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REVIEWS

THE ROLE OF THE REDOX SIGNALING SYSTEM (H_2O_2 AND THE THIOL SYSTEM) IN THE REGULATION OF THE FUNCTIONAL ACTIVITY OF NERVOUS TISSUE IN HEALTH AND DISEASE

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The review highlights the role of reactive oxygen species (ROS) and the thiol system in the regulation of functional activity of neurons. Their controlling function has been analyzed in the context of processes of synaptic plasticity and functioning of neurotrophins, as well as participation in such cellular processes as proliferation, apoptosis, and cell aging. Special attention has been paid to the role of individual components of the thiol system, their interaction with H_2O_2 in the regulation of the redox signaling system of cells. Summarizing literature data reflecting the participation of H_2O_2 in the regulation of key metabolic cascades of nervous tissue and own results we have come to conclusion about the dual nature of the stress system components depending on the functional state of the organism. The manifestation of their toxic effect, first of all, depends on their concentration and chemical structure.

Keywords: oxidative stress; reactive oxygen species; hydrogen peroxide; thiol redox signaling system; nervous tissue

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INTRODUCTION

The functioning of the body is accompanied by activation of common adaptation mechanisms involving oxidative stress (OS). However, these changes are often tissue specific and have different intensity and manifestation in almost every tissue. This may be due to the sensitivity of tissue cells to ROS, the rate of generation and efficiency of ROS use, in particular, H_2O_2 as a second messenger, the potential of the antioxidant system (AOS) and its timely mobilization [1–3].

Each tissue has a certain buffer capacity of antioxidant defense (AOD). It depends on the AOD state of the intercellular fluid and the cells, individual cell compartments. Some tissues, due to their functional and metabolic activity, have increased sensitivity to the OS state, which is associated with the high potential power of the prooxidant system (POS) and low buffer capacity of AOD. Such tissues include the brain, retina, and lungs. This is explained by the important regulatory function that ROS perform. In brain tissue, this may be associated with the transmission of excitation signals, the occurrence of action potentials, and the activation of synapses [4, 5].

Any changes in the external and internal environments of the body are accompanied by a sequential transmission of signals due to the interaction of first messengers with certain receptors of cell membranes. These include growth factors, hormones, cytokines, neurotransmitters, neurotrophins, and other stimuli. When a signal is received, the receptor functions as a transport transmitter of information through various transducers and amplifiers that participate in the formation of intracellular second messengers. Second messengers

Abbreviations used: AD – Alzheimer's disease; AOD – antioxidant defense; AOE – antioxidant enzymes; AOS – antioxidant system; AP-1 – activator protein-1; ARE – antioxidant response element; ASK – apoptosis signal-regulating kinase 1; CREB – cyclic AMP responsive element binding protein; ERK1/2 – extracellular signal-regulating kinase; GGT – gamma-glutamyl transpeptidase; GR – glutathione reductase; GPx – glutathione peroxidase; OS – oxidative stress; GCL – glutamate cysteine ligase; Grx – glutaredoxin; GSH – glutathione; GSK 3β – glycogen synthase kinase-3β; HIF-1α – hypoxia-inducible factor-1α; 4-HNE – 4-hydroxy-trans-2-nonenal; LPO – lipid peroxidation; NF-κB – nuclear factor-κB; Nrf2 – nuclear factor erythroid 2-related factor 2; PD – Parkinson's disease; PDK1 – phosphoinositide-dependent kinase; PKB – protein kinase B; POS – prooxidant system; Prxs – peroxiredoxins; PTCR – protein tyrosine kinase receptor; PtdIns-3 kinase – phosphoinositide 3-kinase (PI3K); PtdIns $3,4,5P_3$ – phosphatidylinositol (3,4,5)-trisphosphate; PTEN – phosphatase and tensin homolog deleted on chromosome 10; PTK – protein tyrosine kinase; RNS – reactive nitrogen species; PUFA – polyunsaturated fatty acids; PTP – protein tyrosine phosphatase; ROS – reactive oxygen species; SOD – superoxide dismutase; Srxs – sulforedoxins; TrkB – receptor tyrosine kinase B; Trx – thioredoxins; TrxR – thioredoxin reductase; UCPs – uncoupling proteins.

