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Endogenous non-enzymatic antioxidants in the human body

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ABSTRACT

The exposure of cells, tissues and extracellular matrix to harmful reactive species causes a cascade of reactions and induces activation of multiple internal defence mechanisms (enzymatic or non-enzymatic) that provide removal of reactive species and their derivatives. The non-enzymatic antioxidants are represented by molecules characterized by the ability to rapidly inactivate radicals and oxidants. This paper focuses on the major intrinsic non-enzymatic antioxidants, including metal binding proteins (MBPs), glutathione (GSH), uric acid (UA), melatonin (MEL), bilirubin (BIL) and polyamines (PAs).

1. Introduction

Reactive species belong to two types of reactive molecules: reactive oxygen species (ROS) and reactive nitrogen species (RNS). Both groups of reactive species include free radicals that are extremely reactive chemical species (atoms, molecules and ions) possessing one or more unpaired electrons [1,2].

Reactive species are normally produced during cellular oxygen metabolism, although in many instances they may also be engaged in numerous pathological processes called “oxidative stress”. Excessive generation of ROS and RNS leads to an imbalance between the rate of their formation and the antioxidant capacity of the biological system. As a result of the oxidation of biological structures, excessive generation of reactive species causes damage to various cellular structures. This may be a primary cause or a secondary complication of contemporary civilization diseases. In chronic disorders, e.g. cardiovascular diseases [3], diabetes [4], cancer and rheumatoid arthritis (RA), oxidative stress plays a major role [5,6].

1.1. Physiological role of reactive species

Oxidative stress is believed to contribute to the development of a number of noncommunicable diseases (chronic diseases). At the same time it is suggested that the generation of reactive species is necessary for the intercellular signaling cascades that regulate various physiological functions. Reactive species account for an important part of many biological processes relevant to proper functioning of the body. Reactive species can act as mediators and regulators of metabolism, e.g. they can induce cell differentiation, proliferation and migration. ROS can activate genes, and induce apoptosis by affecting synthesis, release or inactivation of endothelium-derived relaxing factor (EDRF). They can stimulate glucose transport into cells and affect inter- and intracellular signal transmission [7].

On the one hand, oxidative stress is an essential part of the innate immune system, that is part of defence mechanisms against pathogens [8]. However, reactive species produced by the immune system can be harmful to cells .

1.2. Overview of antioxidant protection

The exposure of cells, tissues and the extracellular matrix to the harmful effects of free radicals causes a cascade of reactions and induces activation of multiple internal defence mechanisms, which provide elimination of free radicals and their derivatives (Fig. 1) [10,11].

These mechanisms are:

- preventive – being the first line of defence, preventing reactions of free radicals and their derivatives with biological substances in the body,
- repairing – involving interruption into a radical oxidation reaction,
- inactivating the products of free radical reaction and their derivatives, by repairing or eliminating structural damage [12].

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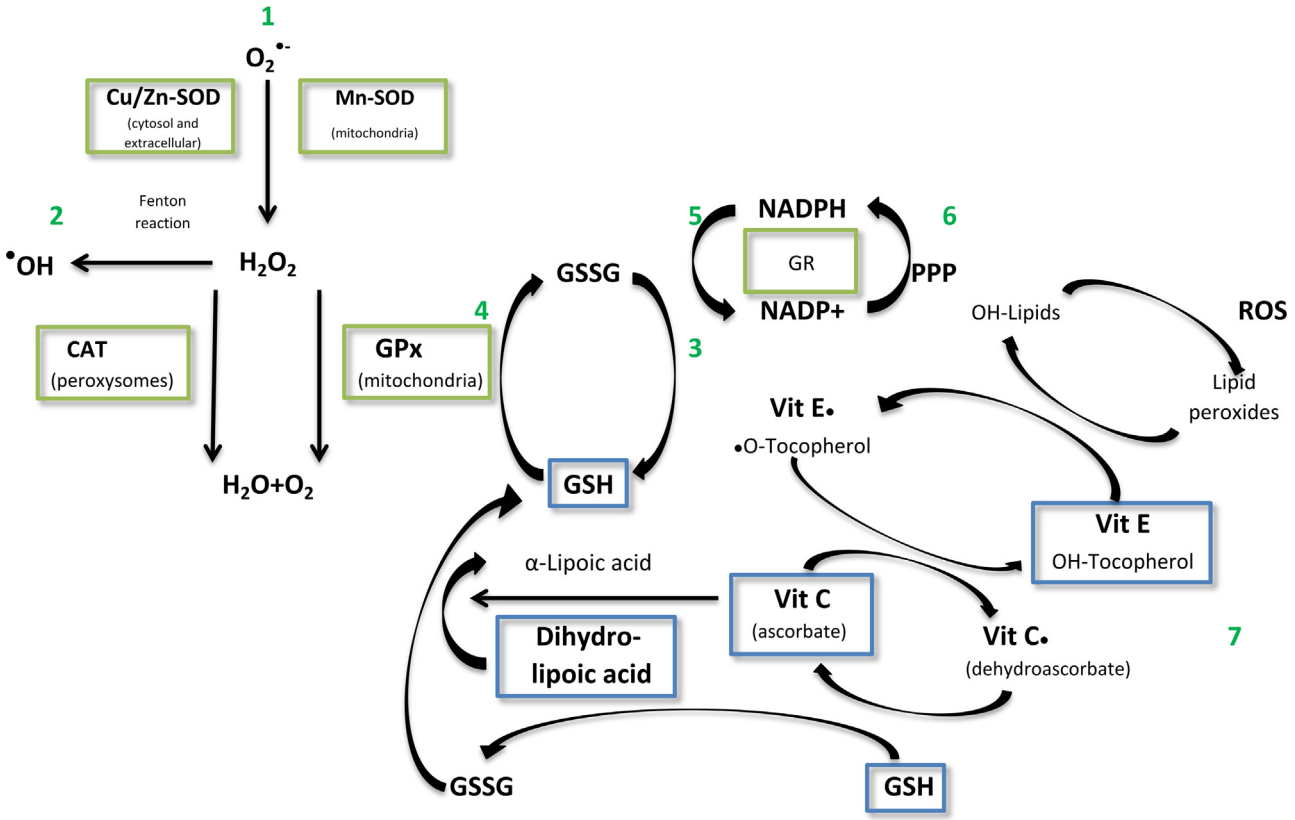

