ECOLOGY
AND NOOSPHEROLOGY

ISSN 1726-1112 (Print)
ISSN 2310-4309 (Online)
Ecol. Noospher., 29(1), 52–55
doi: 10.15421/031809

Oxidative stress, reactive oxygen species, antioxidants: a review

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Article info

Received 23.04.2018
Received in revised form 05.05.2018
Accepted 09.05.2018

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Voronkova, Y. S., Voronkova, O. S., Gorban, V. A., & Holoborodko, K. K. (2018). Oxidative stress, reactive oxygen species, antioxidants: a review. Ecology and Noospherology, 29(1), 52–55. doi:10.15421/031809

Oxidative stress is a disturbance of the balance between the production of reactive oxygen species (ROS) and antioxidants. Oxidative stress is caused by the presence of any of a number of reactive oxygen species, which the cell is unable to counterbalance. The result is damage to one or more biomolecules including DNA, RNA, proteins and lipids. Oxidative stress has been implicated in the natural aging process as well as a variety of disease states, such as neoplastic, metabolic, neurological etc., accompanied by different complications. Risk factors of generation of oxidative stress are oxidizing species, induced by pathologies include alcohol consumption, cigarette smoking, diet, gender, geographic location specifically at high altitude and occupation. ROS are composed of superoxide, hydroxyl, peroxyl, hydroperoxyl and alkoxyl radicals, hydrogen peroxide and singlet oxygen and ozone. These compounds produced endogenous in reaction of autooxidation in respiratory chaine of bioobjects. Among exogenous sources of ROS can be listed exposure of pollutants, toxins, heavy metals, drugs with different chemical origin and effects, radiation, electromagnetic fields, alcohol, cigarette smoke, stresses, allergies, dietary factors, temperature and microscopic form of life, such as bacteria, yeasts, viruses etc. The oxidative stress in biological systems is often characterized by increase in the formation of radicals; decrease in small-molecular-weight and lipid soluble antioxidants; disturbance in cellular redox balance; oxidative damage to cellular components (biomacromolecules). The presence of oxidative stress may be tested in one of three ways: direct measurement of the ROS; measurement of the resulting damage to biomolecules; and detection of antioxidant levels. Directly measuring ROS might seem the preferred method, but many reactive oxygen species are extremely unstable and difficult to measure directly. Many markers of damage are extremely stable and therefore provide a more reliable method to measure oxidative stress. Another approach is to measure the levels of antioxidant enzymes and other redox molecules which serve to counterbalance ROS generated in the cell. At the same time, it must emphasize that oxidative stress not only has a cytotoxic effect, but also plays an important role in the modulation of messengers that regulate essential cell membrane functions, which are vital for survival. For prevention of oxidative stress cells produce or uptake antioxidants – substance significantly delays or prevents oxidation of that substrate. Antioxidants may be enzymatic and non-enzymatic in nature in which enzymatic system directly or indirectly help in defence against the ROS. Antioxidants are involved in the prevention of oxidants and ROS formation; exhibits scavenger of ROS; and repairs the oxidized molecules through sources like dietary or consecutive antioxidants. Among non-enzymatic antioxidants distinguished glutathione, α-tocopherol, ascorbic acid, beta-carotene, and uric acid; these are mostly considered to be chain-breaking antioxidants in that they interrupt the auto-catalytic spread of radical reactions. Among enzymatic antioxidants most known superoxide dismutase, catalase, glutathione-SH peroxidase. The significant correlation found between ROS, parameters of oxidative stress and pathology indicate that there is a need in finding of measures of prevention of endo- and exogenous factors provoke their generation. There is a need to continue to explore the relationship between free radicals, pathological processes and the complications of them, and to elucidate the mechanisms by which increased oxidative stress accelerates the development of complications, in an effort to expand treatment options. Improvement of complications control seems to be a beneficial factor to decrease oxidative stress. For a better investigation of oxidative stress, it would be wise to supplement the clinical research by determination of special products typical for oxidative stress that let to understand mechanism of some pathological processes more clearly.

Keywords: oxidative stress; reactive oxygen species; antioxidants

Introduction

Oxidative stress, defined as a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses.

Oxidative stress is caused by the presence of any of a number of reactive oxygen species (ROS) which the cell is unable to counterbalance. The result is damage to one or more biomolecules including DNA, RNA, proteins and lipids.

