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THE ROLE OF OXIDATIVE STRESS IN THE ONSET OF ACUTE OTITIS MEDIA IN CHILDREN

ULOGA OKSIDATIVNOG STRESA U NASTANKU AKUTNOG OTITIS MEDIJA KOD DECE

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Abstract

The role of oxidative stress (OS) in the onset of various diseases has long been the subject of numerous studies and has been proven that oxidative stress play an active role in the development of AOM and subsequent tissue damage. Oxidative stress is associated with decrease in antioxidants or with increase in the production of oxidants. This leads to the peroxidation of phospholipids and causes damage in the vital substances of the body such as lipids, lipoproteins, proteins and DNA. At the end of the process, polyunsaturated fatty acids are hydrolysed into biologically active compounds and one of the most important representative is malondialdehid (MDA), which reflects lipid peroxidation (LPO) in the body and is commonly used in analytical methods as its parameter. Normally the tissue damage caused by oxidants in the body is controlled by enzymatic and nonenzymatic antioxidant defense systems. The most important antioxidant enzymes are superoxide dismutase (SOD), glutathione reductase (GHPx), and catalase (CAT). Among non-enzymatic antioxidants are allocated glutathione (GSH), which is often used as an analytical parameter of oxidative stress, then tocopherol (vitamin E), ascorbic acid (vitamin C), carotene (vitamin A), urea and albumin AOM is a significant cause of patient's morbidity and cost to the health service. Recent advances in the microbiology, genetics, drug delivery systems and further research of influence of lipid peroxidation status and nonenzymatic antioxidant capacity offer the potential for better treatments of AOM in the future.

INTRODUCTION

According to the results of recent research, acute otitis media (AOM) is the most frequent disease in children worldwide. Pathogenesis of the disease is complex and is the result of several factors of endogenous and exogenous origin.

The role of oxidative stress (OS) in the onset of various diseases is very far back the subject of numerous researches, and it has been documented that the causes of OS play an active role in the onset of AOM and subsequent tissue damage. OS is defined as the state of disturbed cell redox homeostasis caused by decreased activity of an protective antioxidative system or as the increased production of reactive species.

Reactive species (RS) of various origin as the causes of oxidative stress disturb cell's homeostatic processes, lead to the damage of its structures and to the subsequent cell death. The most sensitive site is the cell membrane, due to its high lipid content, where the reaction of oxidative damage begins by causing lipid peroxidation. The result of this process is the production of bioactive molecules which further react with the other structures of cell membrane. The most important representative of this group of compounds is malonaldialdehide (MDA), which is considered as biomarker of lipid peroxidation, and is the most frequently used as a parameter in analytical methods.

Under normal conditions, tissue damage caused by the action of reactive oxygen species in the body, are controlled by enzymatic and nonenzymatic systems of antioxidative

protection The most important antioxidative enzymes are superoxide dismutase (SOD), glutathione reductase (GHPx) and catalase (CAT). Among nonenzymatic antioxidants are distinguished such as glutathione (GSH), which is often used as analytical parameter of oxidative stress, in addition to tocopherol (vitamin E). ascorbic acid (vitamin C), carotene (vitamin A), urea and albumin.

The results of numerous published researches proved that the follow up of oxidative stress parameters are of the great importance in prevention, diagnosis and outcomes of treatment of AOM and similar or combined diseases.

ACUTE OTITIS MEDIA

Acute otitis media (AOM) is a bacterial or viral infection of the middle ear representing the leading cause of morbidity in children [1]. Due to the possible consequences for the development in early childhood and to the complications of hearing damage leading to the increased public health charges, AOM is a significant medical problem [2]. It is estimated that between 50% and 85% of children suffered at least one episode of AOM until the third year of life, with the most appearing at the age between 6 and 15 months [3]. Recent data show that in the relation to the whole world children population, 709 milion new cases appear yearly.

The etiology of AOM is complex and is the result of the interaction of several different factors: anatomical characteristics (dimensions and „immaturity" of Eustachian tube), pathophysiology (the consequence of microbial agents and immune system interaction of the host) and of the biology of the middle ear cells. This is an acute infection characterized by the following signs and symptoms: earache, often with temporary hearing loss, erythematous tympanic membrane, fever and general bad condition.

