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Revista apare lunar

Adresa redacţiei: SC BIBLIOTECA CHIMIEI SA -
REVISTA DE CHIMIE
Calea Plevnei, Nr. 139B, Sector 6
Bucureşti 060011
Tel./Fax: (+40) 021 314 24 47
www.revistadechimie.ro

Factorul de impact pe anul 2014: 0,810
Revista este recenzată de:
CHEMICAL ABSTRACTS, CURRENT CONTENTS
ANALYTICAL ABSTRACTS
şi indexată de
Institute for Scientific Information (ISI) şi
Chemistry Citation Index

REVISTA DE CHIMIE

Bucharest - Romania
Chem. Abs.: RCBUAU 66 (10) (1545 - 1724)
ISSN 0034-7752
Vol. 66, no. 10, October, 2015

- **Societatea de Chimie din România**
- **SYSCOM 18 Bucureşti**
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The Role of Antioxidative Enzyme Mechanisms and of Oxygen Free Radicals in Reumatoid Inflammatory Processes

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Knowing the molecular mechanisms underlying physiological or pathological processes in human body is an essential condition for high quality research and for finding a solution to prevent its deterioration. The balance between the oxidative action of free radicals and the level of antioxidants in the body is the essence of life and characterizes the resistance capacity of the body. The antioxidative enzyme mechanisms and the oxygen-derived free radicals in rheumatoid inflammatory process, by treating and neutralizing the free radicals appeared in rheumatoid polyarthritis, by stimulating the enzyme activity, catalase and superoxide dismutase (SOD), take part in initiating and maintaining the inflammatory lesion, specific to rheumatoid inflammatory diseases, especially the rheumatoid polyarthritis. The role of superoxide dismutase is to catalyse the dismutation reaction of the superoxide anion radical. The study of enzymes (SOD and catalase) with antioxidative role proves that the enzymatic defence mechanisms are more intense in the acute phase of the disease, and the positive response to treatment is characterised by the decrease of MDA (malonyldialdehyde) and of the activity of SOD.

Keywords: enzymes, oxygen free radicals, catalase, superoxide – dismutase, inflammation, rheumatoid polyarthritis

Inflammation is one of the most common pathologic processes that underlies many diseases, which, even with different clinical manifestations, have, in general, a similar inflammation mechanism, at least in the initial phase. Inflammation is a complex reflex reaction of the body to the action of various harmful agents, and even to degradation products resulted in the body.

Participation of "reactive oxygen species" or "oxygen free radicals" (ROS) to the inflammatory processes is very important. The free radicals are autonomous ions or molecules that contain a single unpaired electron in an outer shell.

Modulation of free radicals reactivity is essential for the survival of the aerobic organisms. It involves complex interactive processes between generating free radicals and a series of enzymatic and nonenzymatic systems located in hydrophilic and hydrophobic cell microenvironments, which control these reactive species.

In superior organisms, the controlled releases of oxygen-derived free radicals towards the specialised inflammatory cells are used to fulfil a bactericidal function. The same species are also involved in the physiopathology of various pathological processes, including inflammation, ischemia reperfusion injury, neoplasia, and ageing.

In normal circumstances, ROS are present in all aerobic organisms. Dioxygen, besides its completely reduced form (H_2O_2), generates incompletely reduced species - some of them extremely harmful - free radicals generated from oxygen.

Oxygen activation takes place by reactive species, originating both from atomic and molecular oxygen. The electronic configuration of the oxygen atom explains its instability.

