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DEVELOPMENT PERSPECTIVES OF NEW GENERATION MEDICATIONS BASED ON THE REDOX SYSTEM REGULATORS

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Abstract. This survey paper describes the necessity of the development of new medications influencing the body redox-potential. It supports the most pressing branch of pharmacology, which coincides with logically relevant attempts to shift paradigm of pharmacology from molecular to electronic, quantum-wave. This article covers and logically assort research results of recent years and opinions of wide range of scientists from various countries. The authors also give their own assessment of the possibility to influence body redox potential. It is reported that some biophysical achievements regarded undoubtedly put a new spin in pharmacology of the biophysical level. These research results devoted to the role of redox-potential in regulation of biological systems are considered to open up new opportunities for pharmacotherapy of pathological conditions by developing medications of the new generation – redox-potential regulators - aimed at the induction of the body protective resources. The paper further reports that elaborate study of redox-potential in providing biological systems regulation has resulted in the detailed investigation of Mexidol benefits. Special attention is paid to the general principle of action of endogenous redox regulators: metabolic, energetic and informational. The article also highlights key issues of the regulation of oxidation-reduction processes in the body and, consequently, the role of reactive oxygen species in physiology and pathology. The paper reasonably concludes with the statement on the necessity to turn pharmacologists’ attention not only to improving the existing anti-oxidant preparations, but to developing the redox system regulators, which appear to be medications of the new generation for pathogenic therapy.

Key words: reactive oxygen species, oxygen, reduction-oxidation reactions, redox potential, pharmacotherapy.

Introduction. Use of oxygen to receive energy needed for the life-sustaining activity by substrate oxidation in biological objects is considered to be one of the mainstreams of the living systems evolution [1]. Functioning of the human body as the most highly organized life-form depends on oxygen supply; its deficiency causes multiple pathological conditions. Decrease of energy resources under hypoxia results in multisystemic and multiorganic functional-metabolic changes and, subsequently, death of the whole body.

Oxygen is the leading factor of the biological rhythms control: circadian, seasonal, reproductive, as well as homeostasis, proliferation, differentiation, apoptosis, carcinogenesis, aging, necrosis and some other cellular processes [2-5], and their exact mechanisms can be understood only in the plant cell [6].

Aerobic organisms have oxidative potential, which increases with the increase of tissue blood supply or activation of free-radical particles. Oxygen deficiency, on the contrary, leads to reductive change of potential. Shift of the balance between prooxidants

and anti-oxidants induces oxidative stress characterized by specific changes of the cellular processes: membrane structure is violated due to lipid peroxidation, proteins are oxidated, DNA is damaged, cellular redox potential changes.

There have been recorded instances of more than 200 nosological forms accompanied by oxidative stress: cardio-vascular [7-14], oncological [15], infectious diseases [16, 17], pathologies of the respiratory [18], reproductive [19-21], urinary [22, 23], nervous system, pyoinflammatory processes [24], arthritis of various types, diabetes mellitus, cataract and others [25].

Mitochondrial respiratory chain, microsome electron-transport chain, arachidonic acid metabolism, hypoxanthine-xanthine oxidase reactions, biosynthesis and catecholamine oxidation are reported to be sources of reactive oxygen species (ROS) [26]. Mitochondria are stated to be the main sources of radicals in a cell [27], therefore these organelles need to be constantly protected from damages induced by oxidative stress. Mitochondrial DNA appears to be the most vulnerable target for ROS. There exist a lot of evidences that its oxidative violation and increasing de-energization of oxygen-dependant cells play the key role in the whole range of "mitochondrial diseases" [28, 29], neurodegenerative pathologies [30, 31], as well as body aging [32]. The final stage of this process is necrosis, due to which a cell as a living system stops existing, since transformation systems of substance and energy flows, permeability of cellular and sub-cellular membranes are violated, ion gradients disappear [1]. Currently, the role of mitochondria in regulation of proliferation and differentiation processes, apoptosis and cancerous growth is actively investigated. Change of ROS generation rate under influence of mitochondria may be considered as one of the mechanisms that switch functional activity of a cell [33].

