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REVIEW / PRACA POGLĄDOWA

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POSITIVE EFFECT OF GENERATION OF REACTIVE OXYGEN SPECIES ON THE HUMAN ORGANISM

POZYTYWNE ASPEKTY GENEROWANIA REAKTYWNYCH FORM TLENU W ORGANIZMIE CZŁOWIEKA

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S u m m a r y

For aerobes including human, the oxygen is an indispensable element for life, but simultaneously at too high concentration this gas becomes toxic. On the physiological level, the appropriate concentration of oxygen which is the source of reactive oxygen species (ROS), is necessary for the proper functioning of the organism. O_2 and its derivatives as free radicals influence the maintenance of homeostasis of the human organism by acting at a cellular level on repair, protective, and energetic mechanisms, and at an intercellular level on communication between neighbouring cells and tissues. In turn, excess or impaired removal of ROS lead to so-called 'oxidative stress' that is associated with the pathogenesis of many diseases – from cancers to neurodegenerative, autoimmune and infectious diseases. In the paper the significance of only physiological level of reactive oxygen species in the human organism was presented.

S t r e s z c z e n i e

Dla organizmów aerobowych, w tym człowieka, tlen jest pierwiastkiem niezbędnym do życia, ale równocześnie w zbyt wysokich jego stężeniach staje się toksyczny. Na poziomie fizjologicznym, odpowiednie stężenie tlenu i reaktywnych form tlenu (RFT), których jest źródłem, jest niezbędne do prawidłowego funkcjonowania organizmu. O_2 i jego wolnorodnikowe pochodne wpływając na mechanizmy naprawcze, ochronne i energetyczne komórek oraz na komunikację między sąsiadującymi komórkami i tkankami, biorą udział w utrzymaniu homeostazy organizmu człowieka. Nadmiar RFT lub zaburzenia w ich usuwaniu prowadzą z kolei do tzw. stresu oksydacyjnego, który związany jest z patogenezą wielu chorób – od nowotworów, po choroby neurodegeneracyjne, autoimmunologiczne i infekcyjne. W pracy przedstawiono znaczenie wyłącznie fizjologicznego poziomu reaktywnych form tlenu w organizmie człowieka.

Key words: reactive oxygen species, oxidant-antioxidant balance, human physiology

Słowa kluczowe: reaktywne formy tlenu, równowaga oksydacyjno-antyoksydacyjna, fizjologia człowieka

INTRODUCTION

Nowadays, there is clear that oxygen is a kind of double-edged sword. It allows aerobic organisms to obtain significantly more energy than anaerobic organisms in fermentation processes; moreover, the oxygen is an essential element that allows them to live. On the other hand, aerobic organisms did not feel better at higher concentration of oxygen than atmospheric – then the oxygen is toxic to them. Depending on exposure time and oxygen concentration, toxic effects range from being worse to diseases (neurodegenerative, autoimmune, infectious, cancerous) and permanent organs damage [1-3]. In the paper only physiological importance of oxygen derivatives in the human organism was presented.

SOURCES OF REACTIVE OXYGEN SPECIES IN THE HUMAN ORGANISM

Reactive oxygen species (ROS), including oxygen free radicals (OFR), can be formed in the human organism by an action of external physical factors such as ionizing and ultraviolet radiation, ultrasounds, as well as one of the mildest method of treatment of biological material – lyophilisation. ROS can be also produced as a result of an action of air ionizers, even though producers and dealers ensure that they have a positive effect on our health and ward off allergies [1].

The oxygen is 7-8 times more soluble in organic solvents than in water. This property of oxygen is crucial for the human organism because physical properties of lipid layer of biological membrane are similar to properties of organic solvents. Therefore, the most important sources of ROS in the human organism are endogenous sources. There are many reactions during which intracellular ROS are generated: redox cycling of xenobiotics, respiratory proteins oxidation, reactions inside peroxisomes, oxidation of reduced forms of low-molecular cell components, photoreduction/photooxidation reactions and reactions of some specific enzymes. Nevertheless, a main source of ROS in the human organism is the respiratory electron transport chain [1, 4].