Fig. 1. The mechanism of antioxidant protection. © 2013 Lazo-de-la-Vega-Monroy ML, Fernández-Mejía C. Published in [11] under CC BY 3.0 license. Available from: http://dx.doi.org/10.5772/51788gr1gr1

1. Superoxide radical ($O_2^{\bullet-}$) is formed by a single-electron reduction of oxygen. In a reaction catalysed by superoxide dismutase (Cu/Zn-SOD or Mn-SOD), superoxide radical binds an electron, which leads to the formation of hydrogen peroxide (H_2O_2). In the further reduction of hydrogen peroxide to water and oxygen are involved two enzymes catalase (CAT) and glutathione peroxidase (GPx).
2. In the Fenton's reaction, which is catalysed by transition metals, hydrogen peroxide (H_2O_2) is transformed to hydroxyl radical ($HO^{\bullet}$), which further participates in the free radical chain reactions.
3. Reduced glutathione (GSH), due to the presence of the thiol group of cysteine reacts with free radicals of proteins or other macromolecules, restoring them to the reduced form.
4. Hydrogen peroxide (H_2O_2) is reduced by reduced glutathione in the raction catalysed by glutathione peroxide. The resulting oxidized glutathione oxidizes thiols of proteins.
5. Glutathione disulphide is reduced by glutathione reductase (GR) using hydrogen of NADPH, which is oxidized to NADP+.
6. NADPH is generated in the first oxidative phase of pentose phosphate pathway (PPP). In this phase, glucose-6-phosphate is dehydrogenated by glucose-6-phosphate dehydrogenase to ribulose 5-phosphate, and at the same time two molecules of NADP+ are reduced to NADPH.
7. Vitamin C and α-lipoic acid support the regeneration of GSSG back into GSH. A hydrogen donor Vitamin E scavenges lipid peroxides and terminates oxidative chain reactions as a hydrogen donor. Unoxidized form of vitamin E can be recycled back by vitamin C and glutathione [10,11].

Endogenous antioxidants, which are products of the body's metabolism, may be enzymatic or non-enzymatic. One of the enzymatic antioxidants playing an important role in the first line of defence is superoxide dismutase (SOD). SOD catalyzes the disproportionation reaction of superoxide anion to hydrogen peroxide and molecular oxygen. Other important enzymatic antioxidants in the first line of defence include catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR) and peroxiredoxins (Prxs) These enzymes neutralize hydrogen peroxide, yielding water (catalase glutathione peroxidase) and oxygen molecule (catalase). The non-enzymatic substances taking part in the first line of defence belong to preventive antioxidants and in blood plasma are represented by ceruloplasmin, ferritin, transferrin and albumin. These proteins inhibit the formation of new reactive species by binding transition metal ions (e.g. iron and copper). Also metallothionein plays an essential role in the prevention against reactive species. Its primary antioxidant properties arise from the presence of a large number of –SH groups [13].

The second line of defence against ROS involves non-enzymatic antioxidants that are represented by molecules characterized by the ability to rapidly inactivate radicals and oxidants.

The third line of defence consists in repair mechanisms against damage caused by ROS and free radicals. This form of protection is provided by enzymatic antioxidants, which can repair damaged DNA and proteins, fight against oxidized lipids, stop chain propagation of peroxyl lipid radicals, and repair damaged cell membranes and molecules [14].

Dietary antioxidants such as vitamin E, vitamin C, carotenoids, some minerals (e.g. ZnMn, Cu, Se) and polyphenols (flavonoids, phenolic acids, stilbenes, lignans) can affect the activity of endogenous antioxidants. Endo- and exogenous antioxidants may act synergistically to maintain or reestablish redox homeostasis. Exogenous antioxidants are present in significant amounts in commonly consumed fruits, vegetables, beverages (juices, tea, coffee), nuts and cereal products [15]. Dietary antioxidants can delay the process of aging [16] and may also mitigate complications of diabetes [4] and cardiovascular disease [17].

Considering the mechanism of antioxidant protection, the endogenous substances described in this review can be divided into true scavengers, metal buffering proteins: chelators for redox-active metals (Fe, Mn, Cu) and chelators of redox-stable metals (Zn, Cd).

This paper focuses on the major intrinsic non-enzymatic antioxidants, which include metal-binding proteins (MBPs), glutathione (GSH), uric acid (UA), melatonin (MEL), bilirubin (BIL) and polyamines (PAs). Due to their location, these proteins and low molecular mass substances provide effective mechanisms of intracellular or extracellular defence against ROS and reactive nitrogen species (RNS) (Table 1.).

2. Review

2.1. Metal-binding proteins (MBPs)

The first described endogenous antioxidants were metal-binding proteins (MBPs), i.e. extra- and intracellular proteins, such as albumin (ALB), ceruloplasmin (CP), metallothioneins (MTs), ferritin (FER), myoglobin (MB), transferrin (TF) and lactoferrin (LTF).

MBPs are the main contributors to the plasma antioxidant capacity [9]. Their antioxidant properties involve their ability to bind metal ions. These free-redox-active transition metal ions (Cu^{2+} and Fe^{2+}) can be extremely pro-oxidant, which means that they can react with hydrogen peroxide and catalyze formation of reactive species (ROS) in the Fenton reaction [18]. Some of these proteins can additionally act as true scavengers of reactive species e.g. free sulfhydryl groups of cysteine in ALB and MTs are able to scavenge hydroxyl radicals.

