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Influence of free radical reactions on aging-related development of arterial hypertension

Udział reakcji wolnorodnikowych w rozwoju nadciśnienia tętniczego związanego z procesem starzenia się organizmu

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Abstract

It is suggested in numerous scientific articles that disturbance of oxidative homeostasis has influence on the etiopathogenesis of arterial hypertension. Excessive generation of free radicals with the simultaneous deficit of antioxidative factors may cause the damage of endothelium. This later may lead to the development of arterial hypertension. In this work, there is a thorough literature review concerning the research on the oxidative stress in the aging-related arterial hypertension. (Gerontol Pol 2019; 27; 50-58)

Key words: endothelium, reactive oxygen species, hypertension

Streszczenie

Liczne doniesienia naukowe przypisują istotną rolę w etiopatogenezie nadciśnienia tętniczego zaburzeniu homeostazy oksydacyjnej. Nadmierne generacja wolnych rodników przy deficycie czynników antyoksydacyjnych może prowadzić do uszkodzenia śródbłonka, w konsekwencji czego może dojść do rozwoju nadciśnienia tętniczego. W niniejszej pracy przedstawiono przegląd literatury dotyczącej badań związanych szeroko pojętym stresem oksydacyjnym w kontekście rozwoju nadciśnienia tętniczego towarzyszącemu starzeniu się organizmu. (Gerontol Pol 2019; 27; 50-58)

Słowa kluczowe: śródbłonek, reaktywne formy tlenu, nadciśnienie

Introduction

The extension on human life expectancy is one of the most important achievements of fast developments in the human civilisation [1]. In the light of that, the research concerning molecular mechanisms of cellular aging process plays a crucial role [2]. A thorough familiarization with aspects concerning the cellular aging process facilitates a better understanding of the mechanisms governing the aging of particular tissues, organs and whole organisms. The beginning of research on the human cellular aging process dates back to the second half of 20th century and it commenced as a result of observation that normal cells can replicate a finite number of times [3]. Further observation led to conclusions that certain types of cells differ with respect to proliferative abilities. Furthermore, this feature depends on many factors of exogenous and endogenous character [4]. From the researcher's point of view, the most attractive cells are those which show high proliferative affectivity. This allows for an observation of the inhibition of the speed of the process and noticing the starting point of the aging phase and accompanying peculiar degeneration.

Redox reactions accompany most aerobic metabolic processes [5]. The generation of reactive forms of oxygen and nitrogen is an integral part of aerobic metabolism. The excessive generation of these forms leads to the intensity of the oxidative stress [6]. The term oxidative stress is determined by a condition in which there is an imbalance and severity of the pro-oxidative pro-

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cesses with the deficit of protective and recovery mechanisms, which include non-enzymatic and enzymatic antioxidants. There is then an uncontrolled oxidation of cell structures. This condition becomes dangerous for the cell when there is a disorder of homeostasis between pro-oxidative and oxidative reactions [7].

Oxidative stress

Main cellular source of Reactive Oxygen Species (ROS) is the electrons transport in the respiratory chain in the mitochondrion and electron transport systems in microsomal and nuclear membrane. Furthermore, P-450 and b5 play an important role in the ROS creation cytochrome. Radicals which appear in the moment when activated phagocytes destroy the pathogenic factors, so called respiratory burst, are another source of ROS. External factors which cause the creation of free radicals are factors occurring in the environment which cause its contamination such as pollution (smog), tobacco smoke, UV radiation, xenobiotics, ions of iron and other transition metals, phenolic compounds and polycyclic aromatic hydrocarbons. In the course of evolution, the oxygen organisms adapted themselves by creating the antioxidative system which is capable of eliminating potential dangers [2]. The connection of the aging process with processes in which reactive molecules occur seems a right way to explain the mechanisms of aging [2]. A significant amount of energy needed for the life of the cells is taken in the oxygen mechanism of the cellular respiration. Oxygen plays a role of the electron acceptor in the respiratory chain occurring in the mitochondria based on proteins transporting individual electrons. Partial reduction leads to the creation of free oxygen radicals [2,8].

A free radical is an atom, molecule or compound which energy-wise does not create a stable structure (meaning it has minimum one unpaired electron). This lack of energetic stability causes their high reactivity because they lead to a connection with other molecules, atoms and even single electrons. In order to achieve a more stable state, free radicals may 'steal' protons from other molecules or enter in various ways in reaction with other free radicals with a purpose of creating a stable structure.