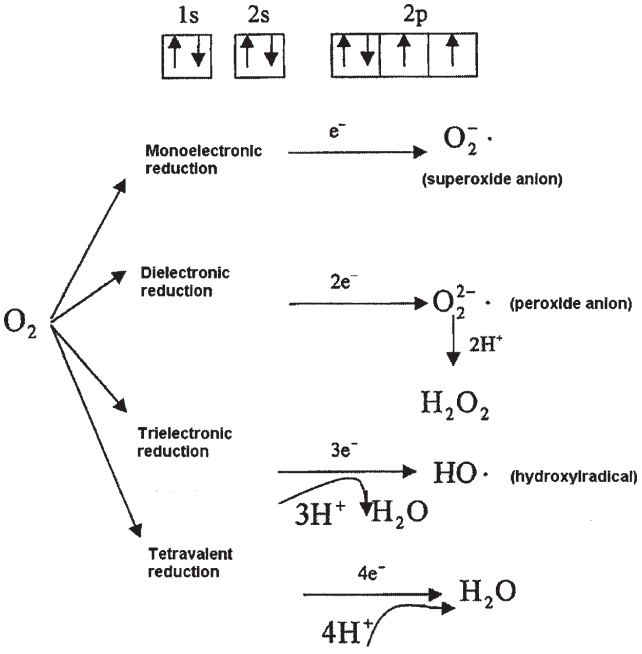

Fig.1. Electronic configuration of the oxygen atom

Peroxidation process

Kinetics of peroxidation

The first stage is initiation, consisting in production of free radicals derived from the R substance, which is subjected to peroxidation.

$$R\cdot + O2 \longrightarrow ROO\cdot$$

$$ROO\cdot + RH \longrightarrow ROOH + R\cdot$$

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The emergence of free radicals in an organic substance is due to one or more external (high temperature, humidity, light, ionizing radiations, UV) or internal factors (slightly oxidative impurities, for instance aromatic compounds, such as diphenols).

Disassembly of some free radicals forms the most effective initiator:

$$2ROOH \xrightarrow{O_2} R\cdot + ROO\cdot + H_2O_2$$

$$ROOH \xrightarrow{h\nu} R\cdot + HO_2\cdot$$

Propagation is the second stage of peroxidation, characterised by continuation of free radical formation. The most important reactions are:

$$R\cdot + O_2 \longrightarrow ROO\cdot$$

$$ROO\cdot + RH \longrightarrow ROOH + R\cdot$$

Termination is the third stage, and represents the consequence of reactions between various free radicals that produce inactive compounds:

$$R\cdot + R\cdot \longrightarrow R{-}R$$

$$R\cdot + ROO\cdot \longrightarrow \text{Inactive products}$$

Peroxidation substrates

Saturated hydrocarbons produce peroxides only by scientific methods specific to organic chemistry. During the initiation period, the first type of free radical arises, produced especially by thermal disassembly of a pre-existing peroxide.

These free radicals, appearing as R· and ROO· attack the hydrocarbons in certain critical sites, such as "allylic position".

Unsaturated fatty acids are linoleic, linolenic, and arachidonic acid, spread in nature as components of the lipids within the membranes. Autoxidation of unsaturated fatty acids arises from a single mechanism, through which a radical, initially R·, produces the extraction of a hydrogen atom from the allylic position, producing again a free radical.

Lipids are a substrate favourable to autoxidation. The most oxidizable compound is the fatty acid, which provides the peroxide radicals to other compounds, too. The free radicals have limited reach and duration, but their effects can perpetuate by build-up of chain reactions, with self-sustaining and self-amplifying potential.

The cellular sources of ROS are: *endogenous* (mitochondrial and microsomal respiration, oxidative enzymes, phagocytic cells, autoxidation reactions) and *exogenous* (ionizing radiations, UV, calorie shock, smoking, alcohol, substances which oxidize glutathione, and oxidative medications).

Insoluble (particle) stimuli of phagocytic synthesis of ROS are represented by: opsonized bacteria, bacterial endotoxins, IgG aggregates, insoluble immune complexes (IgG and IgA for macrophages) and soluble (Calcium ionophores, Complement factor 5, interleukin 1, platelet-activating-factor, soluble immune complexes, tumor necrosis factor, leukotriene B4 and C4, phospholipase C).·

Harmful effects of ROS

In normal circumstances, there is a balance between ROS production and their clearance. In various pathologic states, the balance is destroyed, either by ROS supraproduction, by diminishment of their annihilation capacity, or both.

ROS alterations of cellular compounds are followed by annihilation of activity of nucleotide coenzymes, change of redox function, disturbance of the activity of thiol-depending enzymes, covalent attachment of proteins and lipids, change of lipid metabolism, protein alterations leading to the increase of protein turnover, lipid peroxidation (which alters the structure and function of cell membrane), and transportation disturbances.

