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REVIEW PAPER/*PRACA POGLĄDOWA*

Participation of reactive oxygen species in the pathogenesis of atopic dermatitis, allergic rhinitis and asthma

Udział reaktywnych form tlenu w patogenezie atopowego zapalenia skóry, alergicznego nieżytu nosa i astmy

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ABSTRACT

Reactive oxygen species (ROS) are any usually highly reactive chemical compounds that contain an oxygen atom with an unpaired electron in their structure. In physiological conditions, they are involved in many metabolic reactions in the body, while they are also involved in the pathogenesis of diseases such as atopic dermatitis, allergic rhinitis and asthma. Excessive ROS and antioxidant barrier dysfunction cause oxidative stress, resulting in increased oxidative damage in cells, disruption of their proper functioning and induction of a chronic inflammatory process.

KEY WORDS

atopic dermatitis, allergic rhinitis, asthma, reactive oxygen species.

STRESZCZENIE

Reaktywne formy tlenu (RFT) to zwykle wysoce reaktywne związki chemiczne, które zawierają w swojej strukturze atom tlenu z niesparowanym elektronem. W warunkach fizjologicznych biorą udział w wielu reakcjach metabolicznych zachodzących w organizmie, ale uczestniczą także w patogenezie chorób, takich jak atopowe zapalenie skóry, alergiczny nieżyt nosa lub astma. Nadmierne wytwarzanie RFT i dysfunkcja bariery antyoksydacyjnej prowadzą do rozwoju stresu oksydacyjnego, co skutkuje zwiększeniem uszkodzeń oksydacyjnych w komórkach, zaburzeniem ich prawidłowego funkcjonowania oraz indukcją przewlekłego procesu zapalnego.

SŁOWA KLUCZOWE

atopowe zapalenie skóry, alergiczny nieżyt nosa, astma, reaktywne formy tlenu.

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WHAT ARE REACTIVE OXYGEN SPECIES?

The term reactive oxygen species (ROS) refers to the molecules that can exist independently, and in their structure contain at least one oxygen atom and one or more unpaired electrons on the valence shell. The features that characterize the compounds in question are short duration, instability and very high reactivity (they can quickly initiate reactions, including chain reactions leading to the formation of other free radicals). Thanks to these properties, ROS are capable of taking electrons from other chemical compounds to gain stability [1, 2]. These molecules are most often formed as a result of metabolic changes occurring in the body, most notably the four-step reduction of oxygen to a water molecule [3]. ROS include highly reactive oxygen radicals and other compounds, also highly reactive that can lead to the formation of radicals [2].

WHAT ARE THE SOURCES OF ROS IN THE LIVING ORGANISMS?

ROS are generated in the organism especially during many metabolic processes. Mitochondria are the cellular organelles that produce the majority of ROS. Through the mitochondrial respiratory chain, especially complex I and III, superoxide is generated [2, 4]. Localized in the endoplasmic reticulum cytochrome P450, cytochrome b5 and Ero1p catalyze the electron transfer from thiols to the molecular oxygen resulting in the formation of hydrogen peroxide [2, 5]. In turn, the main ROS, which is generated in peroxisomes during beta oxidation of fatty acids is hydrogen peroxide. Under the activity of cyclooxygenase COX-1 and COX-2 in macrophages and also in phagocytes as a result of the so-called "oxygen burst" involving NADPH oxidases, ROS are also released [1, 6]. Endogenous sources also include the activity of some oxidoreductive enzymes, such as xanthine oxidase [4].

In addition to the basic metabolic processes, ROS in the body can also come from exogenous sources, which include alcohol, cigarette smoke, water and air pollutants, heavy metals (Fe, Cu, Co, Cr), UV radiation, burned or scorched foods and also certain drugs, like paracetamol [2, 4, 5].

WHY ARE ROS NECESSARY FOR THE PROPER FUNCTIONING OF THE BODY? WHAT ARE THE CONSEQUENCES OF EXCESSIVE ROS?

A small amount of ROS is required for the proper functioning of the body. In the physiological conditions, when the balance between ROS and antioxidants neutralizing them is maintained, these molecules play a role as mediators and regulators of many processes [3].

