Vitamin C in Respiratory Diseases

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Introduction

Free radicals (such as RS·, RSO2·, SO2·, NO·, NO2·, LO·, LOO·, CCl3·) and other reactive oxygen species (ROS) (O2·, H2O2, HO·, HOCl) along with singlet oxygen (1O2) and ozone (O3) are highly reactive chemical agents which may oxidize several biological molecules such as proteins, lipids, and nucleic acids, thereby inducing cellular damage [1].

It has been estimated that among the 10^{12} oxygen molecules which are involved in the metabolism of a single cell every day, about 1 out of 100 damages proteins and 1 out of 200 damages DNA [2].

In living organisms, ROS are physiologically produced during normal metabolic reactions. For instance, during mitochondrial oxidative phosphorylation, about 2% of the electrons transferred to cytochrome oxidase are involved in ROS formation [3], and many other enzyme systems may generate ROS [4].

In order to survive, living organisms have developed enzymatic and nonenzymatic mechanisms to prevent the release of ROS and to counteract the toxic effects induced by these agents. However, this balance is perturbed if an excess of ROS is produced or if the availability of antioxidant agents is impaired. This would, in turn, give rise to pathological events eventually leading to a cluster of symptoms or to overt disease [5].

As for the ROS-mediated damage to the respiratory system, the lungs, unlike other internal organs in which ROS are only of endogenous origin, are also exposed to exogenous ROS because of their direct connection with the outside environment. This phenomenon is of particular relevance with respect to the structure and specific function of the respiratory system. The lungs contain about 300 000 000 alveoli, coated by about 95% by type-I pneumocytes [6]. It has been calculated that the alveoli-related surface amounts to approximately 70-100 m².
Across such a respiratory surface, which represents the organism's largest environment-connected area (for comparison, our body surface is about 1.7 m²), about 15 000 l of breathed air flow every day. This means that about 300 000 000 l of air are breathed over an average lifespan [7]. Several types of pollutants are often detected in breathed air, such as those of biological origin (bacteria, viruses, pollens, etc.), physical agents (ionizing radiation, silica or asbestos fibers, dust, etc.) or chemical compounds (O₃, NO⁺, NO₂⁺, gases from fuel, etc.). All these may directly or indirectly induce formation of free radicals and ROS.

In view of the large pulmonary surface and the huge volume of breathed air, it is easy to see how exogenous ROS in the lung may play an important role in lung diseases.

Another important aspect of lung physiology is the presence of several humoral and cellular host defense systems, including resident cells such as alveolar macrophages. These cells modulate a number of complex functions, such as phagocytosis, ROS formation, and neutrophil recruitment. The last-mentioned function appears to be important because macrophage activation triggers a hazardous, self-perpetuating cycle of ROS production and release.

On activation by specific or nonspecific agents, neutrophils and macrophages reduce molecular oxygen to superoxide anion (O₂⁻⁻; Fig. 1) using

![Diagram](image)

Fig. 1. Schematic representation of reactive oxygen species production by activated neutrophils during oxidative killing, with harmful effects on the various types of lung cells. (Modified from [8])