ROS exerts tissular toxic actions by direct and indirect mechanisms:

Direct mechanisms – addressed to nucleic acids, producing DNA denaturation, involving breaks in chromosomes (clastogenic effect), with major consequences on multiplication, transmission and replication or genetic message. Also directly, the radicals act on collagen, which is degraded by depolymerisation of mucopolysaccharides, hyaluronic acid and protocollagen microfibers.

Indirect mechanisms – target the lipid peroxidation. Polyunsaturated fatty acids contained by membrane phospholipids are extremely vulnerable to the action of ROS, due to the presence of double bindings. An autocatalytic reaction takes place, which in the end leads to the alteration of membrane integrity, until their complete lysis.

Superoxide radical - key element of oxygen toxicity

Superoxide radical, produced by polymorphonuclear cells and other phagocytes, is another compound of their bactericide armament, even if the same action can contribute to the damage of tissue, associated with the inflammation.

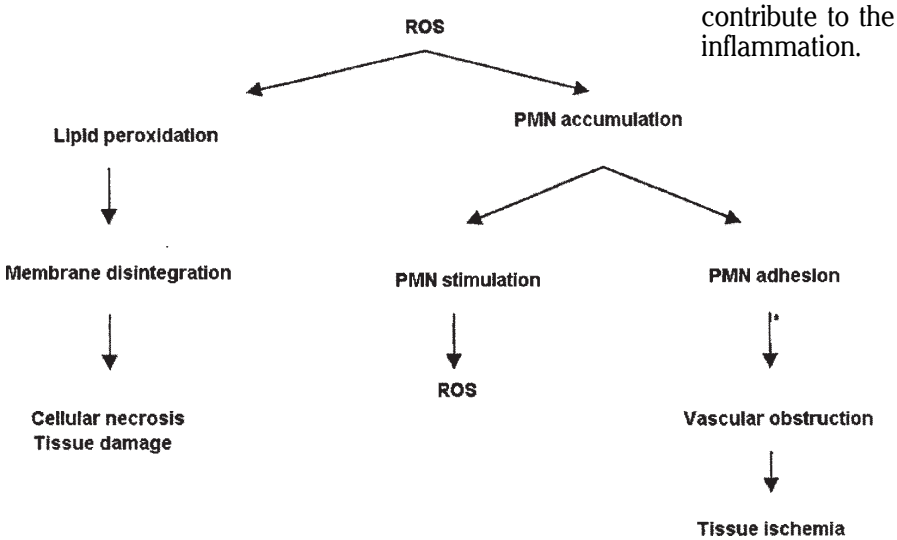


Fig.2. Direct and indirect effects of ROS (Schoenberg)

Production of superoxide radical appears as a result of activation of NADPH or NADH-membrane oxidase, according to the formula:

$$NADPH + 2O_2 \xrightarrow{NADH-oxidase} NADP^+ + 2O_2^- + H^+$$

The genetic incapacity to produce superoxide is life threatening. The capacity of neutrophils to kill the ingested microorganisms is affected, leading to multiple recurrent local infections, and even sepsis.

The result of superoxide overproduction is dangerous for the body, just like a low superoxide production.

Free radicals in inflammatory diseases

In certain situations, the amplitude of inflammatory response exceeds the physiologic barriers, implicitly involving the excessive participation of ROS.

Inflammation is a complex, dynamic process, which may be defined as reaction of the tissue to an aggression. In case of neutralising and repair of the aggression, the final result is an inflammatory granuloma (scar), which will evolve towards absorption or chronic inflammation.

AGRESSORS → INFLAMMATION { Bacterial invasion, physicochemical irritants, traumas, antigen-antibody reactions

Main phases of the inflammatory process

Fig. 3. Inflammation, a complex process, defined as a tissue reaction to aggression

Phase I – *local tissue lesions*, with denaturation of proteins and membranes, slowing down of the vein circulation, local invasion with macrophages, acidosis, increased catabolism of glycogen.