ROS participate in the body's defense mechanisms, including being released by phagocytes due to the oxygen burst, regulating the diameter of the blood vessels (they can cause vasoconstriction or vasodilatation) and also increase capillary permeability [3, 7–13].

These molecules are involved in maintaining genome stability, regulating transcription and signal transduction, in addition, they activate genes, such as the c-fos oncogene, regulate functioning of the cells, are secondary messengers in both growth and apoptosis, and regulate the activity of mitogen-activated protein kinases (MAPK) – proteins that direct cell division. They act as stimulators of glucose and serotonin transport [3, 12, 13].

The responsibility for neutralizing excessive ROS lies with antioxidants. This group of chemicals protect the cells from damage caused by free radicals. There are two main groups of antioxidants: enzymatic, the three most important are superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). These enzymes catalyze the reactions to convert ROS first to H_2O_2 and then to a water molecule. The second group is made up of non-enzymatic antioxidants, these are mostly organic compounds that intercept and inhibit the chain reaction of free radicals. Glutathione is one of the most important non-enzymatic antioxidants found in the body [14].

In the pathological conditions, in which the body's antioxidant defense is impaired, ROS could not be effectively neutralized, their excess leads then to a phenomenon known as oxidative stress. ROS are a key element in the pathogenesis of many diseases, e.g. diabetes, hypertension, atherosclerosis, cancers as well as atopic dermatitis (AD), allergic rhinitis (AR) and asthma.

ROS IN THE PATHOGENESIS OF ATOPIC DERMATITIS

Atopic dermatitis is defined as a chronic or recurrent inflammatory skin disease that affects epidermis and dermis. The disease is characterized by the presence of eczema accompanied by pruritus. It most often begins in early childhood, but can occur at any age [15]. It is estimated that the prevalence of AD among children is 20%, and in 50-60% of cases this disease develops within the first year of life and in 90% of patients by the fifth year [15, 16]. In contrast, AD affects 2–5% of adults [15].

A lot of factors, such as chemical substances, allergens, toxins and infections, directly or indirectly trigger the formation of ROS. Oxidative stress exacerbates inflammatory reactions and damages the skin barrier in skin diseases, including AD (Figure 1). Excess of ROS activates the nuclear κB transcription factor (NF-κB) which participates in the antioxidant response, but primarily has a significant role in the inflammatory and immune processes. Activation of

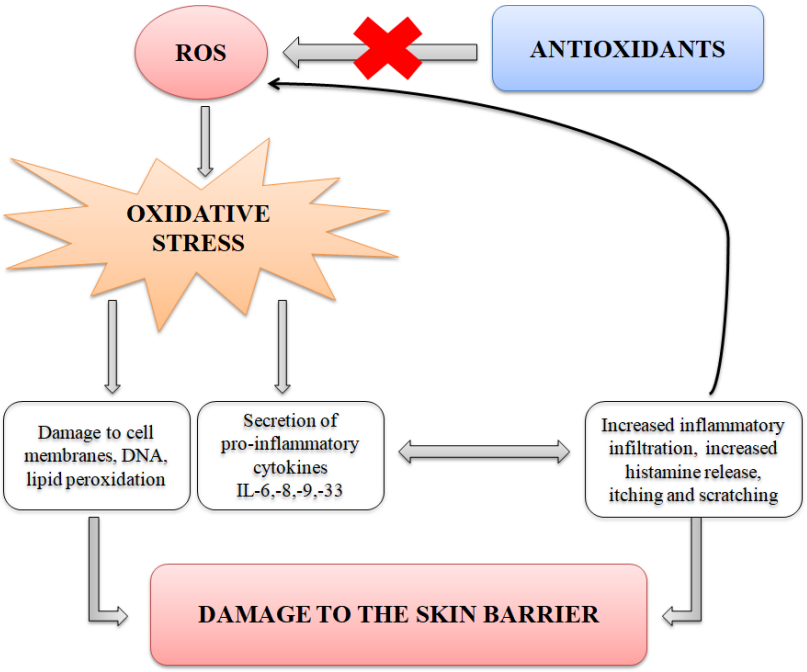

FIGURE 1. Relationship between ROS, oxidative stress, skin barrier damage and inflammation in AD