include ROS, products of lipid peroxidation (LPO), cyclic nucleotides cAMP and cGMP, Ca^{2+}, NO, products of phospholipid metabolism such as diacylglycerol, inositol-1,4,5-triphosphate, arachidonic acid, etc. Second messengers, in turn, transmit information to effectors. Through sensors and effectors, they are actively involved in signal transduction, influencing key links in metabolic processes, which can be characterized as a third link in signal transduction to the cell [2, 6].

In general, this whole cascade of cellular signaling pathways of interactions leads to a certain physiological response associated with the processes of proliferation, differentiation, apoptosis, cellular adhesion, blood clotting, etc. In brain tissue, this is associated with neurogenesis. These processes are carried out with maintenance of a certain redox status of cells. In fact, the redox system determines the diversity of signaling functions, modulating the activity of other signaling pathways, thereby participating in the fundamental mechanisms of regulation of the functional activity of cells [7–10].

The purpose of this review is to highlight the role of hydrogen peroxide, a second messenger and the thiol system, as one of the main components of the redox signaling system involved in the regulation of the oxidation-reduction status of cells in normal and pathological conditions of the brain.

1. THE ROLE OF H_2O_2 IN THE REGULATION OF THE FUNCTIONAL ACTIVITY OF NEURONS

Each cell maintains a certain redox status, which provides physiological pH values in intracellular compartments. The redox status in the cell reflects the ratio of the concentrations of oxidized and reduced equivalents; this ratio depends primarily on the level of ROS and the activity of the thiol system in tissues. Winterbourn considers the oxidation of thiols as the “core” of redox signaling [11].

Their coordinated mutual action is necessary to maintain the vital functions of cells associated with metabolism of proteins, lipids, and carbohydrates, enzyme activity, transcription factors and cell growth, apoptosis, etc. Thus, brain adaptation to changing internal and external conditions is characterized by the concept of “neuroplasticity”, which at the cellular level is manifested in the modification of the growth of dendrites and axons, synaptic remodeling, synaptogenesis [12]. It is known that the processes of synaptic plasticity and the functioning of neurotrophins as growth factors are closely associated with the redox signaling system and, consequently, with ROS and the thiol system. This is determined, in particular, by involvement of H_2O_2 in the control of many cellular processes, including proliferation, apoptosis, and aging of brain cells. Physiological concentrations of H_2O_2 are associated with changes in the conformational state of the lipid-protein layer of membranes. This, in turn, can have a regulatory effect on the downregulation of receptors [13, 14].

H_2O_2 is involved in the regulation of nodal links of redox signaling cascades. The central place in this process belongs to the regulation of post-translational modification of proteins, especially phosphorylation/dephosphorylation [7, 15]. The action of most growth factors, including neurotrophins, cytokines, hormones, is associated with interaction with receptor protein tyrosine kinases (RPTK). Ligand binding induces dimerization and phosphorylation of tyrosine residues of the cytoplasmic domain and activation of tyrosine kinase activity. Participation of H_2O_2 in the reversible inactivation of phosphatases suggests its putative role as a regulator of the phosphorylation/dephosphorylation cycle of proteins and phosphoinositides. This, in turn, influences functions of various proteins, including transcription factors, phospholipases, protein kinases, phosphatases, ion channels (Fig. 1) [6, 16–18].

