



## Reactive Oxygen and Nitrogen Species: Diagnostic, Preventive and Therapeutic Values

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Reactive Oxygen and Nitrogen Species: Diagnostic, Preventive, and Therapeutic Values — this was the title of an international workshop held in St. Petersburg July 8-12, 2002. In this workshop, along with presentations and discussions of posters, more than 60 oral reports were given by outstanding scientists from 14 countries including Russia, USA, and Japan as well as from other countries of Europe and Asia. The main attention of the participants was focused on the application of fundamental knowledge in the field of free radicals and peroxides in medical practice, for diagnostics, prophylaxis, and treatment of human diseases. The greatest attention thus was attracted to two compounds, natural radicals, which are produced by living cells through an enzymatic pathway and carry important biological functions. They are superoxide ( $O_2^-$ ) and nitroxide ( $\cdot NO$ ). Other active oxygen and nitrogen species, such as hydrogen peroxide, hydroxyl radical, organic radicals, including lipid radicals and peroxides, hypochlorite and peroxyxynitrite, are formed in cells as secondary radicals and due to high chemical reactivity and low selectivity, are able to do serious harm to cells, tissues, and the organism as a whole. A huge number of scientific publications deal with a problem of involvement of free radicals in the development of human diseases. About one hundred reviews and thousands of original articles are published annually that have the combination of words “free radicals” and “disease” in their title. It is possible to conclude that in the origin and development of such diseases as cancer, ischemic heart disease, circulatory hypertension, nervous diseases of elderly people (senility, Parkinson disease, and some others), immune distresses, diabetes, chronic inflammatory diseases including rheumatoid arthritis, pulmonary diseases, and many others, radicals play not the last, but in many cases — the main role.

So, in the case when every month brings a huge amount of new ideas demonstrating the involvement of

reactive oxygen and nitrogen species in medical processes, the most representative workshop is not more than “an instant picture” of knowledge accumulated and constantly updating in this field. Fragments of this snapshot are placed in the present issue of the journal. The reader can find here articles of the invited speakers of the workshop. They are mainly original papers, based on the investigations in the authors’ laboratories, or latest reviews. Certainly, this issue cannot give a detailed description of all problems related to the medical application of reactive oxygen and nitrogen species research, but it shows the basic trends in these investigations and presents many interesting new data.

The fundamental idea that passes through most of the publications is the relationship between the beneficial and harmful activity of free radicals. This problem became a subject of detailed consideration in the paper of D. K. Das and N. Maulik, partly in the substantial review of J. Arnhold on the properties and function of myeloperoxidase, and in a concise article of E. F. Sato and coworkers. The rest of the articles can be subdivided into three groups. In the first of these (articles by A. A. Shvedova et al. and by V. Castranova) new data on the role of free radicals in the pathogenesis of some diseases, skin cancer and pulmonary diseases (pneumoconiosis), correspondingly, are given. *Vice versa*, the second group of articles contains evidence on the involvement of free radical processes in the struggle with cancer cells (articles of N. F. Shor et al. and of S. Marshall et al.). The final, third group of articles, most representative, deals with the problem of fighting against free radical excess by means of antioxidants. Papers, presented in this issue are distributed into four partitions according to this scheme.

Let’s have a very brief consideration of each paper presented.

The first group of papers in this issue “Free Radicals — Friends or Foes?” includes three reviews. The most obvi-

ous and beneficial activity of the reactive oxygen specie, superoxide radical, is based on the struggle of phagocytes with microorganisms that enter into the body. However, the result of this struggle depends not only on the appropriate and intensive production of superoxide radical by phagocytes (blood neutrophils), but also on whether it will be promptly transformed into hydrogen peroxide by superoxide dismutase, and then — into hypochlorite by myeloperoxidase. The description of myeloperoxidase properties and its activity the reader will find in the excellent review by J. Arnhold, where the peculiarities of a chemiluminescent assay, which is widely, but frequently incorrectly, used to study the reactive oxygen species production by phagocytizing cells are discussed in detail.

Another extremely urgent problem related both to the beneficial and harmful activities of reactive oxygen and nitrogen species is the problem of the mechanism of apoptosis. As known, apoptosis, i.e., programmed cell death, depending on circumstances, can be necessary or lethally dangerous. It has been proven that the activation of free radical reactions is one of the main determinants or operating mechanisms of apoptosis. The manifestation of reactive oxygen specie activity depends, however, on the induction of genes, a part from which promotes, and part prevents apoptosis. Switching from a signal leading to destruction a cell to a rescue signal has appeared to depend on the free radical level. This uneasy problem is discussed in the very substantial review by D. K. Das and N. Maulik, which contains, in addition, an extensive up-to-date bibliography.