NF-κB induces the pro-inflammatory cytokines, such as interleukin (IL) -6, -8, -9 and -33 expression, resulting in an increase in the intensity of the inflammatory infiltration of the skin and the release of histamine, which only exacerbates the symptoms of AD [17]. ROS can directly cause damage and disruption of normal functions of keratinocytes as a result of DNA damage, loss of cellular enzyme activity and damage to the cell membranes through peroxidation of the lipids therein [17]. One of the most important lipids in the skin are ceramides, they are responsible for maintaining a normal, intact skin barrier. These lipids are composed of sphingosine and fatty acids, their peroxidation by ROS causes a breach in the skin barrier, so the passage of allergens and infectious agents is significantly easier, additionally the damaged skin barrier increases transepidermal water loss [17]. Histopathologically, all these intracellular changes manifest as edema, epidermal spongiosis and disruption of the stratum corneum [17].

It has also been observed that keratinocytes exposed to cigarette smoke (an external source of ROS) increase the production of H_2O_2. In excess, this compound can cause modification, translocation and degradation of the scavenger receptor class B type 1 (SR-B1), a protein that plays an important role in cholesterol transport and thus contributes to the skin barrier permeability [17].

ROS IN THE PATHOGENESIS OF ALLERGIC RHINITIS

Allergic rhinitis is defined as inflammation of the nasal mucosa, the characteristic symptoms of which are nasal discharge or the dripping of this discharge down the back wall of the throat, sneezing, nasal congestion or itching. The aforementioned clinical symptoms are triggered by an immunoglobulin E (IgE)-dependent inflammatory reaction to allergens [18]. AR is a common disease, it is estimated that 25% of children and 40% of adults are affected worldwide. A major part of the symptoms, about 80%, develop before the age of 20, peaking between the ages of 20 and 40, after which the symptoms gradually resolve [19].

The first stage of AR is allergen sensitization. Located in the nasal epithelium allergens are picked up by dendritic cells, which then present the antigen (allergenic peptides) to T lymphocytes. There is an induction of Th2 lymphocytes, which secrete a number of interleukins, such as IL-4, -5, -10 and IL-13. This process causes the transformation of B lymphocytes into allergen-specific IgE producing plasma cells. Then, the released IgE binds to the mastocytes and basophils onto their surface. Upon re-exposure, the same allergen binds to the IgE on the surface of mastocytes and basophils leading to their activation. Various mediators such as histamine and leukotrienes are released from the cells [20].

Oxidative stress is also involved in the pathogenesis of AR (Figures 2 A and B). H_2O_2 is a major signaling molecule in redox signaling, and is involved in the regulation of the activity of several transcription factors, like nuclear factor erythroid 2-related factor 2 (Nrf2) and NF-κB [20]. The Nrf2 and NF-κB signaling pathways have been implicated in the pathogenesis of this disease. The Nrf2/HO-1 signaling pathway plays a very important role in the reg-

