of antioxidants cannot be evaluated [28,29].

There are many kinds of ROS with different reactivities and specificities. This is the same with antioxidants. It is imperative to understand the physicochemical and biochemical properties of ROS, RNS and antioxidants. The reaction rate and pathways depend on reactive species and target molecules. The reactivity of ROS and RNS that may act as signaling messenger toward several physiological antioxidants are summarized in Table 1.

Superoxide is not a reactive radical and it is removed efficiently by either abundant enzyme SOD (>10 μM) or nitric oxide with diffusion controlled rate constant ($k > 10^9$ M^{-1} s^{-1}) to give hydrogen peroxide and peroxynitrite respectively. Nitric oxide is a hydrophobic uncharged radical which can easily permeate cell membranes, while superoxide is much more short-lived and has restricted diffusion across biomembranes. The rate constant for the reaction of vitamin C with superoxide has been measured by several groups and obtained as 6×10^4–3×10^5 M^{-1} s^{-1} under