The targets of H_2O_2 action include protein tyrosine phosphatase (PTP) and PTEN. The presence of a hyperactive cysteine residue in the catalytic domain of tyrosine phosphatases determines their potential inactivation by H_2O_2. Oxidative inactivation of PTPs is associated with tyrosine phosphorylation [7, 10, 19, 20]. The action of PTEN phosphatase is aimed at dephosphorylation of the lipid second messenger PtdIns 3,4,5P_3 (phosphatidylinositol (3,4,5)-trisphosphate). Participation of ROS in the regulation of the PtdIns 3-kinase signaling cascade PI3K leads to inhibition of PTEN phosphatase activity due to oxidation of Cys-124. The phosphorylation process is reversible [6, 21, 22]. Generated PtdIns 3,4,5P_3 is one of the main second messengers of the PI3K signaling cascade system, participating in the regulation of a wide range of cellular processes, including gene transcription, cell growth and apoptosis, synaptic plasticity of hippocampal neurons and Purkinje neurons, and the functioning of astrocyte ion channels. PtdIns 3,4,5P_3 activates PDK1 with subsequent phosphorylation and activation of PKB and ERK1/2. The process of phosphatase reactivation can be carried out by Trx [10, 23–25].

H_2O_2 can participate in activation of various tyrosine kinases. For example, it has been shown that H_2O_2 activates the non-receptor tyrosine kinase Sck without concomitant phosphorylation of growth factor receptors [26, 27].

In fact, H_2O_2 regulates the main signaling pathways that determine the metabolic direction of the processes of survival and functioning of neurons during the ligand-receptor interaction of neutrotrophins with Trk receptors. One of these pathways is associated with the PI3K–Akt (protein kinase B, PKB) signaling cascade. Another pathway involves the ERK1/2 signaling cascade.