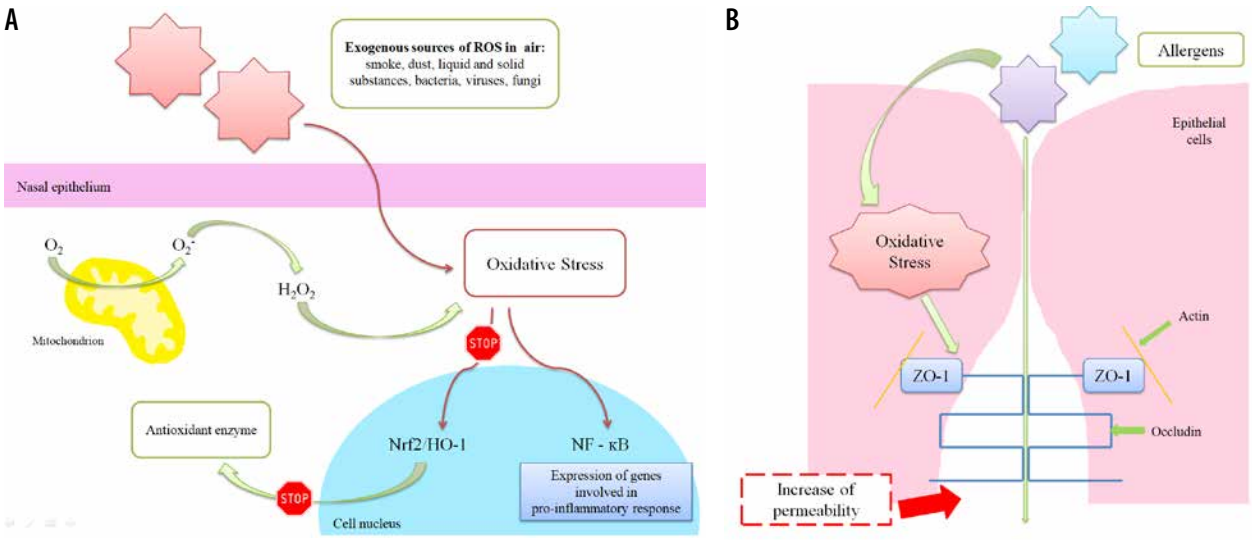

FIGURE 2. **A** – Effect of ROS on NRF2/HO-1 and NF-κB signaling pathways in the pathogenesis of AR. **B** – Effect of ROS and oxidative stress on skin epithelial barrier in AR and related to this consequences