CELLULAR RESPIRATION – THE ELECTRON TRANSPORT CHAIN (ETC)

Aerobic respiration is based on a reduction of molecules of oxygen (O_2) to molecules of water, thereupon the energy is obtained:

$C_6H_{12}O_6$ (glucose) + $6O_2 \rightarrow 6CO_2 + 6H_2O$ + 36ATP

In fact, the molecular oxygen absorbed from the air is metabolised in the respiratory chain that is located at the inner membrane of mitochondria. Four electrons and four protons with cooperation of many enzymes and coenzymes are required to complete reducing by cell the oxygen to the water (fig. 1) [1].

O_2 reduction may also be incomplete by premature electron leakage to the oxygen that occurs. Then, there is usually the one-electron reduction, thus being one of the main source of superoxide radical anion ($O_2^{\bullet -}$) – a harmful OFR that gives next ROS – fig. 1, 2. The oxygen reduction may also be two- or/and three-electron, giving other reactive oxygen species as the end products – figure 1 [5].

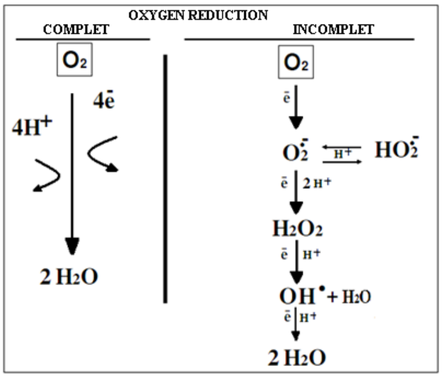

Fig. 1. *Reduction of oxygen in the respiratory chain*
Ryc. 1. *Redukcja tlenu w łańcuchu oddechowym*

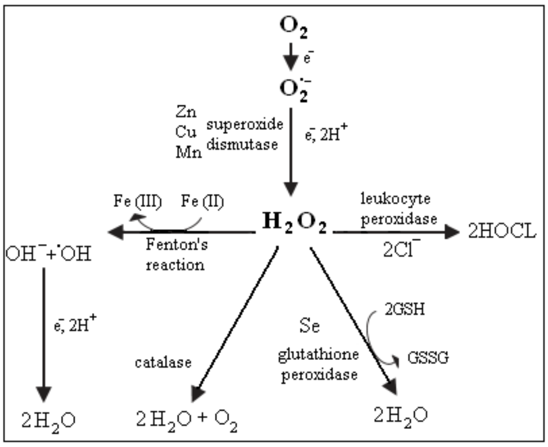

Fig. 2. *Superoxide radical anion as a source of other reactive oxygen species*
Ryc. 2. *Anionorodnik ponadtlenkowy jako źródło innych reaktywnych form tlenu*

