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Introductory Chapter

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1. Introduction

The term "oxidative stress" was first defined by Helmut Sies (1985) as "Oxidative stress" came to denote a disturbance in the prooxidant-antioxidant balance in favor of the former". In order to reflect the findings of last 25 years in the field, such as plural ROS roles and dynamics of their levels we recently proposed one more definition such as "Oxidative stress is a situation when steady-state ROS concentration is transiently or chronically enhanced, disturbing cellular metabolism and its regulation and damaging cellular constituents" (Lushchak, 2011b). Understanding of mechanisms of reactive oxygen species (ROS) formation and operation of the systems responsible for ROS elimination were necessary prerequisites for such formulation. Fenton reaction, enzymatic systems like cytochromes P450, xanthine oxidase or respiratory chains were identified as ROS producers. Studies on catalase and peroxidase since the beginning of 20th century (Loew, 1900; Popov & Zvyagilskaya, 2007), and discovery of superoxide dismutase by McCord and Fridovich (1969), lead to suggestion, that cells have specialized systems for conversion of ROS to less reactive compounds. After introduction, the term "oxidative stress" has been accreting with medical issues. Today, one could find in literature connection of oxidative stress to almost all of well-known diseases. The most important of them are cardiovascular and neurodegenerative ones, diabetes, cancer, viral and bacterial infections, taking millions of lives every year.

In the simplest case, pathology originates from the perturbations in either reactive species formation, their elimination or in both simultaneously. Many of real situations are much more complicated, that is difficult to determine the crucial event for disease origin. In some cases, gene mutations can be responsible for the imbalance in ROS metabolism. In other ones, a range of environmental influences would produce metabolic changes. Antioxidant therapy seems to be useful in both cases. It is often important to know, if oxidative stress was a primary event leading to the disease or it was developed during the disease.

Diseases caused by gene polymorphism are curable hard, and here only really emerging gene therapy could be the best solution. In addition, environment can be changed easier. We need to understand how environmental changes may induce oxidative stress and perturb redox processes. This field is rather broad. Food toxins or even some of usual meals supposed to be safe, cigarette smoke or polluted air, car exhaust fumes or pesticides can be prerequisites for enhanced oxidant formation or impairment in antioxidant defence system.

Evidences for connection of oxidative stress with the stresses induced by other factors are promptly gained. The potency of transition metals, some herbicides and carbohydrates to promote oxidative stress was recently showed (Lushchak et al., 2009a; Lushchak et al., 2009b; Lushchak, 2011; Semchyshyn et al., 2011). The same thing is concerned to many physical factors like heat, sound or ionizing irradiations. After all, inflammation induced by traumatic event or pathogenic agent like viral, bacterial or protist infections can result in oxidative stress. Disturbances in ROS metabolism, caused by multiple external factors or by DNA mutations, lead, eventually, to progressive tissue damage and subsequent degeneration.

Identification of specific targets for ROS is one more thing important for the development of appropriate therapy. Moreover, place of ROS formation and their targets determine often particular connection with certain pathology. Proteins, nucleic acids and lipids are the most critical targets for ROS and their derivatives. Important enzymes, standing on crossroads of metabolic pathways, are frequently inactivated at excessive ROS formation not counterbalanced by antioxidants. Glyceraldehyde-3-phosphate dehydrogenase, aconitase, glucose-6-phosphate dehydrogenase and superoxide dismutase are the most studied examples (Bagnyukova et al., 2005; Lushchak, 2007; Grant, 2008; Di Domenico et al., 2010; Avery, 2011). The list is indeed much longer including representatives for almost all metabolic pathways in different tissues, as well as ion transporters (Unlap et al., 2002), receptors (Anzai et al., 2000), and other proteins. Polyunsaturated fatty acid residues of diverse lipids are mainly subjected to oxidation by ROS in this class of compounds. Protein oxidation results in formation of carbonylated or glutathionylated derivates, whilst non-enzymatic lipid oxidation yields 4-hydroxy-2-nonenal, isoprostanes, malondialdehyde and diene conjugates (Hermes-Lima, 2004b). Reactive species, particularly hydroxyl radical, are also involved in carbohydrate oxidation, what is especially harmful for nucleic acid pentose backbones (Gutteridge & Halliwell, 1988; Hermes-Lima, 2004b). Nucleotides are not any exception. Mutagenesis resulted from guanosine oxidation is widely described (reviewed in Hermes-Lima, 2004b). Cells may possess even special receptors for some products of oxidation, e.g. receptors for F_2-isoprostanes and advanced glycation end products (Fukunaga et al., 1997) or scavenger receptors for oxidized low-density lipoproteins (Ashraf & Gupta, 2011). Increase in ROS production was found to be also regulated via specific receptors (Thannickal & Fanburg, 2000). Production of ROS driven by transforming growth factor-β1, by receptors for endothelial or platelet-derived growth factors, as well as for angiotensin II or advanced glycation end-products (Thannickal & Fanburg, 2000) are among the most discussed examples. These facts suggest robust cellular control for ROS metabolism.