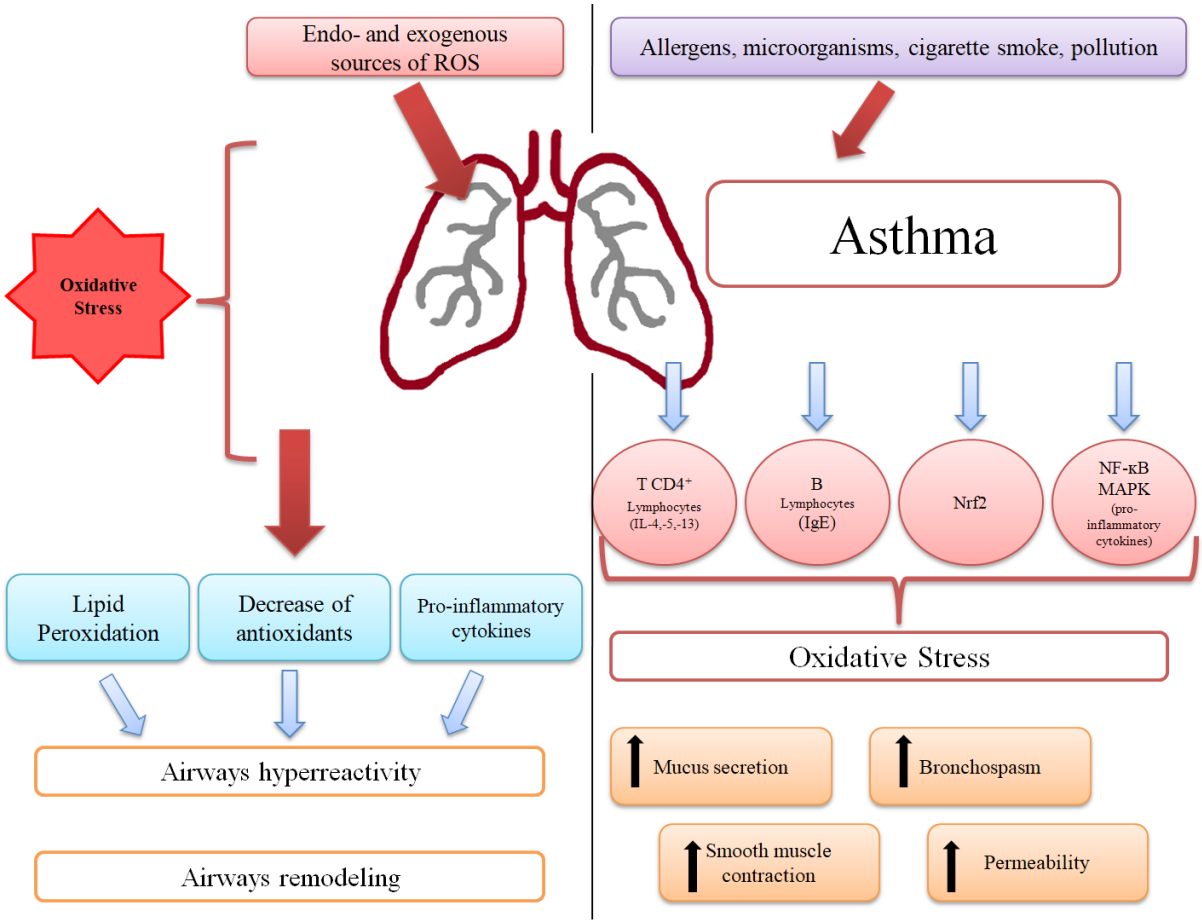

FIGURE 3. Participation of ROS in the pathogenesis of asthma

ulation of oxidative stress. Found in the air dust, smoke, various liquid and solid substances, as well as viruses, bacteria and fungi, exacerbate oxidative stress, resulting in inhibition of Nrf2/HO-1 signaling and decreased activity of antioxidant enzymes [21].

Upon oxidation by H_2O_2, the inhibitory subunit of NF-κB is released, this factor becomes activated causing the expression of genes involved in the pro-inflammatory response [20].

Oxidative stress also causes dysfunction of the epithelial cell barrier in AR. In the nose, this barrier is made up of tight cell-to-cell junctions that consist of zonula occludes (ZO-1, ZO-2 and ZO-3) proteins and integral membrane protein, such as occludin [21].

In patients with AR, altered expression of occludin and ZO proteins leads to damage to the epithelial barrier, and consequently, epithelial permeability is also increased. Due to this, the absorption of allergens and harmful exogenous particles through the nasal epithelium is facilitated [20].

ROS IN THE PATHOGENESIS OF ASTHMA

Asthma is a chronic inflammatory disease of the airways, usually accompanied by symptoms such as a shortness of breath, wheezing, a squeezing sensation in the chest and a cough of variable frequency, especially occurring at night or in the early morning. Many cells are involved in the development of this heterogeneous disease, especially mast cells, eosinophils and lymphocytes. Chronic inflammation is associated with bronchial hyperresponsiveness, which leads to bronchial remodeling [22]. Approximately 300 million people worldwide suffer from asthma [22]. A characteristic feature of the disease entity in question is the increased production of ROS in lungs. Cells, like mast cells, neutrophils, eosinophils, macrophages and monocytes produce ROS naturally, but also after allergen stimulation [23]. In asthmatics, the concentration of ROS in exhaled air is very high, moreover this concentration correlates with the severity of the disease [23].

The lungs of asthmatics have lower levels of antioxidant enzymes, such as SOD, CAT and GPx, in addition, the activity of these enzymes is reduced in asthma. ROS, as in AR, are involved in the regulation of Nrf2 and NF-κB pathways. When oxidative stress remains low, Nrf2 transcription factor, which is responsible for a wide range of antioxidant, anti-inflammatory and cytoprotective activities, is activated. At this stage antioxidants can fully restore redox homeostasis [24]. In contrast, when oxidative stress intensifies and the body is unable to neutralize too much ROS, the Nrf2 signaling pathway is inhibited, activating NF-κB factor and mitogen-activated protein kinase (MAPK), which trigger pro-inflammatory response [24]. Within the respiratory tract, ROS react with lipids.

Their peroxidation (oxidation) results in the formation of, for example isoprostane and ethane. In addition, excess ROS inhibit Th1-type response and promote Th2-type response.

Damage to proteins, lipids and nucleic acid as a result of oxidative stress leads to pathological changes in airway epithelial cells, resulting in increased airway permeability and hyperresponsiveness, as well as mucus production [25] (Figure 3).

SUMMARY

It is clear that oxidative stress is involved in the pathogenesis of many diseases. The chronic inflammatory process triggered by the phenomenon in question in AD, AR and asthma is one of the key elements of these diseases. Therefore, there is a need for further studies to better understand the relationship between oxidative stress and the aforementioned diseases, as well as to evaluate the effectiveness of antioxidants as therapeutics.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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