We can distinguish four types of reactions to which free radicals may be subjected:

- *Initiation* – reaction as a result of which there is a creation of a free radical from the molecule not having a radical features.
- *Transfer* - atoms (most likely protons) or group of atoms. This type of a reaction is a propagation reaction in which a radical reacts with other molecule which becomes a hydrogen donor. As a result, the radical becomes energetically stable and the molecule which was a donor becomes a radical.
- *Addition* – similarly as previous one, it also is a reaction of propagation but in this case the radical connects with other stable molecule transforming into a radical.
- *Termination* – two radicals react with each other creating an energetically stable compound. A reaction of disproportion when two identical radicals react with each other but only one of them is an electron donor is another example of a termination reaction. As a result there are two new energetically stable molecules.

Metabolites which lay as a basis for oxidative stress can be divided into reactive forms of oxygen and reactive forms of nitrogen.

Reactive oxygen species

Superoxide anion radical

Superoxide anion radical ($O_2^{\bullet}$) is the most known aerobic metabolite. It is probably because it is a precursor of the subsequent aerobic metabolites which are better known as ROS. Hydroxyl radical ($HO^{\bullet}$), hydrogen peroxide (H_2O_2), hydroperoxide radical ($HO_2^{\bullet}$) belong to the group of $O_2^{\bullet}$ derivatives. It is the protonation of the superoxide anion radical that leads to the creation of even more reactive than $O_2^{\bullet}$ hydroperoxide radical ($HO_2^{\bullet}$). In the reaction between oxide anion radical and nitric acid, the singlet oxygen is produced which does not have features of a free radical but is very toxic for the cellular structures [9]. According to the theory of Brönsted, the superoxide anion radical is an alkali which in aqueous solution, depending on the pH value of the solution, transforms into different states. When pH values are low, it easily transforms into hydrogen peroxide, in the acid-base homeostasis it takes the form of a hydroperoxide radical, whereas in the alkali environment it undergoes a dismutation reaction. As a result of either spontaneous or catalysed dismutation (for instance by one of isoenzymes of superoxide dismutase) the superoxide anion radical is a source of creation of hydrogen peroxide which is a precursor of hydroxyl radical – the most reactive among oxygen metabolites [5].

Hydroxyl radical

Despite a very short lifespan (the half-life in the temperature 37°C is 10^{-9} seconds) and a little ability to diffuse, hydroxyl radical is the aerobic metabolite most

dangerous for biological structures. It is an extremely reactive molecule capable of reaction with all cellular structures [10]. Reactions of detachment of protons from alkanes and their derivatives and reactions of connection of hydroxyl radical to unsaturated bonds of organic compounds are the most common reactions of hydroxyl radical. Reactivity of $HO^{\bullet}$ is so large that the responsiveness of different substances is controlled by diffusion and not by overcoming barriers to energy, necessary for the activation of molecules reacting with each other.

Several possible ways may lead to the generation of this radical. One of them is a result of ions catalysed by iron (or other transition metal ions such as Cu^{+}) decomposition reaction of hydrogen peroxide, so called Fenton's reaction. The interaction of anion radical with hydrogen peroxide in the Haber-Weiss' reaction is another way the formation of $HO^{\bullet}$.

The nitric oxide radical

A bond of oxygen and nitrogen atom resulting in a molecule with an odd number of electrons is another highly reactive form. The nitric oxide radical is capable of reacting with the protein structures of myoglobin and haemoglobin. According to some authors, the release of iron from ferritin may be caused by nitric oxide radical [11]. Under physiological conditions, the nitric oxide is produced from arginine by nitric oxide synthase and plays a very important role, both in physiology as well as in pathology, as a regulatory molecule, inter alia, in the regulation of blood pressure. Nitric oxide is produced in enzymatic reaction oxidation of L-arginine. Nitric oxide synthase (NOS E.C. 1.5.1.19) is an enzyme catalyst in the formation of NO [12].

Several forms of this enzyme differing between themselves on the molecular weight were defined. Nitric oxide synthase can be divided into two main groups. The first depends on the Ca^{2+} ions and calmodulin (cNOS) and the second is independent of calcium ions and calmodulin (iNOS). Regardless of the group, all the nitric oxide synthases contain FAD and FMN, and utilize NADPH as a factor in the reduction of arginine to citrulline. Presently, NOS are the only enzymes known to science which simultaneously need to operate five cofactors: FAD, FMN, hem, tetrahydrobiopterin (BH_4) and calmodulin [12].

Nitrogen dioxide radical

In the presence of oxygen, nitric oxide radical transforms into nitrogen dioxide which has the nature of a free radical. Structures that have non-saturated bindings are exposed to the nitrogen dioxide radical attack. As a result of this reaction, there is an emergence of peroxyl and alkoxyl radicals [13]. Superoxide anion radical can react with $NO_2^{\bullet}$ and produce a highly reactive oxidising agent, which is the peroxynitrite anion that is capable of in the cell to diffuse for long distances.

