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Review

The participation of oxidative stress in the pathogenesis of bronchial asthma

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ABSTRACT

Reactive oxygen species are produced during oxygen reduction and are characterized by high reactivity. They participate in many important physiological processes, but if produced in high concentrations they lead to oxidative stress development and disturb pro-oxidative/anti-oxidative balance towards the oxidation reaction – leading to damage of lipids, proteins, carbohydrates or nucleic acids. Asthma is a chronic inflammatory disease of the airways of various pathogenesis and clinical symptoms, prevalence in recent years has increased significantly. Recently published literature point out the involvement of reactive oxygen species in the pathogenesis of asthma. Changes in the protein and lipid oxidation lead, among others, to pathological changes in the respiratory epithelial cells, an increase in vascular permeability, mucus overproduction, smooth muscle contraction or airway hyperresponsiveness (AHR).

The aim of this study is to present the current state of knowledge on the influence of oxidative stress parameters on asthma development.

Contents

Abbreviations: CAT, catalase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; GSSG, glutathione disulfide; MDA, malondialdehyde; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; SOD, superoxide dismutase; TAA, total antioxidative activity; TAC, total antioxidant capacity; TAS, total antioxidative status; tGSH, total glutathione; TOS, total content of oxidants.

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1. Introduction

Asthma is one of the most common syndrome in adults [1,2]. The incidence of asthma is growing – it is estimated that the world population of asthma sufferers is 300 million and in Europe – 30 million people are affected by the disease [3]. Each year about 250,000 people die prematurely of this disease. In 2010, asthma was related to 3404 deaths in U.S. [3,4]. Chronic inflammation in asthma is closely associated with airway hyperreactivity and leads to recurrent clinical symptoms such as shortness of breath, wheezing or breathing problems. These symptoms occur particularly frequently in the night and/or in the morning. The disease is therefore a significant medical, social and economic problem. Risk factors for the development of asthma, the impact of which has been well documented and confirmed include: genetic, environmental (e.g. air pollution, climate, smoking, passive exposure to tobacco smoke) and etiological (allergens, infectious agents) factors [5]. Recent reports point out the involvement of reactive oxygen species in the pathogenesis of asthma. Changes in protein and lipid oxidation lead, among others, to pathological changes in the respiratory epithelial cells, increase in vascular permeability, mucus overproduction, smooth muscle contraction or airway hyperresponsiveness [6–8].

The aim of this study is to present the current state of knowledge on the influence of oxidative stress parameters on the asthma development.

1.1. What we know about oxidants?

Reactive oxygen species (ROS) are called "oxidants". They are characterized by their ability to lead independent life and react with other compounds, leading to a formation of new ROS. They can react directly with lipids, proteins, and even with DNA [9–16]. ROS can be divided into two groups [17]. Free radicals are characterized by the loss of one or more electron and always strive to make up for the missing electron. Representatives of that group are: the hydroxyl radical, superoxide anion or alkoxy radical. The molecular oxygen also belongs to the radicals as it contains two unpaired electrons, and therefore it can be considered as a biradical [16–19]. Non-radical forms also include active forms of oxygen. These non-radical forms have "a full set of electrons" on valence orbitals. These compounds are able to lead to a formation of a free radical reaction and include: singlet oxygen, hydrogen peroxide, ozone or organic hydroxides [20–25].

1.2. Where do ROS come from?

Reactive oxygen species can come from two sources: endogenous and exogenous, and exposure to these sources can lead to changes in the physiology of the body [22,26].

The endogenous sources may include: mitochondria, peroxisomes, enzymes of cytochrom $P_{450,}$ NADPH oxidases, nitrogen oxide synthases and xanthine oxidases. Endogenous sources can be much more numerous. They might also include: epithelial cells, the endoplasmic reticulum, the heme proteins, the reaction of metal ions e.g. iron, copper or lung endothelial cells [27–32] (Fig. 1). NADPH oxidase, xanthine oxidase (XO), myeloperoxidase (MPO) and eosinophil peroxidase (EPO) play a key role in the endogenous formation of reactive oxygen species [33–39]. An important role is attributed to the NADPH oxidase, which is responsible for the formation of superoxide anion [40,41]. This enzyme is contained in neutrophils, eosinophils, monocytes and macrophages [40,42,43]. The essence of the formation of ROS is the activation of NADPH oxidase (Nox2). A corresponding signal activates the C5a receptor or N-formyl-methionyl-leucyl-phenylalanine (fMLP) receptor located in the phagocytic cell membrane. This leads to connecting to the p22 phox transmembrane subunit to gp91 phox, which together form cytochrome b558. Cytochrome b558 is present in the cell membrane. Then, by translocation of cytosolic complex, consisting of subunits p47 phox, p40 phox and p67 phox the cytochrome gets phosphorylated. By the activity of GTP, Rac protein binds to the 5 subunits. This leads to a formation of an active complex which consists of six subunits and is responsible for the production of $O_2^{\bullet\,-}$ [40,44]. Myeloperoxidase (MPO) plays an important role in catalyzing the formation of the reaction including HOCl, HOBr, and it does it with the application of H_2O_2, Cl-/Br- [45,46]. Mitochondria are responsible for the endogenous formation of active forms of oxygen [27–30]. NADH-CoQ oxidoreductase is responsible for the oxidation of NADH. In its structure it contains flavin mononucleotide (FMN) and centers of iron-sulfur (Fe-S) which play an important role in the transmission of electrons. The electrons are transported between complexes, due to appropriate proteins. Ubichinon (coenzyme Q-CoQ) is responsible for the transfer of electrons from complex I to III. Once it has accepted two electrons and two protons it converts into ubiquinol. Unfortunately, not always all the electrons are passed on. Then free radicals are formed [47]. Monoamine oxidase (MAO) and p66Shc are also involved in the production of ROS. MAO belongs to the flavoenzyme group, catalyzes the oxidation of amines and serves as a neurotransmitter. It is responsible for generation of $O_2^{\bullet-}$ and H_2O_2 [47]. p66Shc is responsible for the production of ROS at a time when it associates with cytochrome c [26]. Peroxisomes are responsible for e.g. fatty acid oxidation. They contain many oxidative enzymes leading to the formation of H_2O_2 e.g. xanthine oxidase (XO), which also produces $^1O_2$, but also to its degradation – catalase. They also generate the formation of superoxide anion ($O_2^{\bullet\,-}$) and hydroxyl radical ($^{\bullet}OH$) [26,32,48] (Fig. 2).

Exogenous factors play an important role in the production of ROS. Their presence is mostly a consequence of environmental and industrial pollution; e.g. compounds present in the air such as ozone, asbestos, and especially cigarette smoke [49,50,52]. Some other factors contributing to the production of ROS include: too strenuous exercise (which causes enhanced inhalation, and thus an increased amount of oxygen in the body), and ionizing radiation [51]. Various exogenous sources of ROS have been shown in Table 1.

1.3. What are the dangers of ROS in the body?

Too high level of ROS interferes with physiological processes in the body, finally leading to the pathogenesis of many diseases [53–58]. Imbalance of oxidation-antioxidant results in damage to lipids, proteins, DNA [59–62]. Lipid peroxidation can affect the nature of the cell membrane, particularly its fluidity. It also decreases