Phase II - *catabolic,* especially characterized by proteolysis and release of mediators (histamine), which increase the capillary permeability.

Phase III- *reaction*, characterised by hyperthermia and increase of membrane permeability, vasodilatation. An edema occurs, the osmotic pressure decreases, the fibrinogen, globulin and serum glycoproteins increase, while the albumin and serum iron decrease.

Phase IV- *anabolic*, characterised by increase of protein biosynthesis, ATP nucleotides. A neoformation of connective tissue, blood vessels and collagen occurs, with accumulation of fibroblasts.

Phase V – *formation of a granuloma*, composed from a central necrosis area, surrounded by fibroblasts and a lymphoplasmocitary conglomerate disseminated in the fibrous tissue.

Research showed that the destruction of the pathogenic agent by phagocytes implies a very complex biochemical process, to which several enzyme systems take part, and that the destruction of bacteria is owed to the activated forms of O_2, released both by the radicals, and by H_2O_2.

All types of leucocytes have a highly variable consumption of O_2, from very small, in case of neutrophil, to significant, for macrophages. The increase of respiration contains the intensification of four reactions, depending on the activity of a single enzyme, NADPH - oxidase, which catalyses the univalent reduction of O_2 to superoxide - O_2, using NADPH as electron donor.

$$2O_2 + NADPH \rightarrow 2O_2^- \cdot + NADP^+ + H^+$$

The enzyme is located in the plasmatic membranes. Most of consumed O_2 passes into H_2O_2, formed as a result of superoxide dismutation under the action of SOD.

There are also reactions which produce free radicals - singlet and hydroxyl -, arising as a result of Haber-Weiss reaction. O_2 also arises as a result of H_2O_2 decomposition, catalysed by myeloperoxidase. The presence of these radicals has been proven by studies of the electron spin resonance or by chemiluminiscence.

The involvement of peroxides is legitimated by the profound changes of the cell membranes, necrosis, release of substrates (PUFA-arachidonic acid) and pro-oxidative factors (hemoproteins).

Administering the arachidonic acid (PUFA) parenterally intensifies the biosynthesis and has a vasodilator effect through the release of a contractant factor. If we accept that AGPN peroxidation in the membranes is a reaction associated with the changes of cell membranes in inflammation, then administering the arachidonic acid amplifies the inflammatory process, and the nonsteroidal anti-inflammatory drugs inhibit the action of this acid.

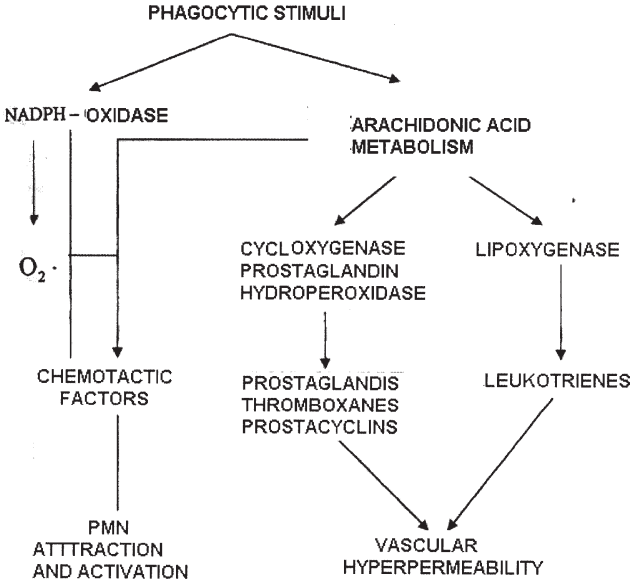


Fig.4. ROS in inflammatory processes induced by phagocytose (Sies)

Unfortunately, because of the inflammatory process, the effect of administering the arachidonic acid is not clear, first of all by the contradictory action of the prostaglandins, endoperoxides and prostacyclins of favouring or inhibiting the reactions in inflammations.

The most comprehensive papers related to peroxidation in inflammations focus on detecting the free radicals in inflammations, especially the O_2 originating from the activation of microphages and phagocytosis, visible both by chemiluminiscence and by determining the activity of SOD in synovial fluid, which it protects.

