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Advanced oxidation protein products — biological marker of oxidative stress

Zaawansowane produkty utleniania białek – biologiczne markery stresu oksydacyjnego

Anna Cwynar[1], Dorota Olszewska-Słonina[1], Bartosz Czerniak[1], Magdalena Źyła[2]

[1] Katedra Patobiochemii i Chemii Klinicznej, Collegium Medicum w Bydgoszczy

[2] Katedra Psychiatrii, Collegium Medicum w Bydgoszczy

ABSTRACT

Advanced oxidation protein products (AOPPs) are mostly derivatives of oxidatively modified albumin. The results of many experimental studies confirm intensification of oxidative modifications of proteins and an increase in concentration of advanced oxidation protein products (AOPPs) in different pathological conditions, particularly those with well documented involvement of oxidative stress in their etiopathogenesis, but also those where its role is not yet well understood. Currently intensive research is carried out on the possibility of using AOPPs as useful indicators for diagnosing, prognosis and monitoring of diseases.

Keywords: advanced oxidation protein products, autoimmune disease, oxidative stress

STRESZCZENIE

Zaawansowane produkty utleniania białek (AOPPs), to najczęściej pochodne zmodyfikowanej oksydacyjnie albuminy. Wyniki licznych badań doświadczalnych potwierdzają nasilenie oksydacyjnych modyfikacji białek i wzrost stężenia zaawansowanych produktów utleniania białek (AOPPs) w różnych stanach patologicznych, szczególnie tych o dobrze udokumentowanym udziale stresu oksydacyjnego w ich etiopatogenezie, ale także takich, w których jego rola nie jest jeszcze dobrze poznana.. Obecnie trwają intensywne badania nad możliwością wykorzystania AOPPs, jako użytecznych wskaźników do diagnozowania, prognozowania oraz monitorowania chorób.

Słowa kluczowe: zaawansowane produkty utleniania białek, choroby autoimmunologiczne, stres oksydacyjny

INTRODUCTION.

Advanced oxidation protein products – AOPPs, were first identified and described in 1996 by Witko – Sarsat et al. These are oxidized derivatives of albumins, n, fibrinogen and lipoproteins. The system myeloperoxidase - hydrogen peroxide (H_2O_2) - halide is most important in the formation of AOPPs [1, 2].

Dityrosine, carbonyl groups and cross link are the most abundant in the structure of AOPPs. Advanced oxidation protein products has biological properties similar to those which are shown by advanced glycation end products (AGEs). It was indicated that AOPPs are indentified and bound by the same receptor – RAGE (receptor for advanced glycation end products), which induces generation of intracellular changes and extracellular disorders [3].

Physiologically AOPPs are formed lifelong with a slight intensity increasing with age. Advanced oxidation protein products, as agents participating in the etiopathogenesis and progression of diseases with inflammatory and autoimmune origin, have become the object of intensive research due to involvement of oxidative stress in their course, despite often different causal mechanisms [4, 5].

There have been described suggested mechanisms determining biochemical and clinical changes under the influence of increased oxidative stress (OS) in these diseases.

MECHANISM OF DEVELOPING AOPPs.

Increased oxidative stress and related generation of reactive oxygen species (ROS) play the key role in formation of AOPPs. Additional stimulus leading to the release of considerable amounts of ROS are glycation protein products stimulating phagocytic cells. Increased processes of oxidation and glycation are closely linked and referred to collectively as processes of glycooxidation. AGE, after binding to specific receptors, activate monocytes and macrophages and also modulate the activity of neutrophils inducing inflammatory processes. Advanced oxidation protein products, binding through the same RAGE receptors, have similar clinical effects [3, 6].

Activated mononuclear phagocytic cells may create reactive forms of oxygen, which are products of excitation Or reduction of molecular oxygen. Superoxide anion ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2) are substrates for further transformations involving metals and myeloperoxidase (MPO). Hydrogen peroxide, under the influence of neutrophil MPO, in the presence of halide ions (mostly Cl^-) participates in the formation of very active, oxidizing halogenated compounds, such as hypochlorous acid (HOCl) [3, 6, 7].

Hypochlorous acid is one of the strongest physiological non-radical oxidants. Its reaction with ammonia and amino groups of proteins results in formation of reactive chloramine (NH_2Cl). Halogenated compounds (HClO and NH_2Cl) are directly involved in degradation of native protein structures and their transformation into AOPP particles. Tyrosine residues are especially susceptible to the oxidizing action, being transformed into dityrosine which induces the formation of aggregates and cross-linking in protein structure [3, 7].