Reactive oxygen forms that are not free radicals

In addition to oxidants that are free radicals, there are also non-radical oxidants. The most representative are hydrogen peroxide, singlet oxygen and ozone. Hypochlorous acid and semi thiocyanic acid also play an important role. Acids oxidise mainly thiol groups, iron-sulphur centres and transition metal ions such as iron. They also react with cholesterol and saturated bindings in fatty acid chains and phospholipids [14].

Hydrogen peroxide

It is a compound which, as previously mentioned, is a product of dismutation of superoxide anion radical. The reaction catalysed by superoxide dismutase is the main source of H_2O_2 in the cell. In general, the hydrogen peroxide alone is not a molecule that has high reactivity, but like superoxide anion radical, it can be easily disproportioned [15].

Hydrogen peroxide, in spite of its low reactivity, is a very important cell oxidant because it can become a source of hydroxyl radical. If one takes into account the fact that the H_2O_2 has a huge capacity to diffuse through cell membranes, it is very probable that, as a result, it may be a threat to the cell structures, in which, under physiological conditions, it doesn't happen [16].

Singlet oxygen

The singlet oxygen can react with amino acids such as histidine, methionine, tryptophan, tyrosine, cysteine in order to transform into a triplet state. Halliwell points out that in the reaction of singlet oxygen with cholesterol, another product than in the reaction with hydroxyl radical appears [17]. Singlet oxygen can react with polyunsaturated fatty acids (PUFA), resulting in a creation of lipid peroxides. It may contribute to a damage of nucleic acids, because it particularly easily reacts with guanine and other purine bases [17].

Ozone

Ozone can react with PUFA, but it is the participation of ozone in the creation of free radicals that is more important. Alkoxyl and peroxide radicals may occur as a result of the reaction of ozone with alkenes and PUFA.

The hydrogen peroxide and $HO^{\bullet}$ or $HO_2^{\bullet}$ radicals can appear in aqueous solutions of ozone [18].

Peroxynitrite

It is formed in the reaction of nitrogen dioxide with oxygen. It is a very reactive oxidant, capable of diffusing on long distances in biological systems. It may contribute to the oxidation of proteins. Both thiol groups and unsaturated bindings in PUFA are particularly vulnerable to its attack. As a result of the reaction with peroxynitrite, there may be a nitration of amino acid residues in proteins. Peroxynitrite can cause damage to the respiratory chain by an inhibition of cytochrome oxidase. Peroxynitrite can also adversely affect the overlap of the citric acid cycle in cell by inhibiting aconitase [19].

Structures damaged by ROS in the cell

Lipid peroxidation

Lipid peroxidation, understood as reactions of molecules exhibiting the properties of free radicals with PUFA, is the most commonly researched consequence of oxidative stress in the cell. However, there is a distinction between enzymatic lipid peroxidation and non-enzymatic oxidation of fatty acids caused by ROS. The enzymatic lipid peroxidation are the processes associated with the formation of biologically important factors such as prostaglandins, leukotrienes or thromboxane. Therefore, with reactions related with cyclooxygenase activity and processes associated with the integration of oxygen molecules in the specified structure caused by lipoxygenase. [20]

In contrast, a reaction associated with non-enzymatic peroxidase of PUFA is a process that can lead to the destruction of the cell. This process is initiated by a separation of a hydrogen atom from the lipid particles caused by the hydroxyl radical $HO^{\bullet}$, peroxide lipid radical $LOO^{\bullet}$ or alkoxyl radical $RO^{\bullet}$[18]. Some authors also mention ozone, boric acid, nitric oxide or sulphur dioxide as factors capable of initiating the process of peroxidation. The peroxide lipid radicals, which play a key role in the oxidation process chain, occur as a result of the radicals' attack on the unsaturated bindings in the fatty acids. According to this scheme, there is a chain reaction the peroxidation of PUFA, which can lead to damage of the membrane lipid and biological dysfunction of the cells by destroying the cell compartments. Transition metal ions play an important role in the process of peroxidation of PUFA. According to some authors, transition metal ions may even initiate the peroxidation process [18]. They play a role in catalysing the lipid oxidation process. The process of lipid peroxidation is stopped when there is a reaction between two free radicals, for instance two alkyl or superoxide radicals or any two radicals occurring in the system in which there is a chain peroxidation reaction.