Oxidized derivatives of proteins and lipids may also damage other molecules exacerbating consequences of oxidative stress. For instance, 4-hydroxy-2-nonenal was shown to modify proteins through the interaction with amino group of lysine, cysteine or histidine residues. That results in the formation of Michael adducts. The formed adducts can impair considerable number of metabolically important proteins like transporters of glucose and glutamate, GTP-binding proteins, ion-motive ATPases and so forth (reviewed in (Mattson, 2009)). Ability to initiate protein carbonylation was also demonstrated for MDA (Burcham & Kuhan, 1996).

Nowadays, the knowledge about important signalling role for some ROS has gained in addition to their known deleterious roles (Thannickal & Fanburg, 2000; Dröge, 2002). It is known that ROS, namely hydrogen peroxide, can regulate c-Jun N-terminal kinase pathway, apoptosis initiation, tumour suppression by means of p53, ion channels and G-protein-coupled receptors (Thannickal & Fanburg, 2000; Dröge, 2002; Ushio-Fukai, 2009).

The term "reactive oxygen species" has itself seems become insufficient. It would be difficult to speak today about oxidant metabolism considering only ROS. In many contemporary studies, ROS are examined along with reactive nitrogen species (RNS), reactive carbon species (RCS), reactive chlorine species (RChS), and reactive sulphur species (RSS) (Hermes-Lima, 2004b; Ferreri et al., 2005). Formation for most of them is driven by specialized systems and is finely controlled (Dröge, 2002). It suggests a bunch of important roles for these highly reactive molecules. Some of these roles may even not be discovered. More and more interactions between ROS, RNS, RCS and RSS are found from study to study. The formation of peroxinitrite, a powerful oxidant and RNS, in reaction between nitric oxide and superoxide anion radical is a commonly known example in this case. Similarly, thiyl radicals, which are considered to be RSS, can be formed under the interaction of peroxyl or hydroxyl radical with thiol-containing compounds (Ferreri et al., 2005). Thus, once the formation of ROS has overwhelmed cellular detoxifying capacity, there is a big potential for generation of other highly reactive molecules with different properties and targets.

Ischemia, atherosclerosis, stroke and different types of inflammation were, probably, the first recognized pathological states closely connected with oxidative stress. The strong association between ROS and pathological states were disclosed here. At all these states, probability of ROS formation is much higher than in normal physiological state. For instance, mitochondria of ischemic cells increase the steady-state level of electrons which may escape electron carriers under reperfusion leading to one-electron reduction of oxygen (Hermes-Lima, 2004a). During inflammatory processes, ROS are produced purposely by NADPH oxidases (Lassègue & Griendling, 2010). In both these cases ROS seem to accompany disease flow, but are not the cause. A relation between oxidative stress and commonly known neurodegenerative disorders and diabetes was also found. These diseases are believed to be caused by ROS. It is known that alloxan, a compound broadly used for experimental diabetes induction, is a redox-cycling compound damaging insulin-producing pancreatic β-cells (Lenzen, 2008). Alzheimer's and Parkinson's diseases are connected with impairment of mitochondrial function resulting in enhanced ROS generation (Henchcliffe & Beal, 2008). The key proteins composing protein aggregates in Parkinson's and Alzheimer's diseases, α-synuclein and β-amyloid, respectively, were found to be capable to produce ROS themselves (Atwood et al., 2003; Wang et al., 2010). Diabetic complications are found to be induced by the formation of advanced glycation end products which interact with specialized receptors and promote ROS production (Forbes et al., 2008).

The term "human disease" has been defined as a condition worsening usual human being and working capacity, and in some cases leading to death. Illness state is also a disorder of homeostasis connected with impairment of important parts of either whole organism, or specific proteins, whole cells, and even whole tissues and organs. In this context, ROS role as damaging agents would seem to be evident in disease origin. Despite that ROS in many

works are described in their halo of harmfulness, especially in concern with diseases, there is also a complementary view on beneficial role of ROS in adaptation to stress (Ristow & Schmeisser, 2011; Lushchak, 2011a). Protein oxidation may also not always be harmful. Particularly, reversible oxidation of some key enzymes may respond to metabolic reorganization promoting to some extent cell adaptation to enhanced ROS production (Grant, 2008). Even protein carbonylation may have signalling role in vascular system (Wong et al., 2010) and in some examples activates proteins (Lee & Helmann, 2006). These findings should also be taken into account at analysis of association between oxidative stress and particular diseases. Participation of ROS in signaling, their roles in regulation of apoptosis and cell adaptation significantly complicate our view on them as a cause of diseases. Consequently, the view on oxidative stress should also be altered. Now, it is emerging impression that oxidative stress is not only the state when oxidation prevails. It is more resemble to the state of disturbance redox control mechanisms when "harmful" and undesirable for cell survival oxidation is prevailing, and physiological functions of ROS are altered or reprogrammed to promot cell death (Jones, 2006). Using this approach, one can suggest that cell death may result not only from several dozens of oxidized proteins and lipids. If we would not have any oxidation events, disturbance of physiological ROS metabolism might turn several dozens of processes in wrong direction. It may have more systemic effects, spread on whole organism, rather than causing cell death in particular tissue.