O_2 is released mostly by the surface contact of the macrophages with various agents (e.g., bacteria, aggregated immunoglobulins IgG).

SOD and catalase prevent the synovial fluid depolymerization by OH; injected SOD ameliorates the inflammation, while the leukocytes of rheumatoid patients under treatment have a low SOD activity.

The function of the superoxide-dismutase was described by Mc Cord and Fridovich in 1969. SOD is a means of defence of the body from the superoxide anions.

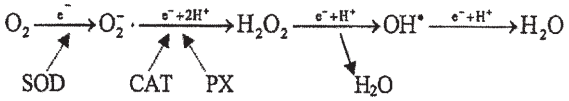
In rheumatoid diseases, ROS production in joint inflammation is completed by their apparition by certain mechanisms that are specific to ischemia-reperfusion

disorders, escalated in this case by effort, as a result of pannus development and increase of the quantity of the intra-articular fluid.

It is possible that ROS takes part also to osteoclastic activity in this disease, interfering with the cytokines action.

Protection systems against the peroxides in the body

Due to the presence of substrates, favourable to peroxidation, such as polyunsaturated fatty acids, and pro-oxidative agents, as metallic ions (Fe, Co), the evolution of aerobic life, superior organized, depended on creating effective protection systems from the oxygen toxicity, concretised in production of activated forms of O_2 and by peroxides.



Enzymatic antioxidants:

1.CYTOCHROME OXIDASE system – tetravalent reduction of O_2

2.SOD

3.Catalase → detoxifies H_2O_2 : $2H_2O_2 \rightarrow 2H_2O + O_2$

4.Glutathione peroxidase → peroxide decomposing

$$ROOH + 2GSH \rightarrow ROH + GSSG + H_2O$$

5.Non-specific peroxidases

Superoxide - dismutase (SOD)

SOD is the first enzyme in the enzymatic chain that protects against O_2 toxicity; it catalyses a dismutation reaction, through which a tetravalent reduction of O_2 in H_2O_2 occurs.

$$O_2^{\cdot-} + O_2^{\cdot-} + 2H^+ \rightarrow H_2O_2 + O_2$$

It looks like SOD protects the aerobic organisms from potentially damaging effects of the superoxide. The enzyme is present in a few compartments of the cell. It is made from two similar subunits, each containing an equivalent of Cu^+ şi Zn^{2+}, while the mitochondrial enzyme contains Mn^{2+}.

The antioxidant system also contains catalase and glutathione-peroxidase. SOD activity in extracellular space (plasma, synovial fluid) is very low. There are mutual correlations between ROS and their cleansing enzymes. Thus, SOD is inactivated by H_2O_2 and CAT by O_2. We can therefore understand that the two enzymes protect each other, which explains the therapeutic superiority of the mixed product SOD +CAT.

Catalase

Catalase is universally spread in nature, its activity being present in all aerobic microorganisms, in the cells of the plants and animals. Inside a cell, the enzyme is almost exclusively located in the peroxisomes of most of the cells, reducing the level of hydrogen peroxide. Catalase reduces the level of hydrogen peroxide in peroxisomes, but it is not present in chloroplasts. Hydrogen peroxide is the most stable species out of all active species of the oxygen, a very strong nucleophilic oxidant. Therefore, it is an enzyme that neutralises the excess of H_2O_2. It is present in all aerobic cells that contain cytochrome system, being located in

$$H_2O_2 + H_2O_2 \longrightarrow O_2 + 2H_2O$$

peroxisomes and mitochondria. It catalyses the reaction in a very effective way:

Considering that H_2O_2 toxicity is 1000 times higher in the presence of transition metals, it is understandable why the aerobic organisms, implicitly the human body, need two major defence classes with complementing role: catalase and enzymes associated with glutathione. Catalase has as prosthetic group 4 hem nuclei that coordinate one atom of Fe^{3+} at a 248.000 molecular mass. Apoprotein is made from a polypeptide chain per hem subunit and contains 16 groups of SH, out of which 0 appear only after acid denaturation.