ROS comprises a lot of transitional products of oxygen metabolism producing in the body; they, in turn, having high reactive capacity can lead to violation of practically all structural components of the biological system [2, 33-36]. Increased ROS levels result in initiation of free-radical oxidation – the process of immediate oxygen transfer on substrate with formation of peroxides, ketones, aldehydes inducing reactions of peroxide oxidation. This ancient natural destructive mechanism that has a hold over all the organic compounds is necessary for the following renovation of cells and tissues, their adaptation for the changing environment, body protection against infections, participation in

formation of biologically active compounds. This implies the fact that presence of free radicals in a body has specific, physiologically important significance [37].

On the other hand, it is beyond argument that functional properties of some enzymes, carbohydrates, proteins, DNA and RNA are changed under the influence of free-radicals so that a cell loses its regulatory functions [2]. Concurrently there may appear abnormal proteins; secondary destructive processes may be stimulated apart from direct damaging action.

Discussion. The leading role in pathogenesis of radiation damage, inflammatory processes of various localization and origin, development of hyper- and hypoxic conditions, post-ischemic, reperfusion and hyperoxic disorders, wound processes, stress, acute and chronic hepatic diseases, myocardial infarction, strokes, atherosclerosis, carcinogenesis, aging and so on belongs to lipid peroxidation. Influence of free-radicals on structure and functions of biological membranes is one of the most important pathogenic mechanisms in hypoxia.

There is a multilevel physiological system of protection against oxidation agents in a body – the antioxidant system supporting oxidative-antioxidative balance in all organs and systems [38, 39]. The antioxidant system includes the whole complex of enzymes: superoxide dismutase (SOD), catalase, glutathione-dependant peroxidases, transferases etc., as well as a range of cellular metabolites: lipoic, ascorbic, uric acids, tocopherols, carotenoids, flavonoids, polyphenols, carnosine, bilirubin, coenzyme Q10 and other compounds aimed at maintaining the normal reactions of the body in various pathological conditions, including hypoxia [2, 32, 40-50]. Malfunctioning of these systems is stated to be one of the most significant factors in violation of prooxidant-antioxidant balance and oxidative stress development [51, 52]. Some research studies have demonstrated that ROS formation and multicomponent anti-oxidative protection constitute the unified system being in the dynamic balance and having capacity for self-regulation [35]. Due to the associated functioning of the ROS generation and anti-oxidative protection systems oxidation-reduction balance is established in a cell, in other words redox status. Redox potential formation reflecting balance status of the pro- and antioxidant body systems [53] is greatly influenced by protein components of blood plasma, catalase enzyme activity and, possibly, alpha-synuclein level [54].

The importance to maintain such balance for the living system was marked by A. Szent-Györgyi [55] in the mid-XXth century; he considered the balance between electron donors and acceptors to be one of the basic life parameters.

Associated redox system representing combination of redox cycles of carbon, nitrogen, oxygen and sulphur, has been formed during the evolution process [56]. Redox potential of the normally functioning cells is maintained at the constant level and changes only under specific actions [1, 34, 57-59]. In spite of the fact that oxidation-reduction reactions are the basic reactions of the bioenergetic processes and regulate cellular activity as a whole [27], there is no clear understanding of their role in the intra- and extracellular pathogenesis, signaling processes, homeostasis regulation. However, redox homeostasis acquires conceptual significance in some pathological body processes [60].

Redox potential reduction shift forms the basis of triggering hypoxic necrobiosis and damaging specific oxygen-sensitive cells; redox potential oxidation shift forms the basis of developing free-radical necrobiosis and apoptosis of trophic cells [1]. Oxidative and nitrosative stress removes SH-SS balance towards oxidated thiols that causes neurons necrosis and death [61].

Insignificant redox-potential shifts through a biological cycle give an opportunity to rhythmically regulate phases of functional activity of the living systems with resting phases; and its significant shifts lead to activation of cellular death processes. Thus, for example, correlation of reductive and oxidated glutathione levels plays role of a special "switch" from proliferation phase to differentiation phase and further to apoptosis [62].