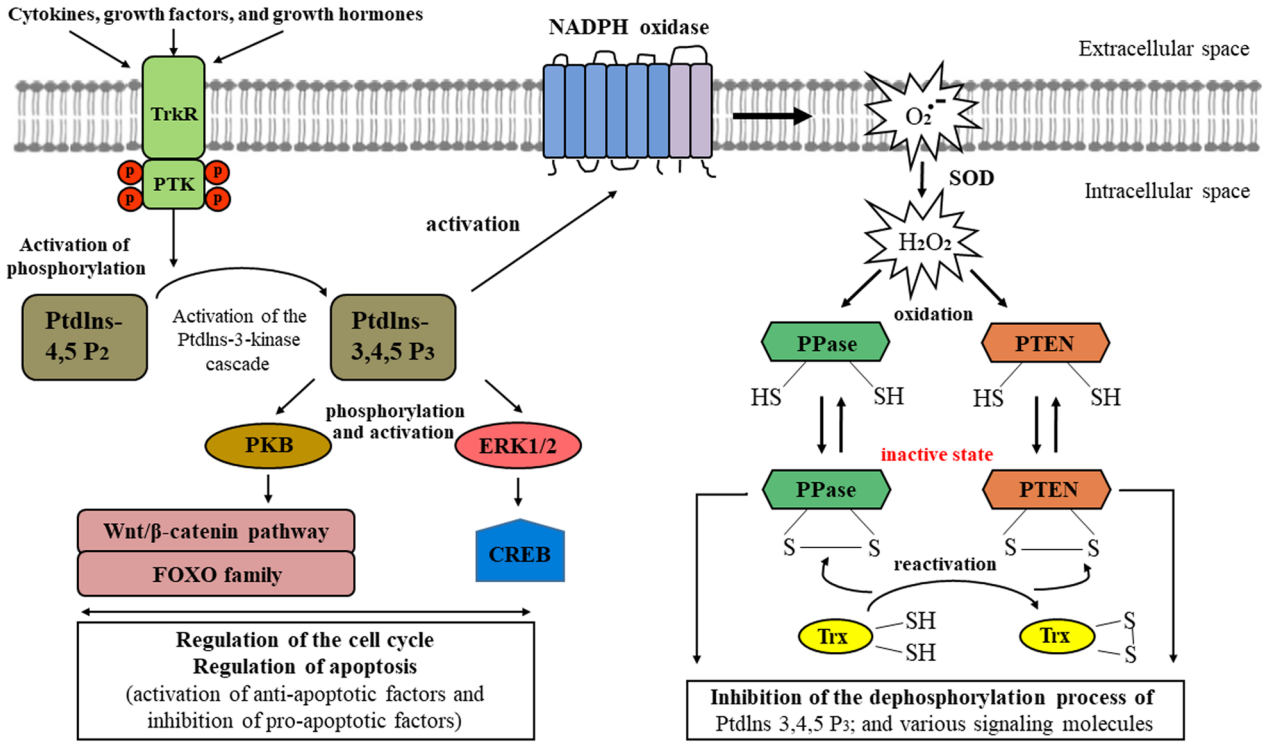

Figure 1. The role of H_2O_2 in the regulation of nodal links of the redox signaling cascades.

H_2O_2 is involved in the regulation of this process as a phosphatase inhibitor. In the active state, PKB through the canonical Wnt-catenin pathway and the FOXO1, FOXO3a, FOXO4 family members, and ERK1/2 through the CREB transcription factor participate in the regulation of the cell cycle [3, 28].

Cell cycle initiation is associated with the influence of extracellular signals that cause the expression and activation (deactivation) of special regulatory proteins. For example, the active form of ERK1/2, through phosphorylation of the transcription factor CREB, is involved in regulating the activity of transcription factors of the E2F family, thereby influencing the transition of cells from the G1 phase to the S phase [28].

In parallel, the PKB and ERK1/2 signaling systems cause inhibition of individual components of apoptosis. For example, the PI3K system is associated with modulation of apoptosis due to a decrease in the expression of the pro-apoptotic factor Bim, inactivation of the pro-apoptotic factor Bad due to phosphorylation of Ser-136 [29, 30].

PKB also stimulates the activity or expression of anti-apoptotic proteins, including BCL2. This helps to maintain a balanced ratio of proliferation and apoptosis, which is one of the fundamental factors in maintaining neurogenesis and synaptic plasticity of nervous tissue.

All this leads to an increase in the number of neurons, their redistribution in neural networks and the activation of certain synapses in response to appropriate signals. In fact, neural stem cells, through neurogenesis, restore the composition of nerve cells integrating into the neural network. The central and primary link in the transformation of neural stem cells is proliferation. Due to apoptosis, the most viable proneurons are selected and a pool of mature integrated neurons is formed [31].

Thus, under normal conditions, depending on the needs of the body, caused by the influence of various signaling factors of the external and internal environment of the body, the degree of tolerance, a dynamic balance is maintained between the processes of cell proliferation and apoptosis. Such a balance is possible due to the preservation of mobility and interconnection within the transduction signal cascades themselves. In this context, studies on the role of glycogen synthase kinase (GSK3) in regulating the activity of a number of GSK3-inhibited enzymes represent a good example. It is known that Akt can not only inhibit GSK3, but GSK3 itself can regulate Akt when it is in a complex with the β-arrestin protein. PTP is involved in this process. Activation of the dopaminergic receptor induces association of β-arrestin, Akt, GSK3, protein phosphatase 2A (PP2A). This accelerates PP2A-mediated dephosphorylation of Akt and GSK3, leading to inhibition of Akt and activation of GSK3, which, in turn, leads to inhibition of the PI3K signaling system of cells [32].

Good evidence now exists that ROS can directly participate in excitation processes. It is known that activation of NMDA receptors on the postsynaptic

membrane of the glutamatergic synapse is associated with the formation of excitatory potential as a result of opening channels permeable to Na^+, K^+, Ca^{2+} ions [33]. This activation of ionotropic receptors is accompanied by intracellular generation of ROS, affecting the conformation and activity of receptor proteins.

ROS-induced modification of NMDA receptors is considered in the literature as an example of redox regulation of ionotropic receptors. According to these concepts, the balance between AOS and POS in neurons has an impact on the formation of the so-called long-term memory and learning processes [34]. Currently, it is believed that the generation of ROS, including H_2O_2, can be induced only by the activation of ionotropic, but not metabotropic glutamate receptors [34, 35]. Regulation of H_2O_2 neurotransmission is of great physiological importance, since pathological changes in schizophrenia and Parkinson's disease (PD) are associated with an imbalance in the H_2O_2 level [36, 37].