Due to this high content of SH groups, catalase is inhibited by a series of thiols, such as cysteine or glutathione; the latter might be one of modulators of enzyme activity. Catalase activity is inhibited by titration of the 6 SH groups, but the peroxidase activity is very low. GSH action is owed to the production of changes in conformation by establishing reversible mixed disulphides.

Elucidation of the action mechanism of catalase provoked numerous controversies, left without an answer. The catalase and peroxidase activity starts with the formation of complex I between the first molecule of H_2O_2 and heminic Fe (fig. 5).

$$Protein - Fe^{3+} - OH + H_2O_2 \longrightarrow Protein - Fe^{3+} - OOH + H_2O$$

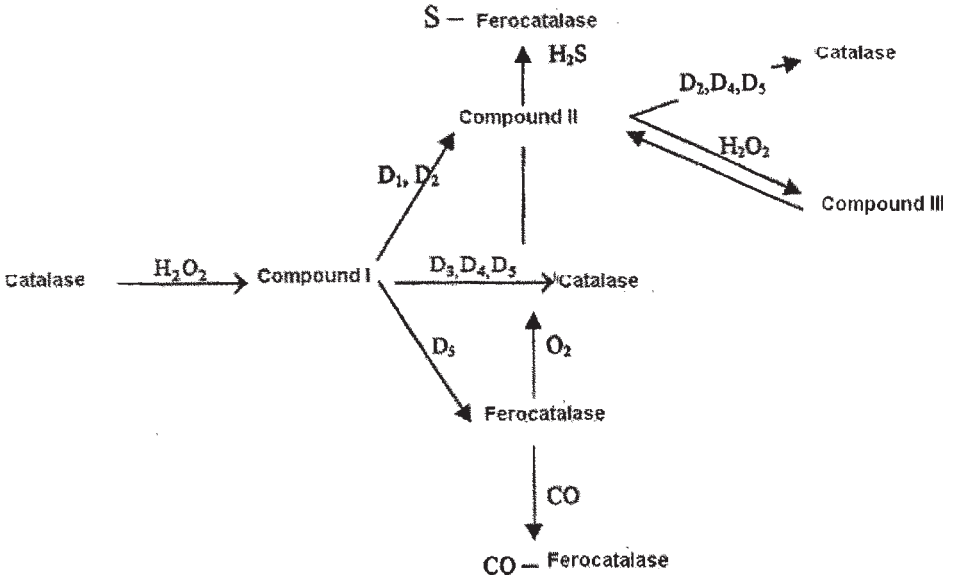


Fig.5. Catalyse activity and peroxidase activity of catalase

Once formed, the complex I may react in three directions. In catalase activity, the complex reacts to the second molecule of H_2O_2, according to the reaction bellow, remaking the initial catalase:

$$\text{Protein} - Fe^{3+} - OOH + H_2O_2 \longrightarrow$$

$$\longrightarrow \text{Protein} - Fe^{3+} - OH + H_2O_2 + O$$

Intermediate compounds formed through the action of catalase

In peroxidase activity, catalase needs the presence of a hydrogen donor (A), producing complex II, inactive, according to the reaction:

$$\text{Protein} - Fe^{3+} - OOH + AH_{2K7} \longrightarrow$$

$$\longrightarrow \text{Protein} - Fe^{3+} - OH(II) + A + H_2O$$

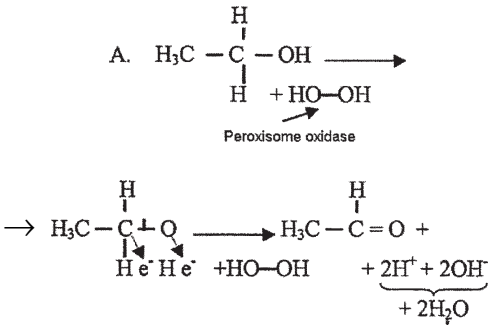
Such donors are ascorbate, phenol, and ferrocyanide. It is accepted that the catalase activity prevails at a concentration of $H_2O_2 > 10^{-4M}$, when the enzyme is in a large quantity (red blood cells). Peroxidase activity needs smaller concentrations, the presence of a donor or various substrates, such as inferior alchilic peroxides.