Such MBPs as transferrin (TF), ferritin (FER) and lactoferrin (LTF) are chelators of redox-active iron (Fe^{2+}), which can be effective free radical inhibitors in the Fenton reaction [19].

In contrast, ceruloplasmin acts as a reactive species inhibitor by binding free copper (Cu^{2+}) and iron ions (Fe^{2+}), or as a chain-breaking antioxidant [20].

In turn, albumin (ALB) is a multifunctional antioxidative protein, which binds redox metals (Fe II and Cu II) and can also act as a true scavenger reacting with hydroxyl radicals [21,22].

Myoglobin (MB) is another MBP, which is mainly an effective NO scavenger [23].

Metallothionein is capable of binding redox-active metal ions, e.g. Cu and redox-stable metal ions e.g. Zn and Cd, protecting cells against toxic metals. It also acts as a scavenger of reactive species (e.g. $O_2^{\bullet -}$) [24].

Iron is necessary for most living organisms, both simple and higher, and it possesses numerous biological functions in the human body. The general function of iron is associated with oxygen distribution in tissues, with the involvement of hemoproteins, such as hemoglobin and myoglobin. Moreover, iron is essential for enzymatic functions of oxidases, peroxidases, catalases and cytochromes. It also participates in hormone synthesis and catabolism [25]. Iron is involved in the formation of ROS, which play an important role against pathogens, such as bacteria and viruses [26]. High concentrations of these compounds, however, can be harmful to cellular structures and lead to oxidative stress.

Table 1
Intra- and extracellular non-enzymatic antioxidants.

Non-enzymatic antioxidants	
Intracellular	Extracellular
Ferritin	Transferrin
Myoglobin	Lactoferrin
Metallothioneins	Albumin
Coenzyme Q10	Ceruloplasmin
Glutathione	Uric acid
Melatonin	Bilirubin
Polyamines	

The role of iron in metabolic reactions is associated with its specific chemical properties. It usually occurs in two oxidation states (Fe^{2+} and Fe^{3+}), hence iron can be both a donor and an acceptor of electrons. Due to the redox activity, Fe could participate in the multiple biological redox-dependent reactions in the human body [27].

The major part of iron in the body is bound to hemoglobin in erythrocytes (60–70%), and approximately 5–6% is contained in myoglobin and various enzymes. Less than 1% of iron is bound to transferrin. The remaining 20–30% is accumulated in hepatocytes and liver macrophages [25].

The negative consequences for the organism are associated with both low and excess concentration of iron. Low concentration can cause anemia, while excess iron leads to increased production of ROS, which act destructively on the majority of cell particles, causing DNA damage and impairing protein, carbohydrate and fat synthesis mechanisms.

The unbound redox-active ions are primarily responsible for the oxidation of compounds, which are cofactors in the reactions of free radical formation (Fenton reaction). High levels of iron in the brain, for instance, have been found in various neurodegenerative disorders including Parkinson's and Alzheimer's disease [28,29,20].

Living organisms have been adapted to the assimilation of transition metals by the production of specific proteins that enable binding, transport and storage of iron in non-toxic soluble forms. Due to high reactivity of iron ions, they are usually present in the body bound to proteins [27]. The proteins involved in absorbing, transporting and storage of iron are: transferrin (TF), ferritin (FER) and lactoferrin (LTF). Due to their iron-binding ability, these proteins are classified as antioxidants [30–32].

Food proteins are vast sources of amino acids that demonstrate antioxidant activity. For example, aromatic amino acids such as tyrosine, phenylalanine, tryptophan and sulphur-containing cysteine have an ability to donate protons to free radicals. Several studies have found bioactive properties of peptides from both animal and plant sources. Rice endosperm protein, for instance, scavenges hydroxyl radical and superoxide radical, thus inhibiting autooxidation of the linoleic acid system, and exerts a chelating effect on iron ions [33]. Egg white hydrolysates may prevent oxidative stress by inhibiting lipid peroxidation and increase radical-scavenging properties of plasma [34–36].

2.1.1. Transferrin (TF)

Transferrin (TF) is a blood plasma protein that transports iron absorbed from the intestine to the bone marrow, where red blood cells are produced. Iron is essential for normal functioning of various metabolic processes and thereby its homeostasis must be precisely regulated. TF is the main iron carrier in the plasma [37,38], able to transport about 25 mg of iron daily [39].

Transferrin is considered to be an antioxidant due to its ability to reduce the concentration of free ferrous ions, which catalyze the conversion of hydrogen peroxide to highly toxic hydroxyl radical (OH) during the Fenton reaction (Fig. 2.). Iron has a potential to generate OH, which is the strongest ROS.

Free iron can be a risk factor for several diseases, e.g. atherosclerosis [40,41]. Disturbed iron metabolism has also been observed in both Parkinson's [28,42–44] and Alzheimer's [29,43,45] disease. TF and ceruloplasmin (CP) are the main antioxidant proteins synthesized in several tissues including brain

$$Fe^{3+} + {}^{\bullet}O^{2-} \longrightarrow Fe^{2+} + O_2^{\bullet}$$
$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + {}^{\bullet}OH + OH^{-}$$

Fig. 2. Fenton reaction.

tissues. Extensive research has shown that oxidative stress plays a key role in the pathology of several other neurological diseases such as autism [46,47], Down syndrome [48–50] and schizophrenia [51]. The levels of transferrin in autistic children have been found to be significantly decreased compared to healthy children. Low levels of major proteins, such as transferrin and ceruloplasmin, lead to disturbances in the metabolism of iron and copper, and thus contribute to increased oxidative stress [52].