SELECTED EXAMPLES OF MOST IMPORTANT RADICALS

The most abundant and important radicals in the human organism are those located on carbon, oxygen, sulfur, and nitrogen atoms. The carbon-centered radicals such alkyl (RC$^{\bullet}$HR'), hydroxyalkyl (RC$^{\bullet}$HOH), acyl (RC$^{\bullet}$=O), α-(alkylthio) alkyl (RSC$^{\bullet}$HR') radicals are formed mostly due to hydrogen atom elimination from organic molecules. Especially significant among the oxygen-centered radicals are: hydroxyl ($^{\bullet}$OH), peroxyl (ROO$^{\bullet}$), alkoxyl (RO$^{\bullet}$), phenoxyl (ArO$^{\bullet}$), and semiquinone (HO-ArO$^{\bullet}$) radicals and a superoxide radical anion ($O_2^{\bullet -}$). While the $^{\bullet}$OH is the most reactive among the O-centered radicals in biological systems, ROO$^{\bullet}$ is probably the most numerous and, except for $O_2^{\bullet-}$, these radicals are oxidants. The representative of S-centered radicals is the thiyl radical ($RS^{\bullet}$) which is an intermediate in the one-electron reduction of thiols (RSH) to disulfides (RSSR). Some sulfur radical cations ($R2S^{\bullet+}$, $(R2SSR2)^{\bullet+}$, $(RSSR)^{\bullet+}$, $Ar2S^{\bullet+}$) have also attracted interest for their application in biochemical synthesis as intermediates in biological redox systems. N-centered radicals (the most common: $^{\bullet}NO$, $^{\bullet}NO_2$ and $^{\bullet}NO_3$) have great importance in the field of physiological functions of the human organism, especially nitric oxide ($^{\bullet}NO$). This molecule may have antioxidant or oxidant properties depending on $O_2^{\bullet-}$ concentration. Superoxide radical anion gives in reaction with nitric oxide peroxynitrite ($ONOO^-$), as strong oxidant [1, 2].

MOLECULAR IMPORTANCE OF ROS

ROS are the most numerous oxidants in the cell, while reducers (antioxidants) are a group of their scavengers. The ratio of the one to the other *id est* the redox potential of the cell determines whether, a cell will divide, differentiate or die [6, 7] – figure 3.

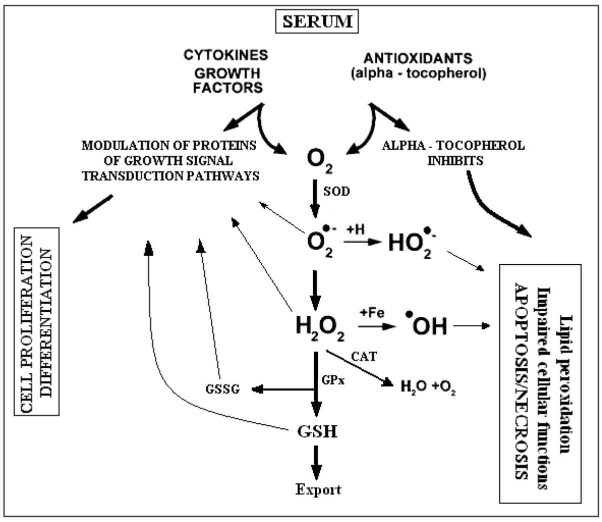

Fig. 3. *Redox regulation of the cell activity; SOD – superoxide dismutase, GPx – glutathione peroxidase, CAT – catalase, GSSG – oxidized glutathione, GSH – reduced glutathione [7]; own modification*

Ryc. 3. *Regulacja reakcji utleniania i redukcji w komórce; SOD – dysmutaza ponadtlenkowa, GPx – peroksydaza glutationowa, CAT – katalaza, GSSG – glutation utleniony, GSH – glutation zredukowany [7]; w modyfikacji własnej*

A temporary increase of ROS concentrations due to the release of various growth factors during a stimulation of tissue, such as cytokines and hormones, including insulin, is accompanied. This is not a side effect, but necessary factor for the correct response of the cell to these ligands actions. ROS are necessary in mitogenic signal transduction, gene expression, metabolic regulation and repair processes within the cells [7-15].