Peroxidation of proteins

ROS may also lead to the oxidation of amino acid residues that builds protein structure [8]. Damages to the amino acids residues are usually initiated by the detachment of a hydrogen atom from the carbon alpha amino acid. The results of studies have shown that hydroxyl radical also takes an active part in the separation of a hydrogen atom from the carbon alpha amino acid which comes from the main polypeptide chain [21].

Detaching hydrogen atom initiates a chain reaction, in which at a later stage, a radical localized on the carbon atom is formed, and this, in turn, in the presence of oxygen, is transformed into a peroxide radical [22]. Then, the resulting peroxide radical can be converted to alkyl peroxide. Production of alkyl peroxide may happen as a result of the reaction of unportioned forms of superoxide anion radical or by the removal of a hydrogen atom from subsequent molecule of the amino acid.

Subsequent reactions with $HO_2^{\bullet}$ can lead to the creation of alkoxyl radical, which as a result of the further reaction of $HO_2^{\bullet}$ leads to hydroxyl derivatives. Radicals $HO^{\bullet}$ and $HO_2^{\bullet}$can be created from hydrogen peroxide as a result of ionizing radiation. However, under physiological conditions, from the same hydrogen peroxide the above radicals can appear, as a result of reaction involving transition metal ions such as iron and copper.

In addition to $HO^{\bullet}$ and $HO_2^{\bullet}$ radicals, peroxyl radical ($ROO^{\bullet}$), alkoxyl radical($RO^{\bullet}$), superoxide anion radical($O_2^{\bullet-}$) and non-radical substances such as hydrogen peroxide, hypochlorus acid, peroxynitrite, singlet oxygen or ozone can contribute to the peroxidation of proteins [23]. Oxidative damage of proteins in the active centre leads to the loss of their biological activity. It is proved that ROS can result in breaking of the peptide bonds and hence a fragmentation of protein structures [24]. Most often it is the amino acids residues of proteins belonging to the cysteine, methionine, lysine, histidine, tryptophan, phenylalanine, tyrosine, and arginine that are damaged [25].

Damage to nucleic acids

Nitrogenous bases that make up nucleic acids are quite resistant to damages caused by the ROS, and only hydroxyl radical or singlet oxygen can cause oxidation

of bases included in the nucleic acids. Hydroxyl radical may also react with sugar residues and disrupt the phosphodiester bindings. Hydroxyl radical poses the biggest threat to thymidine because it transforms it into free radicals (cis-6-hydroxy-5-hydroperoxy-5.6-dihydrotymidyne, cis-5-hydroxy-6-hydroperoxy-5.6-dihydrotymidyne and 5-hydroperoxymetylo-2 '-deoxyuridine), which react with oxygen and transform themselves into peroxides. Cis-glycols of thymidine, which are considered to be one of the markers of lipid peroxidation of nucleic acids, are created from these peroxides.

In the case of purine bases, the most positions in the scientific literature are devoted to 8-hydroxy-2'-deoxyguanosine and 8-hydroxyguanine [26]. These are the successive, markers of nucleic acid damage caused by ROS, similarly to thymidine glycols. These compounds are formed by the reaction with purine ring in position 8, which can lead to the destruction of the imidazole ring. Cells have mechanisms for repairing damaged DNA fragments, however, there may be a mutation when repair mechanisms fail and not all modified by ROS bases are removed. The damaged nitrogen bases in DNA are cut by them and, mostly intact, excreted from the organism. However, there are still all the damages which are not always removed, which can lead to mutations and thus to impairment of cell function.

Antioxidant defence

A series of enzymes is involved in defence of the antioxidant. Non-enzymatic compounds also play an important role. Among the antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT) should be mentioned first. Peroxidases (GPx) and glutathione reductase which cooperate with them (GR) are also enzymes with an important role in antioxidant defence [27]. Whereas glutathione in a reduced form (GSH), vitamins C and E, uric acid, bilirubin, coenzyme Q, melatonin, and ceruloplasmin -a protein exhibiting ferroxidative activity are among substances that are not enzymes but play an important role of antioxidant [28].

Enzymatic antioxidant system

Superoxide dismutase (E. C. 1.15.1.1) is the most known and the most important antioxidant enzyme. This oxidoreductase catalyses the dismutation reaction between two superoxide anion radicals which produce hydrogen peroxide and molecular oxygen.

Eukaryotic cells have several isozymes of superoxide dismutase. Depending on the location, amount of subunits and metal building enzyme, we can distinguish cytoplasmic dismutase that is homodimer that contains copper and zinc (SOD-1). Superoxide dismutase in the mitochondrial matrix enzyme is built with four homologous subunits and is combined with manganese (SOD-2) [29].