In schizophrenia, increased production of ROS, particularly in the brain cells that are vulnerable to oxidative stress, can initiate degenerative processes [53]. Brain cells are far more vulnerable to oxidative stress than other cells, due to high content of polyunsaturated fatty acids (PUFA) in the brain cell membranes, which are located in the grey matter [53].

2.1.2. Ferritin (FER)

Ferritin (FER) is an iron-storage protein that can be a source of iron for the synthesis of iron-containing enzymes, when the absorption of iron from food is insufficient. This protein has been found in animals, plants and bacteria [54]. Mammalian FERs consist of two types of chains named H (high) and L (light). The H-chain is responsible for iron oxidation, whereas the L-chain serves as a protein balancer, contributing to iron mineralization [55].

Ferritin plays a key role in the maintenance of intracellular iron balance. The main FER function is cytoprotection. It is able to minimize ROS formation by binding free iron, thus protecting cells against free radical-mediated damage [56]. Some data show positive correlation between anti-oxidative status and FER level in patients with phenylketonuria [57]. However, at the same time FER-rich leukemia cells present greater resilience to oxidative-killing, while leukemia cells with a reduced content of ferritin show lower resistance to oxidative stress [58].

2.1.3. Lactoferrin (LTF)

Lactoferrin is a member of transferrin family. This glycoprotein is present in the secretions of epithelial cells, e.g. in breast milk colostrum, tears, saliva, and genital and respiratory tract [59]. Blood LTF is produced by neutrophils, but its concentration is considerably lower than in the secretions. The physiological spectrum of the roles that LTF may play is very wide. Numerous studies have shown that LTF has antiviral, antibacterial [60] and anticancer effects [61,62]. Antibacterial properties of LTF are due to its ability to store iron, which becomes unavailable to pathogens, thus inhibiting proliferation and growth of microorganisms. LTF can regulate homeostasis of iron ions and serves as an anti-inflammatory protein. It also shows antioxidant properties in the human body [63].

The LTF molecule can bind two ferric ions, and iron chelation by LTF is a necessary step in iron metabolism. LTF participates in the absorption of iron from food and facilitates Fe storage in the liver cells [64]. Transport of iron into the cells takes place with the participation of TF, although LTF has a 360-times greater affinity to ferrous ions than TF [65].

Breast milk LTF is an innate protein with antioxidant and anti-inflammatory properties. The antioxidant effect of LTF results from binding Fe, which initiates and catalyzes free-radical processes, particularly lipid peroxidation in biological membranes [66].

Some studies have shown that LTF can be an effective free radical inhibitor in the Fenton reaction, even more than histidin and mannitol [67].

In healthy people, only 20–30% of TF and 5–8% of LTF bind iron, being ready to bind iron ions present in plasma [65].

2.1.4. Albumin (ALB)

Albumin (ALB) is a multifunctional protein, which demonstrates numerous physiological functions. The primary role of ALB is to regulate osmotic pressure and distribute fluids between different body compartments. It also takes part in transporting bile pigments, cholesterol, fatty acids and drugs. The latest research shows that plasma ALB is the major extracellular antioxidant [18].

Human ALB is composed of 585 amino acids. It shows affinity to bind many types of molecules and ions. Free ferrous and cupric ions are catalyst in the Fenton reaction, in which hydroxyl radicals are generated. Normally, these metal ions are bound to proteins. Copper, for example, possesses high affinity to ceruloplasmin, but at times it can be bound to albumin. Approximately 40–70% of the total antioxidant activity of the human serum ALB is associated with sulphur amino acids, methionine and cysteine, and therefore it is an excellent trap for free radicals, especially a reduced cysteine residue (Cys 34). It is the free sulfhydryl group of cysteine that allows ALB to scavenge hydroxyl radicals [21,22] (Fig. 3) [18].

The antioxidant properties of albumin derive also from its indirect effect, associated with binding of bilirubin and unsaturated fatty acids, which prevents oxidation of these compounds [68].

Plasma ALB concentration in healthy people ranges between 35 g/l and 50 g/l. Lower ALB concentration is closely related to the

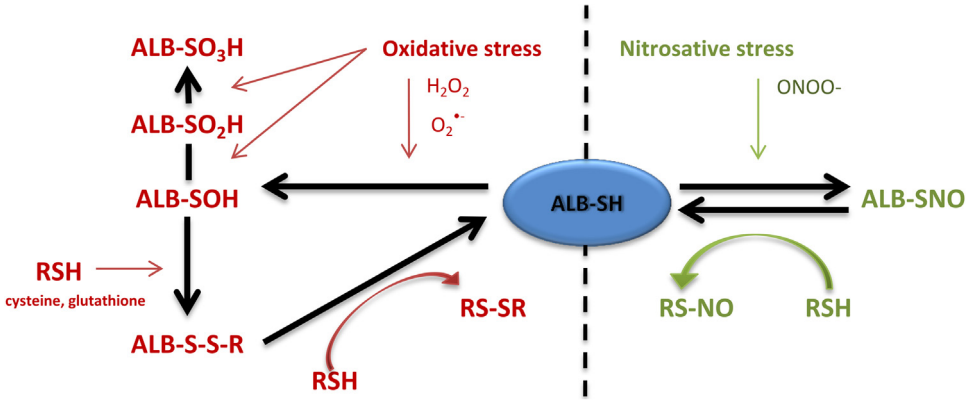

Fig. 3. The mechanism of antioxidant function of albumin. Adopted and modified according to © 2013, Taverna et al.; licensee Springer [18].
The free sulfhydryl group of cysteine of albumin acts as a free radical scavenger and is able to trap various reactive species, such as hydrogen peroxide (H_2O_2), superoxide radical ($O_2^{\bullet}-$), hydrochlorus acid (HOCl) and peroxynitrite (ONOO-). The presence of reactive species results in oxidation of cysteine residue and the formation of sulfenic acid (ALB-SOH), which can be further oxidized to sulfinic (ALB-SO_2H) and sulfonic (ALB-SO_3H) acids. These reactions are irreversible and lead to formation of end products. Sulfenic acid (ALB-SOH) can be transformed into a disulfide (ALB-S-S-R) by the reaction with a low molecular mass thiol e.g. free cysteine (Cys) or glutathione (GSH). This leads to the formation of reduced form of albumin (ALB-SH). Under nitrosative stress the reduced cysteine of albumin transforms into s-nitroso –albumin (ALB-SNO). This reaction is reversed by free cysteine or glutathione [18].