Oxidatively modified albumin has a high affinity to the RAGE receptor in the endothelium. It causes fast activation of intracellular transmitters and proinflammatory mediators. Initiation of inflammatory processes is initiated simultaneously with starting the

production of the nuclear transcription factor B (NF-B) activating the expression of cytokine genes, growth factors and adhesion molecules, which facilitates binding of endothelial cells to activated monocytes and leads to exacerbation of the inflammation. The intensity of reactions stimulated by binding AOPPs – RAGE and the degree of severity of the inflammation process is more marked than in the case of interaction of AGE with the same receptor [4 - 6]

ROLE OF AOPPs IN PATHOMECHANISM OF AUTOIMMUNE DISEASES.

Advanced products of protein oxidation as factors participating in pathogenesis and progression of diseases with autoimmune background have become an object of intensive research due to the involvement of oxidative stress. Most studies concerning the role of AOPPs in the pathogenesis and progression of these diseases refer to disorders within the connective tissue, first of all rheumatoid arthritis (RA). The etiology of these diseases is not completely explained, but the role of inflammatory reaction in their development is well known. The inflammatory mechanism is complex and described in detail in many works [8, 9].

The role of AOPPs in the pathogenesis and course of rheumatoid arthritis.

Rheumatoid arthritis (RA) is a long - lasting, systemic inflammatory disorder that may affect the joints and other areas of the body**.** The main pathogenetic factor of RA is the process of autoimmunization, whose primary cause is "breaking" immune tolerance to antigens of own cells and tissues and development of humoral and cellular reactions against them. The etiological agent of RA has not been fully identified, the crucial role of infection with viruses or bacteria is pointed, but free radicals, generated by lymphocytes T infiltrating the synovium, neutrophils, macrophages and local inflammatory reaction, are regarded as the main agent, directly responsible for tissue damage. Another source of ROS in the course of RA may be also subsequent events of hypoxia (during movement) and reperfusion (at rest after performed movement) in the joints [8, 10].

The studies concerning disturbances of oxidant-antioxidant balance in the course of RA showed significantly a decreased efficiency of enzymatic and non-enzymatic antioxidants and an increased concentration of OS parameters, including AOPPs in blood serum of the patients.

AOPPs were regarded as proinflammatory mediators of OS playing an important role in the etiology and pathogenesis of RA [4, 11].

Significantly higher concentration of advanced oxidation protein products in patients with chronic form of RA was connected with deterioration of renal function and At the same time it was also identified as a factor exacerbating disorders of this organ [10].

Also activated neutrophils are indicated as a source for increased synthesis of ROS and a significant factor in the pathomechanism of this disease [4, 12].

PRESENCE OF AOPPs IN HEALTHY PEOPLE.

Slight concentrations of AOPPs are also observed in the blood of health people. Physiologically the process of their formation proceeds with a low intensity and increases with age. The highest concentration of AOPPs occurs in elderly people between 66 a 89 years of age. A relationship between the concentration of advanced oxidation protein products and the kind of eaten products has also been indicated. People using vegetarian diets and high - sodium foods have increased levels of blood AOPPs. Similar relationship is observed in obese people [3].

DEGRADATION AND ELIMINATION OF AOPPs.

In spite of intensive research on the structure and properties of AOPPs, the mechanism of their elimination and degradation has not yet been well understood. RAGE receptors and degradation in lysosomes and proteasomes are most likely to be of utmost importance in this process. However, only slightly oxidized proteins undergo complete degradation. The other oxidatively modified proteins accumulate in the endosomal – lysosomal system. This leads to impairment of function of proteasomes and mitochondria, destabilization of lysosomes, protease leakage into the cytosole and, consequently, to cell apoptosis. Also a possible involvement of scavenger receptors class A and B of macrophages (SRA, scavenger receptor class A and CD36) in removing AOPPs is also observed [3].

SUMMARY.

AOPPs, as oxidatively modified forms of albumin, reflect the degree of damage to the body proteins in conditions of severe oxidative stress. Intensive research are still conducted on possibility of using AOPPs as useful indicators for the diagnosis, predicting and monitoring of diseases.

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