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Review article

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THE UTILITY OF OXIDATIVE STRESS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

SUMMARY

Reactive radical species are formed as a result of many physiological and pathological processes. They are highly reactive and the aerobic organisms, which are constanly attacked by the damaging compound in the air, actuate the defence mechanisms, which exert their action primarly against oxidant substances. Oxidative stress, which can be defined as an increased production of oxidants and/or reduction of antioxidant capacities, plays an important role in chronic obstructive pulmonary diseases. Oxidants are contained in cigarette smoke and are produced by inflammatory cells. They may react with proteins, lipids and nucleic acids, which can lead to cell dysfunction or death. Oxidative stress also promotes inflammation and contributes to the proteinase-antiproteinase imbalance. In the patients with the chronic obstructive pulmonary disease (COPD), it is possible to establish oxidative stress presence.

Key words: **free radicals, oxidative stress, chronic obstructive pulmonary disease, antioxidants**

INTRODUCTION

Over the past few years, a considerable improvement in the knowledge of oxidant radicals pathology has been achieved. Free radicals are formed as a result of many physiological and pathological processes. However, when free radicals are in excess and an oxidant-antioxidant imbalance takes place, it results in the damage to the cell structures, and consequently, in a pathological process. Oxidative stress can be defined as an effective increase in the production of free radicals or a decrease in antioxidant defence, or, more frequently, by both of these events (1). Oxidative stress is observed in many acute pathophysiological states, including sepsis, exposure to ionizing radiation, ischaemia, reperfusion and other inflammatory states. Moreover, due to its anatomical and functional characteristics, the lung is an organ at high risk to oxidative damage, since it is directly exposed to toxic substances deriving from air pollution, cigarette smoke and infective agents. Oxidative stress is also thought to play a role in many lung diseases, including lung cancer, asthma and chronic obstructive pulmonary disease (2).

FREE RADICALS

Free radicals are atoms or molecules containing an odd number of electrons, which results in an odd electron in the external orbit. The radical species are highly reactive, since they posses an odd number of electrons and invariably tend to pair up the odd electron, either by taking an electron from another molecule or by releasing their own electron.

This consequently leads to chain reactions involving a series of transformantions, each of which forms a free radical.

In the human, oxygen, by means of its derivates referred to as reactive oxygen species(ROS), acts as the fundamental oxidant. In the lung, ROS are derived from inhaled gases, mineral and combustion particles and chemicals associated with combustion particles and also released into the milieu of the lung inflammatory cells (3).

Reactive Oxygen Species:

- Superoxide anion radical O_2^-
- Hydrogen peroxide H_2O_2
- Hydroxyl radical OH^-
- Hydroperoxide radical HO_2
- Alkoxyl radical R-O
- Hypochlorous acid HClO

The univalent reaction of oxygen to superoxide anion is the first step in the formation of oxidants. The source of superoxide anion includes primarly the mitochondrial respiration chain. Superoxide anion is then converted to hydrogen peroxide, either spontaneously or under superoxide dismutase (SOD). The reaction of superoxide anion and hydrogen peroxide in the presence of transition metal, usually ferrous ion (Fe^{2+}), produces the hydroxyl radical. This reaction is called Fenton's reaction (4).

Inflammatory cells (macrophages, neutrophils, eosinophils) produce oxidants and released their bactericide activity. Neutrophils produce the potent oxidant, hypochlorous acid, from hydrogen peroxide and chloride by the enzyme myeloperoxidase (1,4).

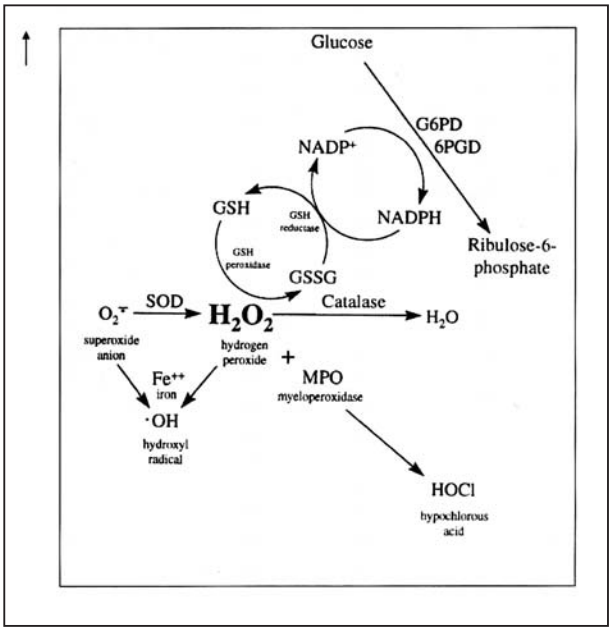

Figure 1. Basic oxygen radical and antioxidant chemistry

ANTIOXIDANTS

The human organism actuates defence mechanisms for cleaning the lungs, which exert their action primarly against oxidant substances. The defence mechanisms, which are defined as natural antioxidants, may be either intracellular or extracellular, and are divided into enzymatic and nonenzymatic systems.