process of aging and development of noncommunicable diseases (also known as chronic diseases), which are strongly associated with the action of ROS and oxidant-antioxidant imbalance [69]. ALB is a major serum antioxidant in diabetes. Increased concentration of blood glucose in diabetes may decrease antioxidant properties of ALB. An impaired antioxidant-oxidant balance in the blood serum may be the cause of complications in such metabolic disorders as diabetes mellitus or cardiovascular diseases [70–72]. Numerous studies have shown that low concentration of serum ALB is linked to the risk of stroke, coronary artery disease, cardiovascular mortality, damage to atherosclerotic plaques and severity of atherosclerosis [25,73].

The antioxidative function of albumin results from its free radical-trapping capacities and various ligand-binding properties. Both functions are closely related to the ALB structure. The ALB is considered the main extracellular molecule responsible for maintaining the plasma redox state. Therefore, albumin as an antioxidant has a substantial importance in various chronic diseases [18].

2.1.5. Ceruloplasmin (CP)

Ceruloplasmin (CP) is a high molecular weight glycoprotein built of more than 1000 amino acids. CP is synthesized in several organs and tissues, such as brain or liver, and plays a number of roles. In the first place it can act as a copper carrier, transporting about 95% of copper in the blood. Secondly, by converting ferrous ions to ferric ions, it demonstrates ferroxidase activity showing its important role in iron homeostasis. This CP feature prevents formation of hydroxyl radicals ($^{\bullet}OH$), and hence CP has a proven antioxidant activity [74,75]. CP is mainly known to be a chain-breaking antioxidant. For example, it can protect the myocardial tissue against oxygen free radicals [76]. Moreover, it plays a key role in protecting polyunsaturated fatty acids in the erythrocyte cell membranes from ROS. This multifunctional glycoprotein can also act as a scavenger of oxygen radicals and may protect cardiovascular tissues subjected to ischemia-reperfusion [74]. Numerous studies have described low serum CP levels in several diseases [52,77]. Low CP plasma concentration has been debated as a marker of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases and autism [77–79].

2.1.6. Myoglobin (MB)

Myoglobin (MB) is a protein which consists of 150 amino acids. The primary function of myoglobin is to store oxygen in the muscle cells, which was discovered in 1939 by Millikan [80,81]. Recent studies have shown that MB can also act as a scavenger of free radical nitric oxide ($NO^{\bullet}$) and it is able to protect myocardial cells against ROS under hypoxic condition [82,83]. Hypoxia causes changes to MB function from $NO^{\bullet}$ scavenger to $NO^{\bullet}$ producer. Some data show that MB can significantly contribute to decreased oxidative stress in the cardiac muscle [84]. Myoglobin is capable of reducing oxidative stress by scavenging ROS, especially H_2O_2 (hydrogen peroxide), which is the most abundant and stable ROS in tissues [84]. It is also able to bind a wide variety of small ligands such as dioxygen and carbon monoxide, thus inhibiting the formation of hydroxyl radicals in the biological systems containing ascorbate [85].

2.1.7. Metallothioneins (MTs)

Metallothioneins (MTs) are low molecular intracellular proteins. They occur in microorganisms, animals and plants. MTs are built of 61–68 amino acids with a distinct predominance of cysteine (30%) [86].

MTs consist of two domains (α and β) linked by a lysine dimer, each binding metal ions. These proteins ensure proper homeostasis of essential metal ions, such as zinc and copper, and also provide storage capacity for these molecules [87] (Fig. 4) [88,89].

MT plays a major role in cell protection against cadmium. Stoichiomeric binding of metal ions by MTs in two metal-thiolate clusters is enabled by the presence of numerous sulfhydryl groups of residual cysteines [87,90]. Besides, free sulfhydryl residues are very important for oxidative stress reduction. The presence of numerous free sulfhydryl residues allows fast reaction with free radicals. MT is capable of scavenging anion superoxide and hydroxyl radicals, thus protecting more sensitive proteins [91,92].

There are four MT isoforms: MT-I, MT-II, MT-III and MT-IV. The classification into classes is based on the position of cysteine residues in the MT polypeptide chain. MT-I and MT-II are located in all tissues, MT-III is brain tissue-specific [93] and MT-IV is expressed in squamous epithelia associated with oral mucosa, esophagus and upper stomach [87,90].