Thus, the interaction of structurally unrelated different classes of glutamate receptors (metabotropic and ionotropic) is the determining factor in the concept of “synaptic plasticity”. The mechanism of these relationships is possibly associated with the action of H_2O_2 as a second messenger, which leads to a change in the membrane potential of the neuron [38].

It is known that oxidants and antioxidants can directly modulate the redox status of cysteine residues of transcription factors; this plays a major role in the process of transcription factor binding to DNA. The action of H_2O_2 in cells is associated with the activation of transcription factors AP-1 and NF-κB [3, 38].

Nuclear factors NF-κB, AP-1 play an important role in the regulation of immune and inflammatory genes, in the regulation of apoptosis and cell proliferation. It should be noted that the inactivation of AP-1 and NF-κB occurs at a higher level of ROS, compared to the processes of their activation. It appears that, starting from a certain threshold level of ROS, the mobilization of cell defenses weakens and the inhibition of transcription factors, particularly NF-κB, probably occurs faster than its activation. ROS cause oxidation of SH-groups and inhibition of the constitutive transcription factors NF-1, Sp1, USF, and MyoD and this is accompanied by downregulation of expression of a number of genes [39, 40].

2. THE THIOL REDOX SIGNALING SYSTEM IN CELL FUNCTIONAL ACTIVITY

Thiols are primary traps on the oxidation pathway. Due to the reversibility of this process, they perform a regulatory function, which includes regulation of the activity of transcription factors, proliferation and differentiation processes, and apoptosis. Thus, thiol compounds exhibiting anti- and prooxidant activity can regulate general signal transduction pathways or differentially modulate growth of cell depending on their redox status [7, 8].

The buffer capacity of the system depends on the ratio of reducing and oxidizing elements of all thiol/disulfide pairs [8, 11, 41]. In addition to the thiol system, which plays a central role in the redox system, ROS and RNS are actively involved in the redox system regulation. The key function of ROS and RNS is to maintain the redox status of cells at a level that ensures the sequential transformation of the signal to the main nodal signaling pathways of the third link of information transmission.

The thiol system includes the glutathione and thioredoxin systems, glutaredoxins and peroxiredoxins. Currently, only two systems are known — glutathione and thioredoxin, which are actively involved in the processes of oxidation/reduction of thiol groups using thiol-disulfide oxidoreductases.

Normally, cells are characterized by a high reduction potential, and GSH plays an important role in its maintenance. It is known that in the cytoplasm, the concentration of GSH varies within 1–10 mM, and 99% of GSH is represented by the reduced form [42]. In fact, the redox balance of the cell is determined by the 2GSH/GSSG ratio. The same algorithm can be attributed to the oxidized and reduced forms of Trx. Reduced forms of GSH and Trx are used in numerous reduction processes associated with H_2O_2 metabolism [42, 43]. The glutathione system is represented by oxidized and reduced forms of GSH, enzymes glutathione reductase (GR) and glutathione peroxidase (GPx). In neurons, the concentration of cytosolic GSH is almost 50% lower compared to other cells (about 5 mM in neurons and 10–11 mM in hepatocytes). The low GSH content is associated with a decrease in the synthesis of the key enzyme glutamate cysteine ligase (GCL), possibly due to low activity and minimal amount of the redox-sensitive transcription factor Nrf-2 [5, 42, 44, 45]. The synthesis of GCL is one of the factors determining the vital activity of neurons [46].