If H_2O_2 is continuously generated in small quantity (reaction of glucose oxidase), the turnover of the general reaction is equally high, since both mechanisms act, because the second molecule of H_2O_2 ca play the role of a donor.

Besides the main action, in which the catalase competes with GSH- peroxidase, the peroxidase reactions of this enzyme seem to be used in many biochemical processes, such as ethyl alcohol metabolization, antimicrobial activity associated with phagocytosis, metabolization of vitamin K3.

Taking into consideration the fact that, especially in the liver, H_2O_2 is continuously generated in small concentrations (10^{-8M}), we can assume that in this organ the catalase acts by peroxidase.

Non-enzymatic antioxidants act in extracellular fluids.



Glutathione, called "protein of life", is a bioactive polypeptide functioning as a coenzyme, present in almost all the cells of human body. It is synthetized in liver from the amino acids cysteine, glutamine and glycine. The cellular level of glutathione is stimulated by the alpha-lipoic acid, glutamine, colostrum, selenium, and vitamins C, B6 and B2. The efficiency of vitamins C, E, and of coenzyme Q10 depends on the level of glutathione in the body.

It is one of the most powerful and important antioxidants of the body; it is called "the magic antioxidant"; oxidative stress produced by glutathione deficit has a major role in pathogeny of cancer, asthma, chronic bronchitis, emphysema, cystic fibrosis, pulmonary fibrosis, autism, ADHD, Parkinson's disease, multiple sclerosis, and schizophrenia.

Inflammatory rheumatoid diseases involving ros in the pathogenic mechanism - rheumatoid polyarthritis

Rheumatoid polyarthritis (RP) is a disease involving a chronic infiltrative-proliferative inflammation of the synovial joint. The cause of the disease is unknown. An important role of the etiology of the disease is plaid by the environmental factors that interact with a susceptible genotype. Out of the environmental factors, the most important ones are the infectious factors. The microorganisms involved in the etiology of RP are multiple, the most significant ones being *Clostridium perfringens*, mycoplasma, and viruses.

It has been proven that in RP patients, the IgG glycosylation is more reduced than normal, as a result of the absence of specific enzyme. This abnormally might be at the origin of the appearance of antibodies type IgM – rheumatoid *factor* - (RF) against this IgG abnormal molecule or its fragments.

It is believed that the causing agent is a triggering element only in individuals with a high genetic susceptibility. The process starts like an inflammatory-exudative synovitis, which progresses towards an infiltrative-proliferative form. Several cells and humoral biological systems contribute to the progression of the disease.

The events develop on two levels: *in synovial* and *in articular cavity*. The first changes occur at synovial level and in the blood vessels. They undergo a double process, one of microthrombosis and one of forming new vessels. Simultaneously with the neovascularization, circulatory lymphocytes pass into the articular synovial, being anchored by the tissue and producing an abundant lymphoplasmacytic infiltrate, arranged pericapillary. Lymphocytes are predominantly T helper type. They stimulate the activity of B lymphocytes, responsible for RF secretion.

Monokines stimulate the uncontrolled proliferation of synoviocytes, but they will contribute also to the stimulation of fibroblasts, increase bone resorption and several systemic manifestations. The hypertrophied synovial tissue is called articular *pannus*, and it invades the joint at the periphery, the first injuries appearing at the bone-cartilage junction.

The subchondral cartilage and bone, capsule and ligaments are affected, and rarer, the tendon sheaths and the bursa. Prostaglandins (PGE_2) and proteinases (collagenase) of lysosomal origin in PMN, macrophages, synoviocytes A and chondrocytes are responsible for these destructions.

The events in the articular cavity have the rheumatoid factor as a central element, secreted by both the joint and in blood, more frequent IgM type, and rarely IgG or IgA type.

Extra-articular effects are dominated by the presence of *rheumatoid nodules*.

The onset of the disease is insidious and it manifests itself through fatigue, loss of weight, myalgia, prolonged morning stiffness, and polyarthralgia.