In the current book, the most topical issues of connection between oxidative stress and broadly known pathologies are examined. They include presumably cardiovascular diseases, hypertension and diabetes. Some attention is paid to well-known neurological diseases and cancer. Issues like reproduction, immunity, hormonal disorders are also affected. Some chapters are devoted to discussion on antioxidant therapy, though antioxidant clue goes through all other chapters as well. It is worth noting, knowledge highlighted in this book is collected all over the world. It implies the topic is long ago out of particular laboratories and elaborated by medical scientists in many countries. In some points concerns of the authors coincide, in other ones they are unique. Thus, the book mirrors many different aspects of pathological roles of ROS. We did not aim to make it comprehensive as much as possible. It is rather impossible taking into account that oxidative stress today has many faces. If someone would like to get specific knowledge on this topic from the beginning, the best advice would be to choose firstly the branch among incomprehensive canopy of oxidative stress studies. The book aimed to show how the field is studied in different countries and what is common for all investigations.

The connection between oxidative stress and diseases is mentioned in introduction of almost every article in the field. However, there is a difference between *in vitro* studies, studies on cell cultures, laboratory animals and clinical studies with humans. The last ones are most complicated for perception, but they provide a picture of reality. In this context, it is a pleasure to realize that some of the authors of this book are physicians whose studies are conducted on patients. The results from these studies are always more difficult for interpretation than those from model experiments carried out at cultivated cells. Nevertheless, clinical studies are highly complicated for understanding of ROS contribution in illness state. Once the implication of ROS in particular disease found, it suggests

possibility of antioxidant therapy. However, how it is mentioned in one of the chapters, under some conditions antioxidants may act also as pro-oxidants. Following redox pioneers, John Gutteridge and Barry Halliwell, here one could say "pro-oxidants can be better for you in some circumstances" (Gutteridge & Halliwell, 2010). Moreover, modulation of signalling pathways linked with ROS may be more effective than simple antioxidant therapy. Most of known antioxidants can act also as signalling molecules, but there are also many compounds important for signaling that are not antioxidants. Other crucial thing is prophylactics. Cardiovascular diseases, diabetes, obesity, metabolic syndrome, neurological and hormonal disorders, impairment in kidney and liver functioning, mentioned in the book and described in terms of free radical biology, are not always strictly genetically conditioned. They are lifestyle and life condition pathologies often with onset in late age. So, they can be prevented. It is, probably, the most important conclusion that can be drawn from the generalized data. Even genetically caused pathologies could be attenuated by wisely arranged prophylactics if the defect is not too serious. That is also the reason for the accumulation, generalization and systematization knowledge obtained at different levels, with different models and clinical studies. We hope that this book will disclose, at least partially, the state of the problem worldwide and the current directions of laboratories focused on studies for implication of ROS in different pathologies. We also believe that it will help researchers to find weak places in current understanding and advise them quite novel and non-standard approaches to find and decipher mechanisms of diseases.

Finally, we would like to thank all authors for their contributions and hard work to match and unify the "philosophy" of this book. We also thank to our colleagues from Precarpathian National University and University of Tampere who supported us and helped us in preparation and edition of the chapters, especially to those who raised complex questions and promoted us to answer them. We are also grateful to the "In-Tech" Publisher personnel, especially Ms. Sasa Leporic, who assisted us in the arrangement of the book and scheduling our activities.

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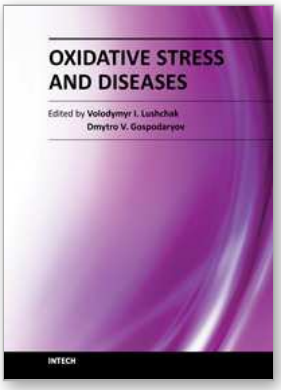

Oxidative Stress and Diseases

Edited by Dr. Volodymyr Lushchak

ISBN 978-953-51-0552-7
Hard cover, 610 pages
Publisher InTech
Published online 25, April, 2012
Published in print edition April, 2012

The development of hypothesis of oxidative stress in the 1980s stimulated the interest of biological and biomedical sciences that extends to this day. The contributions in this book provide the reader with the knowledge accumulated to date on the involvement of reactive oxygen species in different pathologies in humans and animals. The chapters are organized into sections based on specific groups of pathologies such as cardiovascular diseases, diabetes, cancer, neuronal, hormonal, and systemic ones. A special section highlights potential of antioxidants to protect organisms against deleterious effects of reactive species. This book should appeal to many researchers, who should find its information useful for advancing their fields.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Volodymyr I. Lushchak and Dmytro V. Gospodaryov (2012). Introductory Chapter, Oxidative Stress and Diseases, Dr. Volodymyr Lushchak (Ed.), ISBN: 978-953-51-0552-7, InTech, Available from: http://www.intechopen.com/books/oxidative-stress-and-diseases/introduction-chapter

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