JOURNAL OF INTEGRATED OMICS
A METHODOLOGICAL JOURNAL
HTTP://WWW.JIOMICS.COM

LETTER TO THE EDITOR | DOI: 10.5584/jiomics.v10i2.328

Bioradical homeostasis as new complex parameters of different biological systems

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Received: 05 February 2020 **Accepted:** 27 June 2020 **Available Online**: 31 August 2020

ABSTRACT

The current state of free radical biomedicine allows us to formulate a fundamentally new parameter of homeostasis – bioradical homeostasis, understood as a state of free radical processes, reflecting the optimal intensity of the body metabolism of oxygen, nitrogen and halogens reactive species, carbonyls and other radical molecules. This term allows us to formulate another term – "bioradical stress". It is proposed to understand the effective violation of the physiological level of free-radical processes associated with the formation of active forms of oxygen, nitrogen or halogens and/or a decrease in the activity of systems that limit their damaging effect. It combines all known syndromes associated with bioradical level shifts (oxidative, nitrosative, halogenating and carbonyl stress). The introduction of the concept of bioradical stress involves the study of the effectiveness of various options for specific pathogenetic correction of bioradical stress (the administration of antioxidants, directed stimulation of antioxidant capacity by active oxygen forms, the use of regulatory properties of NO, etc.).

Keywords: *Free radicals, bioradical homeostasis, bioradical stress, oxidative stress, nitrosative stress, halogenic stress*

1. Introduction

Research in the field of free radical biology has been conducted in all countries of the world for several decades. During this time, indicated discipline has formed its methodology, methodological apparatus, as well as terminology base [1-3]. Ideas about the significant role of free radical processes in the functioning of living systems in normal and pathological conditions have not been questioned. Thus, the participation of free radicals in cell membrane renewal and intercellular signaling has been proved [4, 5]. They serve as an essential element of phagocytosis, being a key agent of the phenomenon of "respiratory explosion" of leukocytes [6]. They also realize other physiological functions [3-6].

On the other hand, in recent years, the concept of "oxidative stress" has become widely known in biomedicine [4, 6, 7], interpreted as a significant increase in the concentration of free radicals, occurring in conjunction with a sharp decrease in antioxidant reserves. At the same time, ideas about oxidative stress went far beyond free radical biology, finding application in almost all areas of medicine [4-7]. Knowledge of other possible dysmetabolic disorders, in particular, associated with changes in the level of nitrogen -and chlorine-containing radicals toxic to biomolecules, is also being developed. These conditions received the name as nitrosative and halogenic stress, respectively [8-10].

On the other hand, the above effective (causing disease or pathological conditions) shifts in the concentrations of oxygen, nitrogen and halogen radicals are considered in isolation. At the same time, in the Russian and world literature there is a significant amount of data indicating the relationship of metabolism of these molecules [4, 5, 9]. Therefore, it seems appropriate to analyze the processes occurring with the participation of oxygen, nitrogen and halogen-containing radicals within a single fragment of metabolism, which is the purpose of this work.

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2. Bioradical homeostasis and bioradical stress: the terms

It is known that one of the basic concepts of biomedicine is homeostasis, which is a set of indicators supported by the body at a constant level and limiting its functioning as an independent unit, as well as mechanisms that provide this state [5, 6]. The range of homeostasis indicators includes a wide range of parameters (body temperature, blood pressure, pH of blood plasma, acid-base balance, etc.). The up-to-date achievements of free radical medicine allow us to hypothesize about a new component of homeostasis linked with maintaining a constant concentration of bioradicals. Accordingly, the term "bioradical homeostasis" is interpreted by us as a state of free radical processes, reflecting the optimal intensity of metabolism of oxygen, nitrogen, halogens, carbonyls and other radical molecules. From this concept and on the basis of a critical analysis of information retrieved from literature, as well as the results of our own experimental studies, we hypothesize the concept of "bioradical stress", understood by us as an effective (leading to a negative change in the functional-metabolic status of the organism) violation of the physiological level of free-radical processes associated with the formation of active forms of oxygen, nitrogen or halogens and/or a decrease in the activity of systems that limit their damaging effect. With this in mind, bioradical stress combines all known syndromes associated with shifts in the level of bioradicals – oxidative, nitrosative and halogenating stress. In addition, the advantage of the proposed integrative concept of simultaneous presence of more than one component of bioradical stress in the same patient or animal is substantiated.

Diagnosis of the presence of bioradical stress should consist of the definition of its individual components:

1) intensification of lipoperoxidation on the background of inhibition of antioxidant reserves (component of oxidative stress);

2) improve markers nitrosative stress (in particular, 3-nitrotyrosine);

3) increase of myeloperoxidase activity and other parameters visualizing halogenating stress.

The presence of at least two of these components indicates the presence of bioradical stress.

At the same time, both their specific markers and nonspecific functional-metabolic criteria are used to obtain a complex characteristic of the body's response to the formation of bioradical stress. Given that the concept of the study involves consideration of bioradical stress as a set of three main interacting components – oxidative, nitrosative and halogenating, the study will include the definition of their specific markers:

- diagnosis of oxidative stress is based on the study of the intensity of the processes of lipoperoxidation in the blood plasma in conjunction with the total antioxidant activity of the plasma;
- identifying nitrosative stress based on the definition of level 3-nitrotyrosine plasma and halogensilver activity of myeloperoxidase.