Cells are protected against the negative effects of radical extracellular dismutase (EC-SOD) related to the polysaccharides of cell membranes. EC-SOD like SOD-1 contains copper and zinc, however, this isoenzyme is a tetramer. Catalase (oxidoreductase, hydrogen peroxide: hydrogen peroxide) is another oxidoreductases, which plays a prominent role in antioxidant defence. Tetrametric protein is included in the construction of the hem. In mammalian tissues it occurs mainly in the liver, erythrocytes and the kidneys in the form of a cytoplasmic (T) and peroxymale (A) [29]. This enzyme catalyses the disproportionation of hydrogen peroxide.

Glutathione peroxidase associated with selenium plays an important role in antioxidant defence which is often referred to as the second line of defence. These are enzymes that catalyse the reaction between hydrogen peroxide and glutathione. An oxidized form of glutathione – disulphide glutathione (GSSG – is produced as a result of this reaction. All isoforms of glutathione peroxidase have the selenocysteine in its active centre. There are four peroxidases in the human body [27]. Peroxidase in erythrocytes (cGPX) is most widely known. Apart from it, there are also a gastro-intestinal (GI-GPX), plasma (pGPX) and monomeric peroxidase of phospholipids hydroperoxides (PHGPX). Erythrocytic cGPX is responsible for the protection of the red blood cells against hydrogen peroxide. GI-GPX, which protects against organic peroxides and xenobiotics with food, occurs in the walls of the digestive tract. Plasma pGPX occurs in extracellular fluids and it protects the extracellular space [30].

Non-enzymatic antioxidants

Substances that are present in the body in low concentrations and are considered antioxidants, when compared with substances susceptible to oxidation, cause a slowdown or even prevent oxidation.

There are several types of classification of antioxidants, for instance the nutritional and non-nutritional food ingredients or according to the construction of the particles on the hydrophobic and hydrophilic.

The term non-nutritional combines a series of flavoprotein substances, polyphenols and turpentine present in tea, red wine, onions or apples. Another classification is based on the origin and intracellular antioxidants such

as water soluble Coenzyme Q10, and exogenous antioxidants taken with food such as the above mentioned vitamins, carotenoids and tocopherols. Thanks to the ability to dissolve in fats or in water, antioxidants can be divided into hydrophilic and hydrophobic.

Carotenoids and tocopherols are well soluble in fats and therefore they protect the lipids that make up cell structures from the ROS. Vitamin C is well soluble in water and therefore has a protective role in all body fluids. Whereas nutritional antioxidants are most often vitamins C, A, E and carotenoids. The tri peptide γ-glutamylcysteineglicyne-glutathione is a very important antioxidant in the human body [27]. Glutathione, as a low-molecular antioxidant, plays a major role in many biological processes such as protein synthesis and degradation, the activity of enzymes, protection of cells or apoptosis. Under physiological conditions, reduced glutathione is the prevailing form, whereas an oxidized form being disulphide glutathione is approximately 1% [31].

Glutathione has a hydrophilic nature and it occurs both in the intercellular spaces as well as in intracellular compartments. Reducing properties are the result of having a thiol group, through which glutathione can react with oxidizing compounds and ROS. The glutathione reactions in the organism occur with the participation of enzymes belonging to the peroxidases and glutathione transferases.

Glutathione transfers into oxygenated form when it reacts with free radicals and it becomes a free radical. After the oxidation of thiol groups, two molecules of oxidized form of glutathione react with each other producing a pyridoxine disulphide glutathione. NADPH + H^+ dependent on nitrate reductase peroxidase participates in reconstitution of the reduced form [27]. There is evidence that, along with age, there is an increase in the concentration of the products resulting from the oxidative damage to proteins and the increase in the concentration of the products of lipid peroxidation, including MDA, as well as products of the DNA oxidation. It was repeatedly demonstrated that with age, the activity of antioxidant enzymes, including SOD and GPX GR and CAT decreases.

Harman put forth a so called free radical theory of aging based on research proving that aging is accompanied by an increase in oxidative stress [32]. According to this theory, the increase in free radicals and damage cells caused by the ROS and reduced activity of the antioxidant system is the cause of aging and age-related diseases in the elderly population [32].

Hypertension is one of the conditions associated with old age. It occurs in approximately 65% of people at this age [33].