Oxidative stress has been implicated in the natural aging process as well as a variety of disease states: neoplastic – hematological and solid tumor, metabolic – obesity and diabetes, and neurological – Alzheimer's and Parkinson's diseases (Osman et al., 2012; Palipoch and Koomhin, 2015). Oxidative stress is causative agents of lung diseases, liver diseases, pathology of the cardiovascular system, pathology of the kidney etc. (Keshari et al., 2015; Palipoch and Koomhin, 2015).

ROS such as superoxide and hydrogen peroxide are continually produced during metabolic processes. ROS generation is normally counterbalanced by the action of antioxidant enzymes and other redox molecules. Excess reactive oxygen species must be promptly eliminated from the cell by a variety of antioxidant defense mechanisms. Cellular antioxidant enzymes and other redox molecules serve to counterbalance ROS generated in the cell (Jenkins, 1993; Shinde et al., 2012).

The aim of the research was to descript the main characteristics of oxidative stress in biological systems.

Oxidative Stress

Risk factors which are related to oxidizing species (OS)-induced pathologies include alcohol consumption, cigarette smoking, diet, gender, geographic location specifically at high altitude and occupation.

Alcohol metabolism is linked to ROS generations leading increased oxidative stress biomarkers such as malondialdehyde (MDA) and 4-hydroxynonenal (HNE) and decreased antioxidative defense systems.

Cigarette smoking causes injury to the cardiovascular, pulmonary and other OS related diseases including infertility in men (Palipoch and Koomhin, 2015).

Consumption of high fat diet causes OS through overproduction of ROS resulting in hepatic oxidative damage, thus antioxidant supplementations are good beneficial choices. Gender differences in OS are shown in several diseases such as coronary artery disease and hypertension. Exposure to high altitude causes hypoxia which is associated with OS and resembles ischemia/reperfusion injury by either increased ROS production or weak antioxidant defense system (Adly, 2010; Palipoch and Koomhin, 2015).

The oxidative stress in biological systems is often characterized by the following parameters: (1) increase in the formation of radicals; (2) decrease in small-molecular-weight and lipid soluble antioxidants; (3) disturbance in cellular redox balance; (4) oxidative damage to cellular components (biomacromolecules) (Adenkola, 2013).

The presence of oxidative stress may be tested in one of three ways: (1) direct measurement of the ROS; (2) measurement of the resulting damage to biomolecules; and (3) detection of antioxidant levels. Directly measuring ROS might seem the preferred method, but many reactive oxygen species are extremely unstable and difficult to measure directly. Because of this, many scientists prefer to measure the damage on proteins, DNA, RNA, lipids, or other biomolecules (Horak and Cohen, 2010). While this is an indirect approach, many markers of damage are extremely stable and therefore provide a more reliable method to measure oxidative stress. Another approach is to measure the levels of antioxidant enzymes and other redox molecules which serve to counterbalance ROS generated in the cell. Assays are available to measure the activity of specific antioxidant enzymes, such as catalase and superoxide dismutase. Additionally, there are assays that can test the antioxidant capacity of certain biomolecules and food extracts.

The process of selecting assays to measure oxidative stress should begin with first determining the sample type to be studied. There are many markers of oxidative stress, but some are more easily detected in certain sample types (cells, tissues, urine, blood, etc.) (Osman et al., 2012).

At the same time, it must emphasize that oxidative stress not only has a cytotoxic effect, but also plays an important role in the modulation of messengers that regulate essential cell membrane functions, which are vital for survival. It affects the intracellular redox status, leading to the activation of protein kinases, including a series of receptor and non-receptor tyrosine kinases, protein kinase C, and the MAP kinase cascade, and hence induces various cellular responses. These protein kinases play an important role in cellular responses such as activation, proliferation, and differen-tiation, as well as various other functions. Accordingly, the protein kinases have attracted the most attention in the investigation of the association between oxidative stress and disease (Yoshikawa and Naito, 2002).