The study performed using a culture of hippocampal neurons has shown that transition metal ions (iron, copper) contribute to a decrease in GSH followed by subsequent cell death [47]. Copper causes a more pronounced decrease in the GSH levels compared to iron; this is attributed to more potent inhibition of GCL activity. In turn, GSH depletion leads to an increase in mitochondrial ROS production, impaired Ca^{2+} metabolism, and activation of lipoxygenase [47]. A decrease in GSH levels in the nervous system is associated with impaired cognitive function during the aging process and in CNS diseases. For example, low GSH levels in the hippocampus and prefrontal cortex have been detected in patients with impaired cognitive function and Alzheimer's disease (AD) [48, 49].

During oxidative damage manifested by cognitive disorders and impaired behavioral characteristics, the decrease in GSH in the hippocampal slices of mice was accompanied by destruction of neuronal dendrites [48]. Thus, during OS, a decrease in GSH is an early biochemical indicator of neuronal degeneration of the brain during aging and the development of neurodegenerative diseases.

It should be noted that under certain conditions, extracellular GSH can exhibit a prooxidant effect. The membrane enzyme, γ-glutamyl transpeptidase, cleaves extracellular GSH with formation of glutamate and cysteinyl-glycine. A critical role in the manifestation of the prooxidant effect of GSH is played by the thiol-dependent process of reduction of transition metal ions, particularly, iron, associated with the generation of a reactive thiolcysteinyl-glycine (thiyl radical). The highly reactive thiyl radical participates in the reduction of transition metal ions, which are oxidized to form superoxide anion radical and H_2O_2. Thus, under certain conditions GSH, acting as a powerful antioxidant, can exhibit prooxidant properties [50].

GSH and H_2O_2 can induce the reversible process of glutathionation/deglutathionation of various proteins. Glutathionation is associated with the formation of the PSSG disulfide between GSH and Cys residues of proteins, deglutathionation is associated with the degradation of this complex. The concept of glutathionation/deglutathionation is considered one of the main mechanisms of signal transduction, since it affects a large group of proteins. This process is reversible not only due to the involvement of specific reactive cysteine residues, but also due to enzymatic reduction involving glutaredoxins (Grx), thioredoxins (Trx), and peroxiredoxins [51, 52]. The process of glutathionation involves Grx 1 and Grx 2, glutathione S-transferases and, to a lesser extent, Trx. The central role in this process belongs to Grx, which catalyzes deglutathionation more efficiently than other thiotransferases.

Currently, a family of Grx proteins has been identified; its members performing glutathionation are thus involved in glutathione-dependent redox regulation of cells, operating in various physiological and pathological conditions [53–56].

It is believed that a unique feature of Grx proteins is their ability to carry out glutathione-dependent redox regulation through glutathionation processes: conjugation of GSH with substrates and their reversible deglutathionation [52, 53].

The glutathione process is currently considered as one of the main mechanisms of oxidative signal transduction. Grx is a core in maintaining the balance between glutathionation/deglutathionation, which is especially important for nervous tissue, because of low GSH level. Grx, through the regulation of glutathionylation/deglutathionylation of the cysteine residue Cys-215 of the active site of PTP, regulates and controls the phosphorylation of tyrosine residues [53, 57].

Glutathionation/deglutathionation plays a key role in controlling ROS-induced proton leak involving mitochondrial uncoupling proteins (UCP-2 and UCP-3, but not UCP-1). These proteins play an important role in reducing ROS formation in the mitochondrial electron transport system. All three isoforms of these proteins contain cysteine residues. UCP-2 and UCP-3 are considered as the “first line of defense” against mitochondrial ROS production. A slight increase in ROS generation can stimulate deglutathionation, reducing ROS production. The studies have shown that mitochondrial ROS production is normally cyclical with a periodicity of 20 s [58]. The studied proteins exist either in an active or inactive state depending on the periodicity of ROS generation. At high prolonged levels of ROS, UCP-2, UCP-3 are deactivated by deglutathionation [58, 59]. It should be noted that this process is not induced by OS, but due to its reversibility it is considered, like phosphorylation, as a highly organized system of protein regulation.