Oxidative stress and hypertension

Studying the literature one can find reports suggesting a link between the increase in blood pressure and the seriousness of oxidative stress [34]. Undoubtedly, there is a link between primary hypertension and hepatic impairment of endothelial vessels responsible for maintaining the appropriate voltage arterial walls. One can also link this fact with the ROS modulating the voltage and the structure of the blood vessels. Superoxide anion radical and hydrogen peroxide induce contraction and increase of the smooth muscle cell growth in the blood vessels, and affect the transmission of signals between cells. Free radicals have stimulating effects and boost the migration of monocytes and the formation of oxidized lipoprotein low molecular weight molecules that are toxic to vascular cells and hinder the function of vascular endothelium [35]. In many medical conditions, for instance hypertension and heart diseases, ROS also contributes to the impairment of endothelium of blood vessels function which is related to dysfunction of the synthesis of nitric oxide (NO) [36].

The role of nitric oxide in the endothelium.

Nitric oxide (NO) is one of the most active compounds that is secreted by the vascular endothelium. Its main functions are the inhibition of adhesion and aggregation of blood cells and the maintenance of the blood flow through the vessels. It is an-endothelium-derived relaxing factor (EDRF) and it is now considered the primary vasodilative factor. Tetrahydrobiopterin-dependent oxide synthase is responsible for the synthesis of NO (E.C. 1.14.13.39; NOS).

After the synthesis, NO molecule diffuses into the smooth muscle and there binds to the hem group by activating cyclase GMP which results in the increase in the cGMP concentration, a smooth muscle relaxation and vasodilation [37]. Studies have shown that inhibition of nitric oxide synthase with the analogue of arginine causes an increase in blood pressure. There is a number of reports concerning the reduction of nitric oxide synthase activity in patients with primary hypertension. Reduced activity of nitric oxide synthase in the blood vessels can be caused by the reaction with ROS. Endothelial dysfunction caused by superoxide anion radical is an example of this type of degradation [37]. The reaction with nitrogen oxide is another example of the negative effects of the ROS on the function of endothelial cells mainly including superoxide anion radical but also hydroxyl and lipid radical. It results in the inactivity of NO. Therefore,

there is an advantage of vasoconstrictive effect and an increase of blood pressure [38].

Furthermore, in the indirect reaction, free radicals initiate the destruction of proteins, DNA. and peroxidase of lipids, which result in the increase in permeability of endothelium for the plasma proteins and other macro-elements, including cytokines and inflammatory cells that undermine its function. In favourable conditions, there may also be a reaction of superoxide anion radical and nitric oxide which in consequence leads to a very reactive peroxynitrite. This compound easily penetrates cell membranes and it can be a source of peroxynitrite acid, the reactive nitrogen dioxide and superoxide radical hydroxy acids.

Superoxide anion radical may induce changes in the functioning of the entire circulatory system, also by generating other reactive forms such as peroxynitrite, hydrogen peroxide, hydroxyl radical or perchloric acid. Most of the ROS is formed in the reactions associated with oxidase NAD(P)H, xanthine oxidase and NOS, as well as myeloperoxidase (MPO), cytochrome P-450 and the respiratory chain [39].

NAD(P)H oxidase, which is a membrane enzyme catalysing the single-electron reduction of oxygen uses NADH or NADPH as electron donor [40]. Enzyme activity is regulated by the cytokines and trombone, glucocorticoids, TNFα and PDGF (platelet-derived growth factor), physical factors and tissue hormones including angiotensin II (Ang II). Ang II increases the blood pressure, stimulates the activity of oxidase NAD(P)H and causes the increase of $O_2^{\bullet-}$ concentration produced by this enzyme [41]. Other enzymes can also be a source of ROS, among which there is xanthine oxidoreductase. It is an enzyme catalysing the reaction of hypoxanthine oxidation to xanthine and xanthine into uric acid. Xanthine oxidase uses molecular oxygen as a substrate which may lead to the creation of superoxide anion radical. Xanthan dehydrogenase is another enzyme catalysing the oxidation of substrates and reducing NAD^+ leading to the creation of NADH. There may be an excessive generation of ROS especially in hypoxia conditions. This enzyme is transformed to xanthine oxidase most likely as a result of proteolytic modification, and then it starts to transmit electrons to oxygen and O_2^-- which results in the appearance of H_2O_2 [42]. Just as NAD(P)H oxidases, xanthine oxidoreductase is activated through cytokines and also through interferon -γ (INF- γ) and interleukins 1-β (IL-1β) [43]. The synthase of nitrogen oxide can be, next to NO, a source of significant amounts of $O_2^{\bullet-}$. This situation takes place when there is a deficit of arginine or tetrahydrobiopterin. It occurs for instance among those suffering from hypertension when the NAD(P)H oxidase activity causes oxidation of tetrahydrobiopterin and production large amounts of $O_2^{\bullet-}$ through endothelial NOS [44]. MPO, which is particularly frequent in phagocytes, catalyses the HOCl synthesis and other ROS with H_2O_2, inactivates NO, initiates peroxidation of lipids and generates reactive forms of nitrogen, which in result causes the increase of oxidative stress.