In 1995, it was demonstrated that growth factor obtained from platelet (platelet-derived growth factor – PDGF) for its effect requires the transient increase of concentration of the hydrogen peroxide (H_2O_2). The use of catalase or N-acetylcysteine, which is the precursor of glutathione, inhibits an action of this agent [16]. Metabolic pathways which lead to the increase of ROS levels in cells exposed to growth factors of tyrosine receptors have been described and characterized [17]. Furthermore, the insulin action is regulated by mechanism dependent on redox balance. The short-lived increase of ROS concentrations is essential for the regulation of phosphatases activities [18], which together with kinases control the process of reversible phosphorylation of proteins of the insulin signal conduction [19]. As early as in 1970s it was found that stimulation of adipocytes by insulin is accompanied by elevated ROS concentrations. The necessity of ROS was confirmed in blocking translocation of glucose transfer protein (GLUT4) by the insulin after the supply of catalase to adipocytes [20]. Significance of ROS for the insulin signal conduction was also confirmed by results of the studies where Nox, siRNA and DPI inhibitors mutations were used [21]. The action of angiotensin II [22], 5-hydroxytryptamine [23] and 17β-estradiol [24] cause also the transient increase of ROS concentration within cells.

Moreover, it is very possible that interactions between cells are modulated by changes in concentrations of ROS [7, 8]. Reactive oxygen species act as a second messenger in transmission of intracellular information and can induce sanitation and apoptosis processes, thus they have anti-tumor functions [12, 13]. These compounds also play a key role in inflammation through the activation of transcription factors NF-kappaB [25, 26] and AP-1, and the acetylation/deacetylation of nuclear histone. *In vitro* studies it was shown that many substances like polyphenols, for example curcumin and resveratrol present in a diet, have anti-inflammatory properties [27].

High-reactivity molecules such as ROS have also crucial importance for correct functioning of locomotor system. During a rest, free radicals are produced into muscles as a consequence of activity of the mitochondrial electron transport. Inside of working muscles, capillary endothelial enzymes (xanthine oxidase, nitric oxide synthase – NOS), phospholipase A2 and in the myocardium NADH oxidoreductase are responsible for their additional production. This way, generated reactive oxygen species such as: $^{\bullet}NO$, $ONOO^{-}$, $O_2^{\bullet-}$ and $^{\bullet}OH$, significantly contribute to the achievement of maximum force of the muscle contraction and increase strength of tetanic contractions of the muscle [4].

In the human organism nitric oxide and other N-centered radicals which create reactive nitrogen species group (RNS) are particularly important [2]. $^{\bullet}NO$ was described as endothelium-derived relaxing factor (EDRF) that plays an important role in the regulation of blood pressure [28]. It is also significant neurotransmitter [2] and takes part in regulation of the activity of NF-kappaB [25, 26]. Moreover, the nitric oxide-derived radicals may nitrosate and oxidize tyrosine residues of proteins and affect their phosphorylation, thus they can modulate activities of enzymatic proteins [29]. The next important function of RNS is to destroy pathogens in the process named the respiratory burst of phagocytes (neutrophils, macrophages and monocytes) [30]. The respiratory burst is initiated by creation of active complex of an enzyme – the NADPH oxidase. This enzyme is activated due to numerous mediators which include cytokines, which react with a suitable receptor on the surface of the cell. It allows production of superoxide anion ($O_2^{\bullet-}$) as a result of displacement of an electron from NADPH to molecular oxygen (O_2). Created $O_2^{\bullet-}$ undergoes a dismutation to hydrogen peroxide (H_2O_2). The dismutation reaction is catalyzed by superoxide dismutase (SOD) but may also be spontaneous. In the presence of ferrous ions hydroxyl radicals ($^{\bullet}OH$) are produced and due to an action of myeloperoxidase a hypochlorous acid (HOCl) is formed that can react with amines to form chloramines. The high activity of inducible nitric oxide synthase (iNOS) inside of activated phagocytes is another source of antibacterial agents. Initially, a created nitric oxide (NO) reacts with $O_2^{\bullet-}$ and a highly bactericidal peroxynitrite ($ONOO^{-}$) is produced. The nitric oxide in high concentrations has also antiseptic properties [28-30].

Reactive oxygen species (ROS), including oxygen free radicals (OFR), play a significant role in a regulation of proper functioning of human organism. Still more facts show that inside of the human body ROS are produced continuously and their concentrations are tightly controlled by intra- and extracellular antioxidants.

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