Redox potential shift has an effect on realization of metabolic processes, work of the signaling transduction system, gene expression, activity of transcription factors [63-66], change of activity and biological full value of both intracellular compartments and a cell as a whole [67]. When changing redox potential status cellular strategy is mostly defined by the status of signal transmitting systems [68]. Redox potential has been demonstrated to be an indicator of cellular functional activity and effectiveness of anti-oxidated protection [69].

Organic substances (vitamins, aminoacids) and compounds of inorganic origin – macro- and microelements - take part in redox potential regulation alongside with oxygen; even insignificant change of concentration of inorganic substances has an effect on the functioning of the whole body [1, 70]

The data obtained on the leading role of redox potential in maintaining the biological system regulation give new opportunities for pharmacotherapy of pathological conditions including hypoxic one. Currently the amount of theoretical, experimental and clinical data is sufficient to create a theory of developing highly effective medications of new generation – redox regulators – based on the study of functional biological multivaluedness of redox-active agents.

The enormous list of modern preparations for chemotherapy is represented by chemical compounds foreign for the biological system, having xenobiotic load on a body and, consequently, causing side effects. Therapeutical effect of any xenobiotic is restricted by the blockage of adaptational body reactions to a damage and replacement of the proper protective resource into the artificial one until its atrophy. Besides, introduction of foreign medications can result in resistance that increases danger of overdose and individual hypersensitivity. Severe drawbacks of modern medications are reported to be a narrow range of pharmacological activity and absence of selectivity towards a biotarget; that is why a positive result in vivo for a foreign compound is accidental; this fact is proved by rare successful cases of numerous chemicals screening.

Synthesis of effective and safe medications – natural participants of enzymatic reactions and metabolism compatible with biological structures and systems, - is possible by applying electrophilic replacement, redox vitamin modification and complex formation. The example of redox vitamin modification appears to be an effective polyfunctional preparation – mexidol – vitamin B₆ modification (redox oxypyridine active centre) with succinate [71].

Analysis of numerous investigations of this medication allows concluding that vitamin B₆ easily entering a cell through its own natural canals transfers a succinate; this makes mexidol an irreplaceable pathogenetic preparation in complex therapy of post-hypoxic conditions [72, 73]. Vitamin B₆ as an active redox agent participates in the regulation of oxidation-reduction processes in cytosol and membrane, and a succinate metabolite – succinic acid – reactivates cell respiration. Due to such synchronic tandem cells living activity remains unchanged and a chance to restore cellular functional activity under oxygen deficiency increases.

Impact of succinate on the energy exchange has been studied more in details for all substrates of the Krebs cycle [74]. Predominant use of succinate is natural cell protection against hypoxia. At that,

replenishment of the substrate fund may occur as a result of the Krebs cycle reactions, both – linear and reverse. Such a peculiarity of oxidative phosphorylation provides an opportunity to reverse reaction at the di-carbon stage of the Krebs cycle with transition of fumarate into succinate and increasing amount of the latter. Mechanism of inversive fumarate transformations during the Krebs cycle explains the efficient use of fumarate-containing preparation – sodium fumarate, mafusol, polyoxifumarin, konfumin, as well as the complex fumarate + Hydroxyethylstarch, which is successfully passing through the last stage of pre-clinical trials [75, 76]. Preparations of this group have come to stay in the program of fumarate-containing solutions for infusions applied in Accident and Emergency Departments of healthcare facilities in the Russian Federation and CIS-states when delivering medical care to the injured in military conflicts, natural and technological disasters [77].

Currently there has been shown an opportunity of redox potential pharmaco-correction of heart failure caused by ischemic heart disease with adenosine containing reduced NAD form [78]; there have been revealed pre-conditions for HistoChrom application in complex therapy of venous retinal occlusions associated with changes of the redox system [79].