The main natural antioxidants:

– endocellular and extracellular enzymatic substances: superoxide dismutase (SOD), catalase, the glutathione system (glutathione peroxidase, glutathione reductase),

– plasma proteins: albumin, ceruloplasmin, transpherin, α-1-antitripsin,

– low molecullar weight scavengers: bilirubine, methionine, uric acid, vitamine E, vitamine C.

The major enzymatic systems in the lungs are SOD, catalase and the glutathione system (5).

Moreover, three isoenzymatic forms of SOD exist: manganese-SOD, which is inducible and located in mitochondria; Cu-Zn-SOD, which is located mainly in the cytoplasm; and nucleus and extracellular SOD, located in the extracellular matrix, especially in areas rich in type I collagen, generally in areas around blood vessels and in larger airways.

Another enzymatic system is catalase, which resides primarily in peroxisomes. In the presence of hydrogen peroxide it catalyses the following reaction: $H_2O_2+H_2O_2=2H_2O+O_2$. However, due to its confirmation, catalase can not metabolise oxidants of large dimensions such as lipid hydroperoxides that form during lipid peroxidation.

The third enzymatic system is glutathione (GSH), a low molecular weight tripeptide that presents in a high concentration in each cell and in the lung epithelial lining fluid. GSH protects alveolar macrophages, epithelial cells and endothelial cells from oxidative damage and also has a role in protecting cells against oxidative stress mediated apoptosis. GSH intracellular concentration is used as an oxidative stress marker (6).

Among the nonenzymatic systems, the mucus layer which lines the airway surfaces plays a key role, since it contains defence compounds such as glycoproteins and albumin. Moreover, it should be underlined that vitamins also have a pelicular antioxidant function (1,5).

Antioxidants which have good bioavailabilitiy or molecules which have enzyme activity may be therapies that not only protect against the direct lung injurious effects of oxidants, but may fundamentally alter the inflammatory events that play an important part in the pathogenesis of COPD.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND OXIDATIVE STRESS

The Chronic Obstructive Pulmonary Disease is one of the commonest chronic diseases in the world. It is the forth-leading cause of chronic morbidity and mortality. COPD is a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lung to noxious particles and gases. The mechanisms involved in the pathogenesis of COPD include inflammation, disbalance between proteases and antiproteases, and oxidative stress.

COPD risk factors include host factors and environmental exposures, and the disease usually arises from an interaction between these two types of factors. Exposures include tobacco smoke, occupational dusts and chemicals, outdoor and indoor air pollution, infections and socioeconomic status. Host factors include genes, airway hyperresponsiveness, gender, nutrition and lung growth. However, the most striking relationship is between cigarette smoking and COPD. Nearly 90% of all COPD patients are smokers or ex-smokers. Yet, for unknown reasons only 20% of cigarette smokers develop COPD (7).

Cigarette smoke is a rich source of oxidants. That is a complex mixture of over 4700 chemical compounds, including high concentration of free radicals. One of these radicals is the semiquinone radical that reduces oxygen to superoxide anion. Nitric oxide (NO), a free radical physiologically produced by the organism, is also present in cigarette smoke in concentrations of 500-1000 ppm. This compound reacts quickly with the superoxide anion to form peroxynitrite. Nicotine, the main compound of cigerette smoke, decreases the activity of antiproteases, primarly α-1-antitrypsin. Hydrogen peroxide increases the antioxidant capacity of cigarette smoke. It has been demonstrated that cigarette smoke causes the burst of inflammatory cells, especially neutrophils (8).

Biopsies from the lung of COPD patients and specimens from peripheral airway walls contained an increased number of neutrophils and alveolar macrophages. Neutrophils recovered from the blood of smokers who have elevated peripheral blood leukocyte count elaborated more superoxide anion than leukocytes recovered from non-smokers. Also, leukocytes recovered from COPD patients have enhanced chemotaxic, proteolytic and myeloperoxidase activities *in vitro* (9). The activation of neutrophils and other inflammatory cells into the lung may also involve production of interleukin-8 (IL-8), which levels are increased in the sputum recovered from COPD patients (10). Interleukin-8 is also a potent chemotaxin for polymorphonuclears in vitro (11).

Congenital α-1-antitrypsin deficiency is known to lead to an imbalance between proteases and antiproteases, alteration of lung elastic structures and, eventually, to early development of emphysema, especially in smokers. In individuals without α-1-antitripsin deficiency it has been demonstrated that the enzyme is inactivated by oxidants by means of oxidation of methionine sites in position 358. This explains why emphysema develops even without genetic defect. The nicotine decreases the activity of α-1-antitrypsin. Inactivation of α-1-antitrypsin is followed by the activation of neutrophil elastase, which degrades elastin, membrane proteins and glycoproteins, producing epithelial lesions in the air spaces (12).

