BASIC SCIENCES
Reviews
Symposium: Antioxidant and Redox Regulation of Cellular Signaling

Antioxidant and redox regulation of cellular signaling: introduction

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ABSTRACT

SEN, C. K. Antioxidant and redox regulation of cellular signaling: introduction. *Med. Sci. Sports Exerc.*, Vol. 33, No. 3, 2001, pp. 368–370. Oxidation-reduction (redox) based regulation of gene expression appears to be a fundamental regulatory mechanism in cell biology. This basic information has been exploited to develop novel strategies in clinical therapeutics. In contrast to the conventional idea that reactive species mostly serve as a trigger for oxidative damage of biological structures, we now know that low physiologically relevant concentration of reactive oxygen species can regulate a variety of key molecular mechanisms. Physical exercise causes redox changes in various cells and tissues. The molecular implications of such change are yet uncharacterized. The five component articles of this symposium discuss skeletal muscle contraction, cell adhesion, heat shock proteins, programmed cell death, and carbohydrate metabolism as they relate to physical exercise. **Key Words:** ANTIOXIDANT, GENE EXPRESSION, SIGNAL TRANSDUCTION, IMMUNE FUNCTION, THIOL

Oxygen has been at the focus of exercise science research ever since the discipline was conceived (1,6,15,26). Initial interests were limited to uptake, transport, and utilization. Biological oxidation processes "burn" substrate and provide us with the energy to survive and function. The "combustion" is not, however, a direct reaction of molecular oxygen with the substrate but a transference of electrons mediated by several enzyme systems, in which oxygen is the final electron acceptor. Work processes such as muscular contraction are driven by energy trapped and stored chemically as pyrophosphate bonds (25). The process of reduction (electron acceptance) of oxygen is complicated by the fact that the oxygen molecule has two parallel spinning unpaired electrons in its outermost orbital. In order to be reduced in one step, an oxygen molecule would need two electrons, spinning in the opposite direction with respect to the valence electrons of oxygen but spinning in the same direction with respect to each other, to enter its outermost atomic orbital simultaneously. This is not possible according to the Pauli exclusion principle. Thus, the only way out is the univalent reduction of oxygen that is the reduction of oxygen molecule by one electron at a time. Because of this, intermediates in the oxygen reduction process are free radicals—molecules containing an unpaired electron (radical) that are capable of independent existence (free) (7). For example, when the oxygen molecule is reduced by a single electron, the resultant species, the superoxide anion radical (O_2·-), still contains one unpaired electron. The superoxide radical is short-lived, and in the presence of an excess of protons, as is the case in most biological situations, it rapidly dismutates to form hydrogen peroxide (H_2O_2). Although hydrogen peroxide is not a free radical by definition, it is a potent oxidant. Oxygen-derived free radicals and related by-products that are capable of inciting oxidative damage to biological structures are collectively referred to as reactive oxygen species. It is estimated that under resting conditions, 2–5% of the total oxygen consumed by tissues may contribute to the development of reactive oxygen species. In biological systems, an imbalance between the generation of reactive oxygen species and antioxidant defenses in favor of the former results in oxidative stress (22). Oxidative stress has been implicated in numerous pathophysiological situations (7,18,20,22).

The Redox Concept

Just as the transfer of hydrogen ions between chemical species determines the pH of an aqueous solution, the transfer of electrons between chemical species determines the redox (oxidation-reduction) potential of an aqueous solu-

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tion. The oxidation number of an element indicates the number of electrons lost, gained, or shared as a result of chemical bonding. Oxidation can be defined as "an increase in oxidation number." In other words, if a species starts out at one oxidation state and ends up at a higher oxidation state, it has undergone oxidation. Conversely, reduction can be defined as "a decrease in oxidation number." Any species whose oxidation number is lowered during the course of a reaction has undergone reduction. When an iron nail rusts, the iron is oxidized and oxygen is reduced. Here the iron gave electrons to the oxygen. Oxidation and reduction always occur at the same time. This is one of the basic laws of chemistry. Because the laws of chemistry govern biology, oxidation and reduction also occur at the same time in biochemical reactions. Such reactions are usually referred to as "redox reactions."

Exercise-Induced Oxidative Stress

Under resting conditions, oxygen content in arterial and venous blood of the skeletal muscle tissue is 20 and 15 mL per 100 mL blood, respectively. Physical exercise may increase skeletal muscle arteriovenous oxygen difference by three-fold and blood flow through the tissue by 30-fold. As a result, we may have up to 100-fold increase in oxygen flux through the active skeletal muscles during exercise (12). In exercise physiology, the aerobic capacity of an individual is considered to be a widely accepted index for physical fitness. Thus, one of the primary goals of coaches, physical trainers, and athletes is to enhance the ability to consume atmospheric oxygen. Oxidative metabolism is very energy cost efficient and avoids lactate formation during energy supply. In 1978, Al Tappel's laboratory tested whether physical exercise may cause oxidative tissue damage. They reported that in humans moderate intensity physical exercise increased the content of pentane, a possible oxidative lipid damage by-product, in expired air (3).

Electron paramagnetic resonance spectroscopy allows a direct detection of the short-living free radical species. By using this technique, it was shown in 1982 that exhaustive treadmill exercise may increase skeletal muscle and liver free radical concentration by two- to three-fold (2). Numerous studies followed (16,19,20). Studies related to free radicals mostly focused on oxidative damage and soon there was a widespread mind-set that free radicals and reactive species can only be deleterious (23).

Redox Signaling

Work reported during the last 5–10 yr has added a new dimension to our understanding of the role of reactive species in biology (9,11,13,18,21,24). In contrast to the conventional idea that reactive oxygen is mostly a trigger for oxidative damage of biological structures, now we know that low physiologically relevant concentration of reactive oxygen species can regulate a variety of key molecular mechanisms that may be linked with important processes such as immune response, cell-cell adhesion, cell proliferation, inflammation, metabolism, aging, and cell death. Redox based regulation of gene expression appears to be a fundamental regulatory mechanism in cell biology (14,17,18,21). This basic information has been exploited to develop novel strategies in clinical therapeutics (4,27). The recognition of nitric oxide, a reactive species, as a signaling molecule that causes vasorelaxation is a major landmark (10). A signaling role of other reactive species such as hydrogen peroxide has been proposed. It is now evidently clear that several biological molecules those are critically important in cell signaling and in the regulation of gene expression are sensitive to reactive oxygen species at concentration much below that required to inflict oxidative damage (5,8). Thus, much of the current focus has been directed toward the understanding of "redox sensors" in biology (17).

Redox regulated signal transduction is an integral part of the life and death of every aerobic cell. The papers that follow in this symposium discuss selected issues related to redox regulation of processes relevant to physical exercise. The five component articles discuss skeletal muscle contraction, cell adhesion, heat shock proteins, programmed cell death, and carbohydrate metabolism as they relate to physical exercise. Because redox regulation of biological responses represents a late-breaking field, the review articles open more questions than they answer.

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