These non-specific symptoms last for weeks or months, until the onset of specific manifestations. Rarely, the onset is acute, with rapid development of polyarthritis accompanied by fever, adenopathy and sometimes splenomegaly or acute symmetric or non-symmetric oligoarthritis.

Articular manifestations are the expression of the inflammation of synovial, clinically expressed by swelling, pain, and limited mobility.

Articular swelling is the initial result of exudative synovitis, with synovial fluid accumulation and, later, of the proliferative synovitis with synovial hypertrophy and thickening of the articular capsule.

Pain is caused by distension of articular capsule, initially contributing to limitation of mobility. Later, the limited mobility is caused by fibrosis, bone stiffness or contracture of the soft tissue.

Extra-articular manifestations are determined by lymphoplasmacytic infiltrates and/or by vasculitic processes. They appear in severe forms of the disease, and almost constantly, the patients suffer from high titers of rheumatoid factor, cryoglobulinemia, hypo-complementemia, circulatory immune complexes or antinuclear antibodies.

Teguments may have rheumatoid nodules, purpuric elements, and trophic disorders. Subcutaneous rheumatoid nodules appear in 20-25% of the patients.

Rheumatoid vasculitis of small and medium arteries may determine polyneuropathy, cutaneous ulcerations, and visceral infarction.

Felty syndrome usually appears in diseases with a prolonged progress; it is characterised by RP associated with splenomegaly and neutropenia. Blood cytopenia is considered the result of a hyperspenism or autoimmune phenomena.

In *paraclinic investigations,* lab test and imagistic tests are done (radiographies, soft tissue ultrasound), synovial fluid analysis, arthroscopy.

Lab tests: inflammation tests, biochemical tests (hepatic, renal, metabolic) and immunologic investigations.

Early diagnosis is very useful because the therapeutic measures can be rapidly taken.

Differential diagnosis is crucial especially in initial stages, when the disease can be mistaken for many other rheumatoid or non-rheumatoid conditions showing articular manifestations.

The goals of *the treatment* are to reduce the joint inflammation and pain, stop the destructive lesions of the bone and cartilage, and correct the articular mechanics and function.

Steroidal anti-inflammatory drugs, although very efficient in improving the clinical symptoms, must be used for a limited period of time, particularly due to side effects and cortico-dependence.

Background immunosuppressive therapy can be administered as mono- or combined therapy, while the pathogenic treatment offers accurate indications.

Local treatment with cortisone preparations is indicated for mono- or pauciarticular conditions.

Rehabilitation therapy is indicated, while the ortho-surgical procedures are recommended in severe cases.

Variations of some of the enzymes interfering in the oxidative processes formed during the conflict between foreign aggressors (free radicals of oxygen) and the internal environment of the body were monitored.

The efficiency of the therapy with glucocorticoids and salazopyrin is an indirect proof of the intervention of ROS in lesional mechanisms in inflammatory rheumatoid diseases.

Cortisone drugs are more effective in acute spur, inhibiting the infiltration with PMN and monocytes-macrophages in the inflamed areas, blocking the release of chemotactic factors and those that mediate the vascular changes (prostaglandins, leukotrienes, PAF, IL1, TNF). They induce the synthesis of lipocortins, a family of proteins that reduce the release of the arachidonic acid, by inhibiting the phospholipase A2.

Secondary, the production of ROS is substantially reduced, mostly related to cyclooxygenase and lipoxygenase pathway. Salazopyrin is also used in background therapy of rheumatoid polyarthritis, which, by its active principle, 5-aminosalicylic acid, efficiently annihilates the O_2 and OH created by the human neutrophils.

Conclusions

Although there is a multitude of free radicals, the ones derived from oxygen or nitrogen are the class of the most important radicals produced in living organisms.

The changes induced by free radicals have an impact on long living biomolecules, such as collagen, elastin, mucopolysaccharides, lipids in the structure of cell membranes, cell organelles (mitochondria, lysosomes), and compounds of the walls of the blood vessels.

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Manuscript received: 16.02.2015