It has been proven that small children are more prone to AOM, because of the immaturity of the parts of nasopharynx and of the anatomy of eustachium tube which is shorter in children, flexible and positioned horizontally, all of which enables easier pathogen penetration into the middle ear [5]. It is known that the viral infection of the upper respiratory tract (sincicial, adeno and cytomegaloviruses) very often procedes or coincide with AOM episodes, i.e. having the central role in its development, by creating an encirclement alleviating bacterial colonization, their adhesion to the cells and penetration into the middle ear. According to the results of recent research, the most often detected causative infective agents of the upper respiratory tract were *S.pneumoniae* and *H.influenzae* which have been isolated in an effusion content in AOM [6,7,8].

AOM is a disease which development depends not only on the child's genomic characteristics, but also on the exposition to microorganisms and provocative environmental factors such as passive exposition to the tobacco smoke, absence or insufficient breast feeding, collective stay, and the presence of atopic manifestations [9].

OXIDATIVE STRESS

The role of oxidative stress in the developmet of many diseases has been known for a long time. It denotes excessive production, or inadequate elimination of reactive species or free radicals, leading to the damage of biomolecules, cell structures and cell death [10]. These compounds shown in Table 1 are devided into reactive oxygen and nitrogen species are continually produced in the body and in the low concentrations play physiological role, while in the high concentrations are toxic.

Table 1. *Reactive species*

	Reactive species	
[1] ROS	O_2	superoxyl anion radical
	HO	hydroxyl radical
	ROO	peroxyl radical
	RO	alcoxy radical
[2] RNS	NO	nitroxyl radical
	NO_2	nitrogen dioxide radical

[1] ROS – Reactive Oxygen Species,
[2] RNS – Reactive Nitrogen Species

Protective system ahown in Figure 1 act in such a way as to prevent the toxic effects of RS and to maintain homeostasis is called antioxidative system (AOS) and is devided into an enzymatic (superoxydedismutase (SOD), glutathione reductase (GHPx) nad catalase (CAT) et al.) and nonenzymatic (glutathione (GSH), metalotienin, vitamins E and C, coenzyme Q, urea, albumin et al.). It is important to note that besides protective, AOS has repairable role also [11,12].

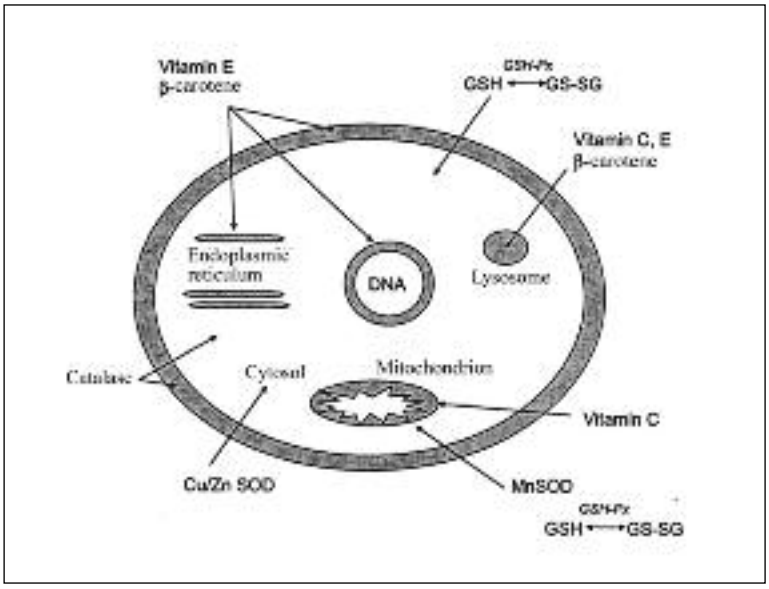

Fig. 1. *Multiple sites of body's antioxidative defense.*

LIPID PEROXIDATION

The great number of studies delt with predisposing factors of AOM etiology and its subspecies snd it has been proven that in the origin of this disease decisive role play genetic factors, malfunction of Eustachian tube, autoimmunity, infection, endotoxins, cytokines, as well as the products of lipid peroxidation produced as a consequence of OS [13]. Reactive species of various origin as causatives of oxidative stress disturb homeostatic cell processes, with the significant role in immune response and metabolism [14]. Defense cells in the body, such as neutrophils, monocytes and macrophages produce RS in the fight against antigenic agents, but their excessive production causes tissue damage, leading thus to he further aggravation and slowing down the recovery of the body and prolonging the time of inflammation [15]. In the cell itself, the most sensitive sites of RS action are cell membrane and cell organelles, due to the high content of polyunsaturated fatty acids, where the lipid peroxidation, reaction of oxidative damage begins [16].