Conclusions

The involvement of oxidative stress in the pathogenesis of hypertension during aging can be examined multidimensionally, both at the molecular and systemic level [45]. Moreover, a crucial correlation between these levels may be observed. Therefore, it may be hypothesised that there is a cause and effect relationship between free radicals processes and aging of the organism. Numerous research studies suggest a correlation between the presence of the oxidative stress and a development of arterial hypertension. There is also a large amount of works describing the advantages from the usage of antioxidants in the course of arterial hypertension, however, there is still lack of convincing proofs confirming hypotensive properties of antioxidants. It is worth mentioning that as far as the influence of aging on the development of the primary arterial hypertension is widely known, the reverse, namely the influence of the primary arterial hypertension on the speed of aging needs a thorough explanation and is still not fully known.

Conflict of interest
None

References

1. Park, B. and Y.J. Lee. Upcoming Aging Society and Men's Health: Focus on Clinical Implications of Exercise and Lifestyle Modification. World J Mens Health. 2019:1-8.
2. Mc Auley, M.T., et al. Modelling the molecular mechanisms of aging. Biosci Rep. 2017;37(1):1-20.
3. Sousa-Victor, P., L. Garcia-Prat, and P. Munoz-Canoves. New mechanisms driving muscle stem cell regenerative decline with aging. Int J Dev Biol. 2018;62(6-7-8):583-90.

4. Bloch, E., et al. Genetic and Environmental Factors Associated With the Ganglion Cell Complex in a Healthy Aging British Cohort. JAMA Ophthalmol. 2017;135(1):31-8.
5. Turell, L., R. Radi, and B. Alvarez. The thiol pool in human plasma: the central contribution of albumin to redox processes. Free Radic Biol Med. 2013;65:244-53.
6. Soysal, P., et al. Oxidative stress and frailty: A systematic review and synthesis of the best evidence. Maturitas. 2017;99:66-72.
7. Ung, L., et al. Oxidative stress and reactive oxygen species: a review of their role in ocular disease. Clin Sci (Lond). 2017;131(24):2865-83.
8. Cakatay, U., R. Kayali, and H. Uzun. Relation of plasma protein oxidation parameters and paraoxonase activity in the ageing population. Clin Exp Med. 2008;8(1):51-7.
9. Cimen, M.Y. Free radical metabolism in human erythrocytes. Clin Chim Acta. 2008;390(1-2):1-11.
10. Rac, M., et al. Oxidative damage of U937 human leukemic cells caused by hydroxyl radical results in singlet oxygen formation. PLoS One. 2015;10(3):1-19.
11. Reif, D.W. Ferritin as a source of iron for oxidative damage. Free Radic Biol Med. 1992;12(5):417-427.
12. Stanhewicz, A.E. and W.L. Kenney. Role of folic acid in nitric oxide bioavailability and vascular endothelial function. Nutr Rev. 2017;75(1):61-70.
13. Agnihotri, N. and P.C. Mishra. Formation of 8-nitroguanine due to reaction between guanyl radical and nitrogen dioxide: catalytic role of hydration. J Phys Chem B. 2010;114(21):7391-404.
14. Panasenko, O.M. The mechanism of the hypochlorite-induced lipid peroxidation. Biofactors. 1997;6(2):181-90.
15. Tolando, R., et al. Reactive oxygen species and proinflammatory cytokine signaling in endothelial cells: effect of selenium supplementation. Free Radic Biol Med. 2000;28(6):979-86.
16. Kuhn, H., S. Banthiya, and K. van Leyen. Mammalian lipoxygenases and their biological relevance. Biochim Biophys Acta. 2015;1851(4):308-30.
17. Halliwell, B. and J.M. Gutteridge. Role of free radicals and catalytic metal ions in human disease: an overview. Methods Enzymol. 1990;186:1-85.
18. Wang, W., et al. Chemistry and biology of omega-3 PUFA peroxidation-derived compounds. Prostaglandins Other Lipid Mediat. 2017;132:84-91.
19. Mustafa, A.G., et al. Scavenging of lipid peroxyl radicals protects plasma lipids and proteins from peroxynitrite. Biomed Rep. 2018;9(5):421-6.
20. Schnitzer, E., I. Pinchuk, and D. Lichtenberg. Peroxidation of liposomal lipids. Eur Biophys J. 2007;36(4-5):499-515.
21. Gregersen, N. and R.K. Olsen. Disease mechanisms and protein structures in fatty acid oxidation defects. J Inherit Metab Dis. 2010;33(5):547-53.
22. Plowman, J.E., et al. Protein oxidation: identification and utilisation of molecular markers to differentiate singlet oxygen and hydroxyl radical-mediated oxidative pathways. Photochem Photobiol Sci. 2013;12(11):1960-7.
23. Cross, C.E., et al. Oxidative damage to human plasma proteins by ozone. Free Radic Res Commun. 1992;15(6):347-52.
24. Hiraku, Y., et al. Oxidative DNA damage induced by aminoacetone, an amino acid metabolite. Arch Biochem Biophys. 1999;365(1):62-70.
25. Milligan, J.R., et al. Peptide repair of oxidative DNA damage. Biochemistry. 2004;43(17):5102-8.
26. Malayappan, B., et al. Urinary analysis of 8-oxoguanine, 8-oxoguanosine, fapy-guanine and 8-oxo-2'-deoxyguanosine by high-performance liquid chromatography-electrospray tandem mass spectrometry as a measure of oxidative stress. J Chromatogr A. 2007;1167(1):54-62.
27. Robaczewska, J., et al. Role of glutathione metabolism and glutathione-related antioxidant defense systems in hypertension. J Physiol Pharmacol. 2016;67(3):331-7.
28. Ghaemi, M.S., et al. Multiomics modeling of the immunome, transcriptome, microbiome, proteome and metabolome adaptations during human pregnancy. Bioinformatics. 2019;35(1):95-103.
29. Azadmanesh, J. and G.E.O. Borgstahl. A Review of the Catalytic Mechanism of Human Manganese Superoxide Dismutase. Antioxidants (Basel). 2018;7(2):1-16.