Redox regulators take the exceptional position among biomolecules, because only redox-active substances are able to transfer electrons intermolecularly. Since charge redistribution is considered to be a basis of a biochemical reaction, then only redox-active elements and molecules specific for the given enzyme play the functional role. This explains synchronization of biological processes occurring at all levels of the systemic organization influenced by associated redox-factors. At that, the significance of the unique organization of a protein molecule or its active polypeptide part is evident.

An attempt to change redox potential of the body liquid media with ionized liquid having either positive or negative potential has been made in the Voronezh N.N.Burdenko State Medical University [80, 83]. Some research studies performed prove safe application of fluids with various redox potential, establish therapeutic range of the redox potential parameter in millivolts [81, 82].

Variety of biological systems, numerosity of active particles and secondary messengers, complexity of the inflammatory reaction mechanism and variety of factors influencing it do not allow creating a precise picture of mechanisms, which

realize protective potential of safe medications. However, universe character of their participation in these mechanisms as a redox potential agent supports not only reasonability but also the necessity of creating such agents.

Redox agents perform an antioxidant function as constituents of the physiological antioxidant system, however, the fact of even greater importance is that they provide functional enzymes activity as co-enzymes, co-substrates and co-factors, i.e. reveal prooxidant activity. More than that, redox agent activity is defined by the redox environment, mainly, protein having signaling transduction.

General principle of endogenic redox regulators impact is aimed at three biological flows: metabolic, energetic and informational; their synchronic interaction at all levels of organization of the living system is achieved due to redox factors incorporation into enzymatic processes. Simultaneously they act as sensors responding to changes of one of the most important indicators of the biological system – redox potential. A received signal is directly or indirectly transformed into activity shift of a specific enzyme.

Currently redox-sensitive elements of the intracellular signal-transmitting systems (p 38 MAP kinase, JNK, transcription factors and proteins of Bcl-2 family) are shown to be molecular targets for therapeutic correction of the apoptotic program violation under oxidative stress [68].

In the extreme (pathological) situation associated with hypoxia anti-oxidants are able to reveal their own protective function acting as an electron buffer. Redox-active agents, on the contrary, produce induction and mobilization of all protective resources at any level of the biological system demonstrating not only anti-oxidant, but pro-oxidant activity as well. The problem to be studied is how to trigger these processes and further regulate them.

If a danger of stress-reaction is insignificant and the amount of operative protective resource is sufficient enough to eliminate its consequences, then participation of endogenic redox regulators may be considered as manifestation of their preventive potential.

Different situation occurs if the amount of protective resource is insufficient and it is necessary to mobilize specific protective proteins, information on which is kept in the genetic material. It is the medication based on modified signaling molecules of proteins that should participate in the mechanisms of induction and mobilization of protective resource. Such varieties of redox-active signaling molecules performing the role of the protective function trigger may claim to be highly effective medications.

Development of organic complexes of biometals seems to be the most universal. In this case organic bioligand being a natural redox-active agent of an enzyme allows an element to be the most effectively included in the metabolic mechanism. Such complex compounds of transitional biometals may reproduce chemical behaviour of metallo-enzymes in a cell. The role of these complexes is restricted by the participation of electrons and redox-reactions typical for this enzyme in the processes of transport. Low-molecular compounds with metals, for example, zink sulfate or gluconate, cannot be referred to the category of redox regulators, since absence of a relevant ligand in their composition deprives these compounds of substrate specificity. Taking into account high level of biological activity of essential bioelements their reliable and fast delivery by transport proteins with easier release appears to be a warrant of high effect.

Conclusion. Thus, any violation of homeostasis results in pathological conditions causing violation of energy production, storage and utilization. Redox-potential is considered to be the basic indicator of metabolic cell status integrating uncountable number of oxidation-reduction reactions. The data available on the leading role of redox-potential changes in providing the biological systems regulation give new opportunities for pharmacotherapy of pathological conditions including hypoxic ones. Development of medications – redox system regulators – aimed at the induction of proper protective body resource appears to be strategic concern of creating new generation pathogenic therapy agents.

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