MARKERS OF LIPID PEROXIDATION/OXIDATIVE STATUS

Lipid damage of cell membrane leads to the changes in its permeability, with consequent formation of bioactive molecules which further react with the other structures of the cell membrane additionally disturbing its integrity [17]. So, for example hydrolysis of polyunsaturated fatty acids arise bioactive aldehide and carbonil species among which is one of the most representative malondialderhyde (MDA) [18,19]. As the terminal product of oxidative damage of polyunsaturated MDA represents the marker of lipid peroxidation (LPO) which is relatively quickly and easily detected by thiobarbituric acid reactive substances (TBARS), and the great advantage of this method is its application in various biological samples. Many papers have shown the correlation between lipid damage caused by oxidative stress and significantly increased values of MDA in blood samples, serum or tissue in children with AOM and COM in relation to the controll group of healthy children [20, 21, 22].

In addition to follow up of the oxidative stress products in the body, it is also very important the determination of the main products of the agents of cell's antioxidative defense system, of which one of the important representatives of this group is glutathione (GSH). Glutathion belongs to the group of nonenzymatic hydrosolubile and very active cell's antioxidants representing the main defense against endogenous Reactive Oxygen Species (ROS) in the process o glutathione redox circle. The consumption of GSH for 20% to 30% may lead to the significant damage of the cell's structures and to the cell death. It has been proven that in the biological samples of children with AOM the values of GSH were significantly decreased in relation to the values for control group of healthy children, representing thus the measure of the response of the body of the body's antioxidative system [23]. Also, it has been proven that due to the inflammatory processes in the middle ear, the increased concentration of ROS appears in the red blood cells to the initation of otitis media [24].

CONCLUSION

Oxidative stress as a pathophysiological mechanism play an important role in the defense of the initiation of the numerous diseases. By following parameters of oxidative stress and the activity of antioxidative system it is possible to diagnose and differentiate the disease of the middle ear (otitis media and acute otitis media) more precisely and improve the therapeutic approach and the possibility of their prevention. The results of so far researches show significant connection between the increased concentrations of oxidative stress poroducts in the tested biological samples with decreased concentrations of the main reductive agents of the cell's antioxidative system in the presence of such diseases.

Sažetak

Akutni otitis media i dalje, a prema skorašnjim istraživanjima predstavlja najčešće oboljenje kod dece širom sveta. Patogeneza ovog oboljenja je kompleksna i rezultat je interakcije više faktora, endogenog i egzogenog porekla. Uloga oksidativnog stresa u nastanku raznih oboljenja odavno je predmet brojnih istraživanja, a dokazano je da uzročnici oksidativnog stresa imaju aktivnu ulogu u razvoju akutnog otitis media i naknadnih oštećenja tkiva. Oksidativni stres se definiše kao stanje narušene redoks homeostaze u ćeliji do koga dolazi usled smanjenjene aktivnosti sistema antioksidativne zaštite ili povećane produkcije reaktivnih vrsta. Reaktivne vrste (*Reactive Species*) različitog porekla kao uzročnici oksidativnog stresa narušavaju homeostatske procese u ćeliji, dovode do oštećenja njenih struktura i posledično do smrti ćelije. Najosetljivije mesto delovanja je ćelijska membrana zbog visokog sadržaja lipida gde započinje reakcija oksidativnog oštećenja odnosno lipidna peroksidacija. Posledica ovog procesa je stvaranje bioaktivnih molekula koje dalje reaguju sa drugim strukturama ćelijske membrane. Najvažniji predstavnik ove grupe jedinjenja je malondialdehid, koji se smatra markerom lipidne peroksidacije i najčešće se koristi u analitičkim metodama kao njen parametar. U normalnim uslovima oštećenja tkiva uzrokovana dejstvom reaktivnih kiseoničnih vrsta u organizmu, kontrolisana su enzimskim i neenzimskim sistemom antioksidativne zaštite. Najvažniji antioksidans enzimi su superoksidna dizmutaza, glutation reduktaza i katalaza. Među neenzimskim antioksidansima izdvajaju se glutation, koji se često koristi kao analitički parametar oksidativnog stresa, zatim tokoferol (vitamin E), askorbinska kiselina (vitamin C), karoten (vitamin A), urea i albumin. Niz istraživanja i literaturnih podataka dokazuje da je praćenje parametara oksidativnog stresa od velikog značaja za prevenciju, dijagnostikovanje i odgovarajući tretman akutnog otitis media i srodnih ili udruženih oboljenja.

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