ROS take part in many different processes as signal molecules in animals (Schieber and Chandel, 2014) and also in plants (Kruszewski and Iwaneñko, 2003). The diversity of these processes is determined by the site of ROS production an d their interaction with a variable set of hormonal signaling compounds such as salicylic acid, abscisic acid and others including the PQ pool and GSH (Kreslavski et al., 2012; Schmitt et al., 2014). Among the recent reviews elucidating the signaling role of ROS, the detailed work of Mitler et al. (Mittler et al., 2011) and Krieger-Liszkay (Krieger-Liszkay, 2005) should be mentioned. The mode of signal in gunder the participation of ROS depends on the nature of stress. ROS can activate physiological responses leading to the development of adaptive mechanisms and improving the stress tolerance (acclimation), or it can trigger a signal cascade causing programmed cell death (Los et al., 2010; Mittler et al., 2011). In both cases, ROS function as signal molecules, which induce molecular, biochemical and physiological responses.

ROS control programmed cell death (Los et al., 2010; Mittler et al., 2011; Schmitt et al., 2014), cell wall formation, salicylic acid-induced stomatal closure (Khokon et al., 2011), and responses to pathogens just to mention as election (Swanson and Gilroy, 2010).

If different environmental stresses can be perceived by only one molecular sensor, a generalized signaling scheme based on ROS might be involved (Los et al., 2010). For example, the histidine kinase of *Synechocystis* was recently found to be a multisensory protein, which perceives cold, salt, and oxidative stresses (Schmitt et al., 2014).

ROS (Reactive Oxygen Species): their types of ros and sources

Most stable molecular species have the electrons in their outer orbital, arranged in pairs. Each electron of this pair has an opposite spin, which is important to stabilize the molecules. A free radical is a molecule with one or more unpaired electrons in its outer orbital, which make the specie very unstable and tending to react with other molecules to pair this electron and thereby generate more stable specie (Adly, 2010).

The most known ROS are hydroxyl radicals, superoxide anions and hydrogen peroxide, produced by different biological systems (Adly, 2010; Schmitt et al., 2014). ROS are composed of superoxide radical ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), peroxyl radical ($RO_2^{\bullet}$), alkoxyl radical ($RO^{\bullet}$), hydroperoxyl radical ($HO_2^{\bullet}$), singlet oxygen and ozone (Held, 2015; Jajic et al., 2015).

Oxidizing agents can be produced by both endogenous source (inflammatory cells, fibroblast, epithelial cells, endothelial cells, respiratory chain, xanthine and NADPH oxidase) and exogenous source (cigarette smoke, exogenous

toxins, pollution, radiation, carcinogens and drugs) (Choi et al., 2014; Nourazarian et al., 2014). Under normal physiological condition, oxidants are removed through antioxidant defense mechanism. If incompletely cleared by antioxidants, oxidants will caused accumulation of oxidizing species (OS). Inefficiency and insufficiency of antioxidant defense system are concerned in some pathological conditions induced by OS (Luchese et al., 2009).

Oxidative stress can cause damage to all molecular targets: DNA, proteins, lipids. All of these targets are significant, but DNA is an most important early target of damage (Adly, 2010).

Generation of ROS have different ways, depending on biological system. For example, bacteria that isolated from natural sources have active aerobic metabolism, lead to accumulation of ROS.

As a result of autooxidation of respiration chain components of *E. coli* cells 0.1-0.5% of used oxygen transform to superoxide anions. Main generator of ROS in bacteria is fumarate reductase – terminal oxidase, induced in aerobic conditions and react with oxygen (Семчишин та Лущак, 2004). At the same time we need to keep in mind, that bacteria have differences in components of respiratory chain and quantity and mechanisms of ROS accumulation can be different.

In human body and in eukaryotic cells ROS generate by processes in mitochondria, mainly in reaction of reduction of O_2 by cytochrome oxidase (Keshari et al., 2015).

ROS have an endo- and exogenous sources. The main endogenous sources of ROS is aerobic respiration. ROS are also produced by peroxisomal β-oxidation of fatty acids, microsomal cytochrome P450 metabolism of xenobiotic compounds, stimulation of phagocytosis by pathogens or lipopolysaccharides, arginine metabolism and tissue specific enzymes (Gille and Nohl, 2000; Adly, 2010; Keshari et al., 2015).