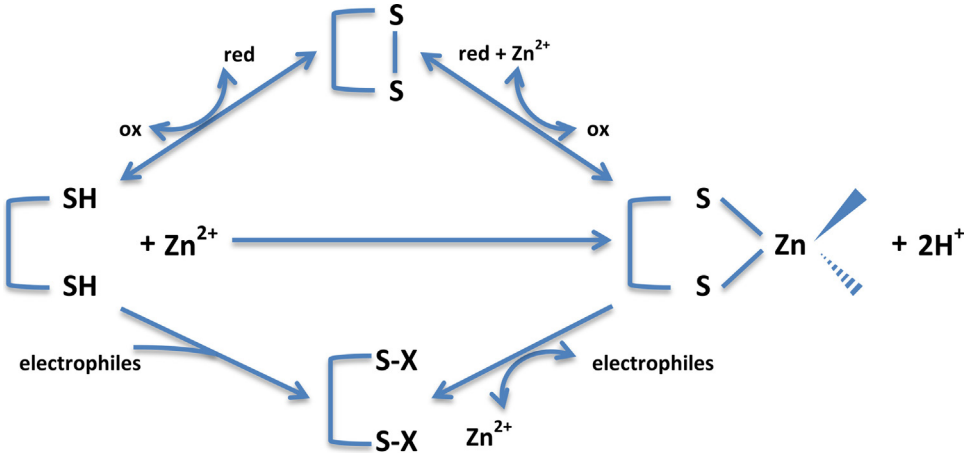

Fig. 4. The role of metallothionein in zinc homeostasis and redox buffering capacity. Adopted from © 2007 Maret W, Krezel A. [88].
MT functions are based on reversible dissociation of its zinc ions and the oxidoreduction of the cysteine sulphur donors in the zinc/thiolate clusters. The presence of reactive oxygen species or reactive compounds (electrophiles) cause oxidation or modification of the cysteine sulphur ligands, which leads to the release of zinc ions from metallothionein. In both instances the oxidized protein is formed.
Free zinc ions are involved in:
- the protection of thiol groups of proteins by binding to these groups
- indirect inhibition of lipid peroxidation dependent on iron ions, by competing for binding sites on a cell membrane with ions of transition metals, what prevents them from generation of free radicals [88,89].

Primarily MT-I, MT-II and MT-III are protective against metal toxicity. The function of MT-IV isoforms is similar to that of MT-I and MT-II. They demonstrate high affinity for transition metals, especially Cu, Zn and Cd. Moreover, as in vitro experiments show, MTs can also bind Fe, Hg, Ni, Ag and Au [94].

The synthesis of MTs depends on such factors as excessive heavy metals, stress hormones, cytokines or factors that are precursors of ROS. Therefore, these proteins are considered important components of the endogenous antioxidant system.

MTs play a beneficial role in a variety of noncommunicable diseases. MT synthesis is induced by the inflammatory process, during which an increase in reactive species can be observed. Therefore, MTs are significant in inflammatory bowel diseases [95] and cancers [96].

2.2. Coenzyme Q10 (CoQ10)

The names for coenzyme Q10 (CoQ10), ubiquinone and ubiquinol, differing in oxidation states, originate from the Latin term *ubiquitarius* which means "commonly found". CoQ10 is one of 1,4-benzoquinone derivatives. Under the normal conditions of homeostasis, coenzyme Q10 is synthesized in all tissues of the body. The substrates for the synthesis of coenzyme Q10 are 4-hydroxybenzoate, formed from tyrosine, and a polyprenyl group resulting from acetyl-CoA [97,98].

In animal species, different homologues of ubiquinol have been found, which differ in the length of the side polyisoprenoid chain. Vertebrates and mammals, including humans, show the presence of CoQ9 and CoQ10, but ubiquinones isolated from yeasts and molds are built only from no more than six, seven, or eight side chain isoprenoid units [99]. Coenzyme Q demonstrates several biochemical functions. Generally, it is involved in the transport of electrons in the mitochondrial respiratory chain and in the electron transport outside mitochondria [99]. CoQ exhibits its activity in the lipid phase and participates in the redox reactions of dehydrogenases, cytochromes or other non-heme proteins [100]. These properties are demonstrated only by the reduced form of CoQ10 – ubiquinol ($CoQ_{10}H_2$), and ubisemiquinone radical ($CoQ_{10}H$). Ubiquinol allows binding of hydrogen to free radicals, which leads to the transformation of ubiquinol and the formation of ubisemiquinone radical ($CoQ_{10}H$). The radical formed in this reaction also demonstrates antioxidant properties, and can react with molecular oxygen and other free radicals [101]. Ubiquinol may also reduce oxidized α-tocopherol. The reduced form of tocopherol shows strong antioxidant properties.

In the healthy population, blood CoQ10 concentration ranges from 0.50 to 1.91 μmol/l [102,103]. Low concentrations of CoQ are closely related to aging and to some diseases, including hypertension and coronary artery diseases, cardiovascular diseases, diabetes mellitus and cancer [104]. Normally, the in vivo synthesis together with sufficient dietary intakes provide adequate CoQ supply. The absorption of CoQ10 from food is estimated to be 10% and less [105]. The best dietary sources of CoQ10 are meat products (pork meat, poultry, fish) and fats (oils) [106], although culinary techniques may lower its food contents. Some studies have determined the effects of different cooking methods on CoQ10 in beef meat (heart, liver and muscle). The greatest losses of CoQ10 are found during frying [107].

Some research shows clinical benefits of CoQ10 supplementation in patients with coronary artery disease, causing a decrease in oxidative stress and an increase in the activity of antioxidant enzymes [105], as well as antioxidative protection against myocardial infarction [106]. CoQ10 is also applicable in cosmetology, since its supplementation shows skin repair, anti-wrinkling and anti-aging properties [104].

2.3. Glutathione (GSH)

Glutathione (GSH) is a low molecular weight compound composed of three amino acids: glycine, cysteine and glutamic acid. GSH is present in all plant and animal cells. In physiological conditions it is synthesized in many different tissues [108], but the most intense GSH synthesis occurs in hepatocytes [109]. Glutathione in the human body is present in several redox forms, among which the most important are reduced glutathione (GSH) and oxidized glutathione (GSSG). In typical cells, in normal conditions, the predominant form of glutathione is its reduced form (GSH) in a ratio of 100:1. Under normal conditions, for instance, reduced GSH is the most prevalent form of GSH, constituting up to 98% of the total GSH pool [110]. Glutathione molecules can also be bound to proteins [111]. GSH is a soluble antioxidant, which in high cellular concentrations (1–10 mM) is present in the cytoplasm, mitochondria and nucleus. The GSH concentration is much lower in the endoplasmic reticulum (up to 2 mM). Mitochondria contain 10% of cellular glutathione [111]. Red blood cells are abundant in glutathione and contain 99% of GSH against 1% present in the plasma [112]. The previous [113] and the latest research [114] show that the extracellular concentration of glutathione in the human body is much lower than its intracellular level. Blood plasma, for example, contains only about 20 μM of glutathione and the dominant form there is oxidized glutathione (GSSG) [115].