30. Battin, E.E. and J.L. Brumaghim. Antioxidant activity of sulfur and selenium: a review of reactive oxygen species scavenging, glutathione peroxidase, and metal-binding antioxidant mechanisms. Cell Biochem Biophys. 2009;55(1):1-23.
31. Adeoye, O., et al. Review on the role of glutathione on oxidative stress and infertility. JBRA Assist Reprod. 2018;22(1):61-6.
32. Harman, D. Aging: a theory based on free radical and radiation chemistry. J Gerontol. 1956;11(3):298-300.
33. Hajjar, I. and T.A. Kotchen. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. JAMA. 2003;290(2):199-206.
34. Rodrigo, R., J. Gonzalez, and F. Paoletto. The role of oxidative stress in the pathophysiology of hypertension. Hypertens Res. 2011;34(4):431-40.
35. McMullen, C.B., et al. The role of reactive oxygen intermediates in the regulation of cytokine-induced ICAM-1 surface expression on endothelial cells. Mol Cell Biol Res Commun. 2000;3(4):231-7.
36. Armas-Padilla, M.C., et al. Nitric oxide and malondialdehyde in human hypertension. Am J Ther. 2007;14(2):172-6.
37. Gongora, M.C., et al. Role of extracellular superoxide dismutase in hypertension. Hypertension. 2006;48(3):473-81.
38. Taherzadeh, Z., et al. The Effect of Creatine Kinase Inhibition on Contractile Properties of Human Resistance Arteries. Am J Hypertens. 2016;29(2):170-7.
39. Radi, R. Peroxynitrite, a stealthy biological oxidant. J Biol Chem. 2013;288(37):26464-72.
40. Dymkowska, D. Oxidative damage of the vascular endothelium in type 2 diabetes - the role of mitochondria and NAD(P)H oxidase. Postepy Biochem. 2016;62(2):116-26.
41. Touyz, R.M., et al. Angiotensin II stimulates DNA and protein synthesis in vascular smooth muscle cells from human arteries: role of extracellular signal-regulated kinases. J Hypertens. 1999;17(7):907-16.
42. Garai, D., et al. Mechanisms of myeloperoxidase catalyzed oxidation of H2S by H2O2 or O2 to produce potent protein Cys-polysulfide-inducing species. Free Radic Biol Med. 2017;113:551-63.
43. Briones, A.M. and R.M. Touyz. Oxidative stress and hypertension: current concepts. Curr Hypertens Rep. 2010;12(2):135-42.
44. Nitenberg, A. Hypertension, endothelial dysfunction and cardiovascular risk. Arch Mal Coeur Vaiss. 2006;99(10):915-21.
45. Akazawa, H. Aging and homeostasis. Chronic inflammation and aging. Clin Calcium. 2017;27(7):963-8.