Among exogenous sources of ROS can be listed exposure of pollutants, toxins, heavy metals, drugs with different chemical origin and effects, radiation, electromagnetic fields, alcohol, cigarette smoke, stresses, allergies, dietary factors, temperature and microscopic form of life, such as bacteria, yeasts, viruses etc. (Семчишин та Лущак, 2004; Kohen and Nyska, 2002; Abdollahi et al., 2004; Adly, 2010; Lushchak, 2011; Sevcikova et al., 2011; Bano et al., 2017; D'Souza, 2017; Koch and Hill, 2017).

Antioxidants (enzymatic and non-enzymatic)

Term antioxidant widely used. Now antioxidant defined as substance, which present at low concentration compared with oxidizable substrate (every type of molecule found in vivo), significantly delays or prevents oxidation of that substrate (Ali et al., 2010).

Antioxidants are classified into 3 categories, as described by Gutteridge and Halliwell (Storey, 1996; Valko et al., 2007): (1) primary antioxidants are involved in the prevention of oxidants and ROS formation; (2) secondary antioxidants exhibits scavenger of ROS; and (3) tertiary antioxidants repairs the oxidized molecules through sources like dietary or consecutive antioxidants (Jenkins, 1993; Shinde et al., 2012).

An important aspect of prevention is the segregation or chelation of metals that can catalyze $OH^{\bullet}$ formation, such as by iron binding to ferritin (Storey, 1996). Nonenzymatic antioxidants include glutathione, alpha-tocopherol (vitamin E), ascorbic acid, beta-carotene, and uric acid; these are mostly considered to be chain-breaking antioxidants in that they interrupt the auto-catalytic spread of radical reactions (Storey, 1996; Adly, 2010).

Antioxidants may be enzymatic and non-enzymatic in nature in which enzymatic system directly or indirectly help in defence against the ROS.

For example, enzyme superoxide dismutase (SOD) remove superoxide by accelerating its conversion into Hydrogen peroxide. SOD enzyme contains manganese (MnSOD), copper and zinc (CuZnSOD) at its active site in mitochondria and cytosol respectively), Catalase, glutathione peroxidase removing enzyme it requires selenium for their action. Glutathione peroxidase enzymes remove H_2O_2 by using it to oxidize reduced glutathione to oxidized glutathione, glutathione reductase. While non-enzymatic antioxidant act as scavenger of ROS. For example, vitamins (E, C and A; glutathione, uric acid and melatonin (Kruszewski and Iwaneñko, 2003). Same effect are known for some aminoacids (cysteine, methionine, taurine) (Keshari and Farooqi, 2014).

The most known and usable non-enzymatic antioxidants are vitamin E, co-enzyme Q and glutathione (Blokhina et al., 2003).

Vitamin E prevents lipid peroxidation. One of it form – α-tocopherol is the most active in human. Hydroxyl radical reacts with it forming a stabilized phenolic compound, which is reduced back to the phenol by ascorbate and NAD(P)H dependent reductase enzymes (Adly, 2010).

Coenzyme Q (CoQ) is an antioxidant localized in the mitochondrial respiratory (Rohr-Udilova et al., 2008). This compound is considered as an endogenously synthesized lipid soluble antioxidant, present in all membranes. The protective efect is extended to lipids, proteins, and DNA mainly because of its close localization to the oxidative cellular events (Gille and Nohl, 2000).

Gluthatione acts as a direct scavenger as well as a co-substrate for glutathione-SH peroxidase (Hensley et al., 2004).

Conclusion

In this review we have given a short overview on the ROS, their generation in different biosystems and role in oxidative stress. ROS play an important role in different processes ranging from pathology of different systems to defense against pathogen attack and signaling system.

ROS represented by different compounds with general effect on cell macromolecules – components of cytoplasmic and inner membranes of cells.

The significant correlation found between ROS, parameters of oxidative stress and pathology indicate that there is a need in finding of measures of prevention of endo- and exogenous factors provoke their generation.

There is a need to continue to explore the relationship between free radicals, pathological processes and the complications of them, and to elucidate the mechanisms by which increased oxidative stress accelerates the development of complications, in an effort to expand treatment options. Improvement of complications control seems to be a beneficial factor to decrease oxidative stress. For a better investigation of oxidative stress in patients, it would be wise to supplement the clinical research by determination of total antioxidant status, lipid peroxidation products and advanced oxidation protein products and other markers that let to understand mechanism of some pathological processes more clearly.

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