An illustration of the beneficial activity of the reactive oxygen species is given in the article of E. F. Sato et al., where oxidative stress of newborns is the cause of apoptosis activation in hemopoietic cells present in liver in the prenatal term. This process induced by reactive oxygen specie signals removes the antioxidant protection of cellular thiols and results in the diminishing of hemopoiesis in the liver of adults.

The second group of papers in the present issue, "Reactive Oxygen and Nitrogen Species and Human Diseases", includes two articles. In the paper by A. A. Shvedova et al. the role of reactive oxygen species in a chemically induced carcinogenesis is discussed. The formation of skin carcinoma was observed in mice only when carcinogen and cumene hydroperoxide, producing free radicals and lipid peroxidation product accumulation, were introduced simultaneously. This effect was suppressed by cyclooxygenase inhibitor, which proves the involvement of this enzyme in carcinogenesis.

The participation of the reactive nitrogen species in the development of pneumoconiosis induced by such dusts as quartz, organic dusts polluted with an endotoxin, or asbestos are considered in a brilliant and clear review by V. Castranova. It was shown that the action of dusts results in the increasing of inducible NO-synthase

(iNOS) and production of nitric oxide ( $\cdot\text{NO}$ ) by alveolar macrophages and pulmonary epithelium cells. Excessive nitric oxide production is linked in time and location to the lung damage by inflammation and progression of disease in response to industrial dusts. The inhibition of inducible NO-synthase by means of inhibitors in intact mice or in mice with knocked out inducible NO-synthase gene decreased the degree of damage. All these observations show that the excessive formation of NO can play an important role in the initiation and development of pneumoconiosis.

The destructive action of free radicals, mediated by apoptosis, can appear to be favorable in the struggle against cancer. This phenomenon is demonstrated in three papers of the unit "Reactive Oxygen and Nitrogen Species in the Struggle Against Cancer". In first of these articles (N. F. Schor et al.), the experience of prooxidant usage to overcome the resistance of tumors to chemotherapeutic drugs is presented. The authors have employed a combined anticancer therapy including simultaneous application of (1) neurotransmitter analog generating oxygen free radicals and accumulated in nervous tissue, (2) compound suppressing free radicals in normal host tissues, and (3) precursors of a drug invoking apoptosis and activated upon chemical reduction in malignant tissue. The preclinical trials have yielded rather encouraging results.

The second article, by S. Marshall et al., is devoted to the photodynamic therapy of cancer tumors. When the photosensitizer meta-tetra(hydroxyphenyl)chlorine (Foscan) is used, the destruction of cancer cells is mediated by the activation of apoptosis by the reactive oxygen species generated in malignant tissue upon irradiation.

At first glance, the proposition to use a tocopherol (a known antioxidant) derivative as an anti-carcinogenic drug seems paradoxical. Nevertheless, in the paper by K. Fukuzawa et al. it is convincingly shown that  $\alpha$ -tocopherol succinate has anti-carcinogenic activity, which can be based on the activation of free radical reactions and induction of NO-synthase. This effect was removed by the application  $\alpha$ -tocopherol, but not by other antioxidants.

The problem of the ambiguous function of  $\alpha$ -tocopherol (which is considered to be antioxidant No. 1 in cell membranes and lipoproteins) was repeatedly discussed in the literature. P. Quinn refers to this item in his review opening the final section of this the issue, "Antioxidants and Prophylaxis". In his opinion, the important biological role of  $\alpha$ -tocopherol is based on physical properties of the lipid bilayer, which have been investigated by a number of biophysical methods.

Unusual biological activity was found for another  $\alpha$ -tocopherol derivative, tocotrienol (article by T. Miyazawa et al. in the same section). It appears that in contrast to  $\alpha$ - and  $\beta$ -tocopherol, tocotrienol can suppress the proliferation of endothelial cells in aorta and formation of a network by prolate endothelial cells in 3D collagen gel. The

authors hope, that this compound can become a candidate in the development of pharmaceuticals or food means preventing angiogenesis in a tumor.

We quite often hear that the consumption of coffee promotes development of cardiovascular diseases. As known, the activation of free radical processes is one of the main risk factors in the development of atherosclerosis and ischemic heart disease. In this connection, the investigations carried out by S. Yukawa et al. on a group of student volunteers are of great interest. He showed that the regular consumption of coffee results in decreasing of

LDL sensitivity to oxidation, of cholesterol level in low density lipoproteins, and of malonic dialdehyde (a lipid peroxidation product) level and thus can reduce the probability of induction of cardiovascular disease.

The final article of this issue, by D. Bagchi et al., serves as a successful example of numerous examinations conducted now in many countries to find natural sources of antioxidants to make new drugs and food additives.

We hope that the reader interested in the problem of reactive oxygen and nitrogen species will find much interesting material in the articles presented in this issue.