3. Possibilities of the correction of bioradical stress

The formation of the concept under consideration creates the prerequisites for its directional correction, which is logical to carry out in accordance with the diagnostic approach, i.e. component by component. At the same time, the possibilities of elimination of individual components of bioradical stress were studied to varying degrees. Thus, the widest range of methods of correction of oxidative stress. First of all, it is represented by ozone therapy and antioxidant therapy. These trends in recent decades have taken a strong place in all areas of practical medicine. In particular, the possibilities of ozone therapy are actively revealed in obstetric and gynecological practice, which uses antibacterial, antiviral, antihypoxic and bioregulatory properties of ozone and the resulting active forms of oxygen [11, 12]. In addition, there is extensive evidence of their use in surgery based on similar effects (mainly on antibacterial action and oxidative detoxification), as well as in traumatology and combustiology, for which the entire range of biological effects of ozone is significant [13, 14].

A similar situation occurs with regard to antioxidant therapy, which is included in the algorithms and treatment schemes for many diseases, both surgical and therapeutic profile [4, 6, 15-17]. The effectiveness of this approach is verified by numerous experimental and clinical studies [15-18], as a result of which several hundred drugs with antioxidant activity are currently known, and their list continues to increase [4, 6].

For other components of bioradical stress, the possibilities of specific correction are significantly more limited. This is partly due to the lack of diagnostic verification [9, 19, 20]. On the other hand, for nitrosative, halogenic and carbonyl stress, antioxidant therapy, acting in this case as a non-specific remedy, is practically the unique way of treatment [3, 4, 21]. Thus, an additional important research task is the development of technologies for the directed correction of these variants of bioradical stress [1, 22, 23].

4. Our data on research for possibilities of the correction of some componentes of bioradical stress

Our team has been working over the past decades to discover new options and opportunities for the use of innovative methods of correction of various components of bioradical stress. Thus, historically, Nizhny Novgorod is one of the leading centers for the study of biological effects and methods of medical use of ozone and ozonated media (in particular, ozonated saline). For example, our studies have established the optimal therapeutic effect of "low therapeutic doses" (less than 1000 μg/l solvent), confirmed by a registered discovery [14, 24]. The features of the effects of ozone in the system subchronic administration (for 30 days or more) were studied [25]. The variants of local and systemic ozone therapy in burn disease, purulent inflammatory diseases of bones and soft tissues (in particular, in osteomyelitis) are disclosed in detail [14].

The therapeutic potential of "alternative" reactive oxygen species is also being actively studied. In particular, we describe the biological and sanogenetic effects of the special high-energy state of molecular oxygen – singlet oxygen. Our researches have allowed to establish that, in contrast to ozone, the gas stream from the generator of singlet oxygen is moderately stimulate the pro- and antioxidant mechanisms, but it has a strong positive effect on the antioxidant system, including its enzymatic component [26]. In addition, the favourable effect of the considered factor on a number of components of energy metabolism (for example, the activity of lactate dehydrogenase in direct and reverse reactions in combination with the level of one of the reaction products - lactate), as well as enzyme detoxification systems in the blood (alcohol dehydrogenase, aldehyde dehydrogenase) was demonstrated. These metabolic changes are reflected in the systemic reactions of the body. In particular, when inhaled singlet oxygen was used, stimulation of microcirculation was observed, mainly carried out at the expense of intravascular NO-dependent mechanisms [27]. These changes ensure the effectiveness of singlet oxygen inhalations in the correction of oxidative stress and hypoxia phenomena arising as a result of experimental thermal trauma.

The second object of our research was NO metabolism and the possibility of its directed correction by exogenous sources of the compound. As the latter, nitrogen monoxide generators and physiological donor of this compound – dinitrosyl iron complexes with glutathione ligands were used [24, 28]. It is established that they have a different effect on the parameters of biological systems [28, 29]. Thus, NO-containing gas stream demonstrates a moderate pro-oxidant effect, but it acts as an antioxidant under the experimental pathological state associated with hypoxia and bioradical stress (for example, severe thermal injury) [30]. On the contrary, dinitrosyl-iron complexes have antioxidant properties in all cases, while encouraging intermediate and energy metabolism [28, 29]. These features of biological effects of NO sources allow us to consider them as a way to correction of bioradical homeostasis (by components of oxidative and nitrosative stress).

In whole, the data obtained by us allow to reveal new methods of specific correction of not only oxidative, but also nitrosative stress.

5. Concluding Remarks

Thus, the current state of free radical biomedicine allows us to formulate a new parameter of homeostasis – bioradical homeostasis, understood as a state of free radical processes, reflecting the optimal intensity of the body metabolism of oxygen compounds, nitrogen, halogens, carbonyls and other radical molecules. This term allows us to formulate conception about bioradical stress. We propose to understand it as the effective violation of the physiological level of free-radical processes associated with the generation of active forms of oxygen, nitrogen or halogens and/or a decrease in the activity of antioxidant systems. It combines all known syndromes associated with bioradical level shifts (oxidative, nitrosative, halogenic and carbonyl stress). The introduction of the concept of bioradical stress involves the study of the effectiveness of various options for specific pathogenetic correction of bioradical stress (the introduction of antioxidants, directed stimulation of antioxidant capacity by active oxygen forms, the use of regulatory properties of NO, etc.).

Acknowledgments:

We would thank the ICU and laboratory technician staff for their contribution in the patient recruitment and samples processing.

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