The concentration and role of GSH are differentiated and cell type-specific. Besides being a potent antioxidant, GSH has a number of functions not related to defence against ROS. For example, it participates in the detoxification processes of electrophilic compounds (xenobiotics), and in the metabolism of prostaglandins and leukotrienes. It is also involved in the transport of amino acids and in the absorption of micronutrients from the intestine, mainly iron and selenium. However, the predominant role of GSH is undoubtedly that of antioxidant. GSH as an antioxidant participates in several lines of defence against ROS. It plays an important role not only as a free radical scavenger, but is also engaged in the repair processes of damaged cells. The antioxidant properties of GSH depend on two characteristic features of its molecule, namely the presence of a special pseudo-peptide bond between the amino group of cysteine and the alpha-carboxyl group, providing an excellent protection against aminopeptidases, and the expression of the thiol group (-SH) deriving from the cysteine residue. Only these fragments of the tripeptide allow its involvement in an impressive number and variety of functions. Due to the presence of the thiol group in the molecule, GSH has an ability to protect other thiol groups in proteins against oxidative damage [111]. Thiol groups (-SH) are among the most reactive chemical species that occur in cells. The most important functions of –SH groups in the biological systems include complexation of metal ions, participation in the oxidation reactions (final product is sulfonic acid), and formation of thiol radicals and disulfides [115].

As an antioxidant, GSH reduces ROS during the enzymatic and non-enzymatic reactions. It regenerates other oxidized small molecule antioxidants, for example vitamin C and vitamin E [116], is involved in the repair of protein molecules, nucleic acids and lipids damaged in peroxidation processes, and in the maintenance of sulphydryl groups of protein in the reduced state [117,118].

2.4. Uric acid (UA)

Uric acid (UA) is one of the low molecular weight organic compounds, which is generated during the metabolism of purines. UA is a hydrophilic antioxidant, which accounts for two thirds of the total oxygen scavenging activity in the blood serum [119].

In reptiles and birds UA is excreted in feces as a dry mass. Humans and other mammals are able to produce small quantities of uric acid. Unlike humans, most mammals can transform serum uric acid to allantoin. The normal level of blood uric acid in humans is therefore higher (3.5–7.5 mg/dL) than in other mammals (0.5–1.5 mg/dL). The inability to convert uric acid to allantoin seems to be a positive factor in the evolutionary process [120]. The positive impact of the loss of urate oxidase activity during evolution leads to increased levels of uric acid, which is a strong reducer (electron donor) and potent antioxidant [121]. UA is a scavenger of various ROS, for example peroxynitrite, hydroxyl radical, singlet oxygen and lipid peroxides. It can probably scavenge nitrogen dioxide and carbonate ions as well [122,123], and form stable complexes with iron ions and copper ions, leading to the inhibition of free radical reactions, such as the Fenton reaction and the Haber-Weiss reaction [124].

In addition, UA contributes to the protection of such antioxidant enzymes as intracellular superoxide dismutase 1 (SOD1) and extracellular superoxide dismutase 3 (SOD3). Physiological UA levels can modulate activities of SOD1 and SOD3, by postponing inactivation of these enzymes by H_2O_2 [120].

The urate radicals formed in the reaction of UA and H_2O_2 have lower oxidative potential than other oxygen radicals, and can react with ascorbic acid and regenerate uric acid [125,126].

Numerous studies have proved positive effects of UA in various diseases associated with oxidative stress. The research concerning free radical scavenging capacity in the serum of healthy people has shown that UA is even more effective than vitamin C [126].

UA plays a key role in the protection against oxidative stress during intensive physical exercise. Its antioxidant properties have been proven to be of biological importance in vivo [127].

Oxidative stress is a major factor of atherosclerosis, significantly contributing to vascular smooth muscle tissue damage. Several years of research have shown a beneficial role of UA against ROS that take part in the degradation of vascular endothelium [128].

Neuroprotective effects of UA have been observed in Parkinson's disease, which is closely related to the ability to chelate iron ions. Therefore, it has been hypothesized that a low UA level can be a risk factor for dementia in Parkinson's disease [129,130].

UA is generally seen as an antioxidant and free radical scavenger, but numerous studies have shown its pro-oxidative properties. The increased levels of UA observed in patients with heart failure have been interpreted in different ways [131]. Some studies demonstrate that UA may be a factor in inflammatory reactions [132] and heart failure [133]. In addition, some research has shown that xantine oxidase inhibitor – allopurinol, may decrease UA levels in the blood, which may have a protective effect against oxidative stress [134]. Therefore, according to an increasing number of reports, UA is not always perceived as an antioxidant, since hyperuricemia may be a risk factor for cardiovascular disease, e.g. in patients with diabetes mellitus [135] and can cause pulmonary arterial hypertension [136]. The metabolic syndrome is often accompanied by elevated levels of serum UA. Recent studies have shown associations between the elevated UA and the accelerated development of complications due to the metabolic syndrome [137], which among other things, included cardiovascular disease and renal failure. Some studies have shown that elevated UA levels in metabolic syndrome may lead to hypertension [138]. Other authors have found that the increased serum concentration of UA may cause deterioration of kidney function in patients with congestive heart failure (CHF) due to reduced urinal excretion of UA. Deterioration of renal function is closely linked with cardiac dysfunction, and some authors have demonstrated elevated levels of UA to be the risk factor of heart failure. Some data show a connection between elevated UA level and diabetes mellitus, arterial hypertension, ischemic heart disease, CHF [139], and some demonstrate lack of association between hyperuricemia and atherosclerosis [140].