It has been observed that in smokers and COPD patients, the transcription factors such as NF-kB which regulate genes for pro-inflammatory mediators such as TNF-α and IL-8, are also produced. These mediators play an important role in COPD (13).

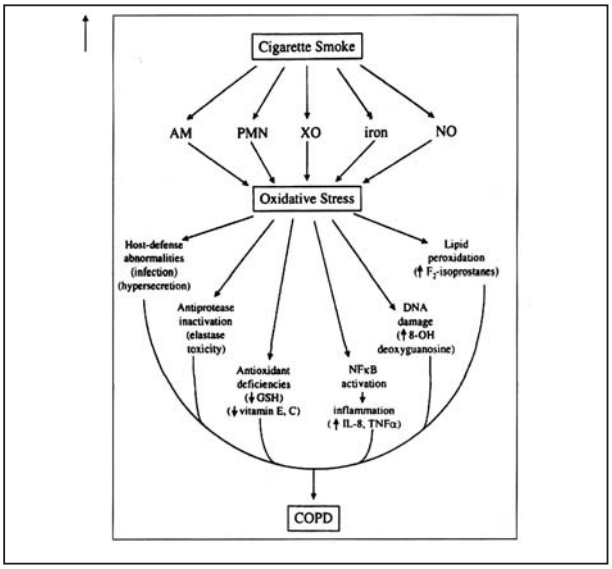

Figure 2. Cigarette smoke, oxidative stress and COPD

The most convincing way to determine the involvement of oxidative stress in COPD is to directly measure oxygen radicals in lung tissue or in exhaled air. However, direct measurement is difficult since oxygen radicals are a highly reactive and short-lived species; an alternative is to measure the biomolecules involved in free radical damage such as lipids and hydrogen peroxides. Patients in a stable phase exhale more hydrogen peroxide than control subjects and the H_2O_2 increases further during the acute exarcerbation (14).

Free radicals also trigger lipid peroxidation chain reaction. The resulting lipid radical reacts with oxygen to make a peroxyl radical, which then transforms polyunsaturated fatty acids into lipid hy-

droperoxides. Lipid hydroperoxides can impair membrane function, increase membrane permeability, and inactivate membrane-bound receptors and enzymes. Lipid hydroperoxides can also interact with antioxidants (such as alpha-tocopherol) or decompose after reacting with metal ions (such as iron and copper) or iron proteins such as haemoglobin, leaving hydrocarbon gases ethane, pentane) and unsaturated aldehydes (malondialdehid) as by-products. Lipid peroxidation products were increased in the plasma and lung lavage in COPD patients. Cigarette smoke exposure produced lipid peroxidation *in vitro*. The plasma levels of isoprostane F2α -III (a series of bioactive prostoglandin F2-like compounds that are made by free radical catalyzed peroxidation of arachidonic acid) were increased in smokers compared with non-smokers. The level of isoprostane F2α-III is a marker of oxidative stress in vivo (15).

CONCLUSION

Free radicals are produced by cells and by exposure to some xenobiotics. They can be extremely toxic to the cell, because they readily react with lipids, proteins, carbohydrates and nucleic acids. Oxidative stress results from an oxidant-antioxidant imbalance. Oxidative stress is thought to play an important role in the pathogenesis of COPD, not only through direct injurious effects, but also by involvement in the molecular mechanisms that control lung inflammation. The consequences of oxidative stress include oxidative inactivation of antiproteases, increased sequestration of neutrophils in the pulmonary microvasculature, gene expression of proinflammatory mediators, and airspace epithelial injury.

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KORISNOST OKSIDATIVNOG STRESA U HRONIČNOJ OPSTRUKTIVNOJ BOLESTI PLUĆA

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SAŽETAK

Slobodni radikali nastaju u mnogim fiziološkim i patološkim procesima. Oni su veoma reaktivni, te su aerobni organizmi, koji su konstantno izloženi dejstvu štetnih supstanci iz vazduha, razvili odbrambeni mehanizam, usmeren prvenstveno prema oksidativnim supstancama. Oksidatvni stres, koji se može definisati kao porast produkcije oksidativnih supstanci i/ili redukcija antioksidativnih sposobnosti, ima važnu ulogu u patogenezi hronične opstruktivne bolesti pluća. Oksidanti se nalaze u duvanskom dimu ili mogu biti oslobođeni od strane inflamatornih ćelija. Oni mogu reagovati sa proteinima, lipidima i nukleinskim kiselinama, što dovodi do disfunkcije ili smrti ćelije. Oksidativni stres takođe podstiče razvoj inflamacije i doprinosi disbalansu između proteaza i antiproteaza. Kod pacijenata obolelih od hronične opstruktivne bolesti pluća (HOBP) može se dokazati postojanje oksidativnog stresa.

***Ključne reči*: slobodni radikali, oksidativni stres, hronična opstruktivna bolest pluća, antioksidanti**