Further investigations, which could explain the effect of UA in the body are underway. A growing number of studies show that either too low or too high UA may lead to increased mortality in vulnerable patients, e.g. dialysis patients [140]. Despite antioxidant properties some research shows that even mild elevations of UA can pose a risk of cognitive decline among older adults [141,142].

2.5. Melatonin (MEL)

Melatonin (MEL) is a low molecular weight compound classified as indol. MEL was discovered in the early 20th century by *McCord* and *Allen*, but was named only in 1958 by *Lerner*. It was separated from the pineal body and called melatonin due to its reaction with frog's skin melanocytes resulting in their discoloration. For many years, MEL was considered a hormone characteristic only of vertebrates. However, latest research has found that MEL is common in nature. MEL, as a compound, can be separated not only from the pineal body, but also from bacteria, algae, higher plants and invertebrates [143]. The omnipresence of MEL in the world of living organisms proves a very early appearance of this compound in the history of the Earth. There are several functions of MEL, including its participatation in the regulation of biological clock, genital maturing and reproduction in mammals. It also takes part in the regulation of metabolism [144].

One of the significant functions of MEL is oxidative stress reduction, resulting from its ability to scavenge free radicals and prevent their formation by regulating the activity of antioxidant enzymes and by stimulating the activities of endogenous antioxidants that metabolize reactive species (indirect antioxidant) [143,145,146]. MEL is a very effective hydroxyl radical scavenger. It has an ability to detoxify some ROS and RNS, namely singlet oxygen, peroxynitrite anion and nitric oxide. It also acts as a regulator of some antioxidant enzymes and prevents generation of increasing ROS levels during mitochondrial activity [147].

Decline in MEL secretion is related to aging, and lower MEL concentration may contribute to severe morbidity in age-related diseases. Due to its small molecular size and specific chemical structure (steroid hormone), MEL can simply cross biological membranes and react with individual components of the cell [148]. Hence, MEL demonstrates antioxidant protection both in the aliphatic and aqueous cell environments.

MEL plays a beneficial role in a variety of conditions and diseases, for example in neurodegenerative diseases, cancer, heart attack and stroke, and even in aging [149,150]. MEL is able to reduce free radical formation in neurodegenerative diseases and decrease interactions between transition metal ions and beta-amyloid [151,152]. In addition, it participates in attenuating oxidative damage in diabetes mellitus [153].

2.6. Bilirubin (BIL)

Bilirubin (BIL) is a degradation product of hemoglobin and other heme proteins by the mononuclear phagocyte system. After the dissolution of erythrocytes, the heme residue of hemoglobin is enzymatically decomposed to biliverdin by heme oxygenase (HO), and subsequently biliverdin is reduced to BIL by biliverdin reductase (BVR). This process is reversible and the oxidation of BIL results in the formation of biliverdin. Indirect (unconjugated) BIL (uBIL) circulates in plasma bound to albumin, from where it is taken up by the liver. In the liver, uBIL is conjugated with glucuronic acid and in this form it is excreted in bile into the intestine. In some diseases of the liver, the excretion of bile is obstructed and the level of bilirubin in the blood increases. For this reason, BIL is considered to be a marker of liver function.

Under certain conditions bilirubin can be toxic, especially to neonates [154], yet several beneficial properties have been attributed to moderate BIL concentrations, such as anti-inflammatory [155], anti-atherosclerotic [156,157] and anti-adiposity [158] effects. In biological studies uBIL shows potent antioxidant properties [159,160]. Strong antioxidant potential of BIL against peroxyl radicals has been demonstrated in the polar media such as aqueous lipid bilayers [161].

2.7. Polyamines (PAs)

Polyamines (PAs) such as spermidine, spermine and putrescine are biogenic amines with antioxidant properties. PAs in small quantities are present in every human, animal and plant cell. PAs are necessary for cell growth, renewal and metabolism [162]. Among other functions, PAs act as antioxidants and free radical scavengers [163].

In microbiological studies, for example, PAs were the main scavengers of free radicals in *Escherichia coli* colonies, and under strong stress PAs mainly acted as positive modulators of antioxidant genes [164].

Similar results concerning the role of PAs as antioxidants have been reported [165], showing that putrescine, spermidine and spermine demonstrate antioxidant properties against hydrogen peroxide in red blood cells, and suppress and decrease hemolysis of erythrocytes. This protective effect of PAs is attributed to the stabilization of lipids in the cytoplasmic membranes.

PAs protect cell membranes from hydrogen peroxide, superoxides and peroxy radicals, e.g. peroxyl radicals derived from polyunsaturated phospholipids. Negatively charged phospholipids contained within cell membranes can react with positively charged amino groups. Spermine due to four amino groups is a more effective scavenger than spermidine and putrescine [165]. PAs can also protect DNA from damage induced by ROS. In physiological pH, positively charged PAs can remain in close association with negatively charged nucleophilic macromolecules, and thus protect them against oxidation [166].

3. Conclusions

The antioxidant defence system includes endogenous (enzymatic and non-enzymatic) and exogenous (dietary) antioxidants that interact in establishing redox homeostasis in the body. Recently more attention has been directed to exogenous antioxidants, which are present mainly in food and supplements. Endogenous antioxidants described in this review are among the most important, although certainly they are not the only internal antioxidants. They provide efficient mechanisms to prevent damage to cells and tissues by oxidants. This review summarizes the roles and functions of some of the most important internal antioxidants in the human body.

Conflict of interests

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