Recent studies have shown that glutathionation/deglutathionation processes, as well as phosphorylation/dephosphorylation processes, are involved in the regulation of various signaling pathways, controlling cell proliferation and apoptosis in health and disease. Impairments in the glutathionation/deglutathionation ratio has been identified in malignant tumors, immunodeficiency states, neurodegenerative diseases, pulmonary fibrosis, etc. [60–62].

Analyzing the role of thiol system components in the regulation of the redox system of cells, special attention is paid to the cysteine residues of proteins themselves, which can serve as key targets of redox effects [8, 59].

For example, S-glutathionylation of cysteine residues at the catalytic sites of procaspase-9 and caspase-3 is a significant post-translational redox mechanism of the reversible process of activation/inactivation of the apoptotic enzymes. Thus, the redox pair GSH/GSSG, often functioning in the complex with the thioredoxin system, represents a cellular redox system that plays an important role in the redox regulation of apoptosis [63, 64]. Currently, much attention is paid to a number of families of Trx-like oxidoreductases, which include thioredoxins, peroxiredoxins, GPx, and glutathione-S-transferases. Despite the large differences in amino acid composition, all these families are characterized by a three-dimensional structure known as a common thioredoxin fold [65].

Trx, together with thioredoxin reductase (TrxR) and NADPH, also functions as a redox buffer. Like the glutathione system, the thioredoxin system regulates the redox status of many proteins, thus

participating in the regulation of the activity of signaling proteins. A special feature of TrxR is that it contains selenocysteine in the C-terminal active site. FAD is located in the N-terminal region. The enzyme catalyzes electron transfer from NADPH to FAD, and then to the C-terminal active site.

Trx regulates apoptosis by inhibiting ASK1 or by regulating denitrosylated forms of mitochondrial caspases. Another function of Trx is the regulation of the activity of peroxiredoxins (Prxs), low-molecular antioxidant proteins involved in H_2O_2 metabolism [59, 66].

It should be noted that, in contrast to GSH, cellular Trx concentrations are significantly lower; however, Trx plays a key role in reactions with proteins of the main signaling systems in the third signal transduction system, especially in the regulation of the activity of transcription factors. Trx is involved in the redox regulation of a large group of proteins, which include the AP-1 protein, the transcription factor NF-κB, the transcription factor regulating the cell cycle, the apoptosis effector p53, glucocorticoid and estrogen receptors, and the hypoxia-inducible factor HIF-1α. Trx is a redox-regulated protein with antioxidant activity; it is considered as one of the indicators of OS, since in pathology it actively enters the blood plasma from cells. This is especially important in cases of brain tissue damage (strokes, AD, PD, multiple sclerosis, etc.) [67].

The Prxs family is a widespread family of antioxidant proteins present in the cytosol, mitochondria, and other cellular compartments; members of this family differ in the number of cysteines (1 or 2) in the active site and features of the enzymatic reaction [6, 65, 68–70].

In mammals, there are 4 typical (2-Cys-containing) Prxs (Prxs 1, 2, 3, and 4), involved in the detoxification of hydroperoxides and the regulation of H_2O_2-mediated intracellular signaling; although they have been initially considered as weak H_2O_2 scavengers; recent studies have shown that their action may be comparable to that of catalase and GPx [71]. It should be noted that they are able to interact with numerous regulatory thiol-containing proteins. This is one of the determining factors for their participation in many cellular processes. Currently, Prxs are considered to be the main regulator of H_2O_2 levels in tissues [65, 72].

In neurons, the Prdx-Trdx system plays a major role in regulating H_2O_2 metabolism [5, 73]. Prxs usually act as antioxidants or regulators of cell signaling systems, eliminating peroxides. It is assumed that Prxs function as floodgates. Prxs actively destroy low H_2O_2 concentrations due to their peroxidase activity, but at high H_2O_2 levels, they are inactivated (Fig. 2) [11, 74].

In the reduced state, Prx cysteine is attacked by H_2O_2 with formation of sulfenic acid. The fate of –SOH can be different depending on the ROS concentration, the state of protein scavengers, and their functional

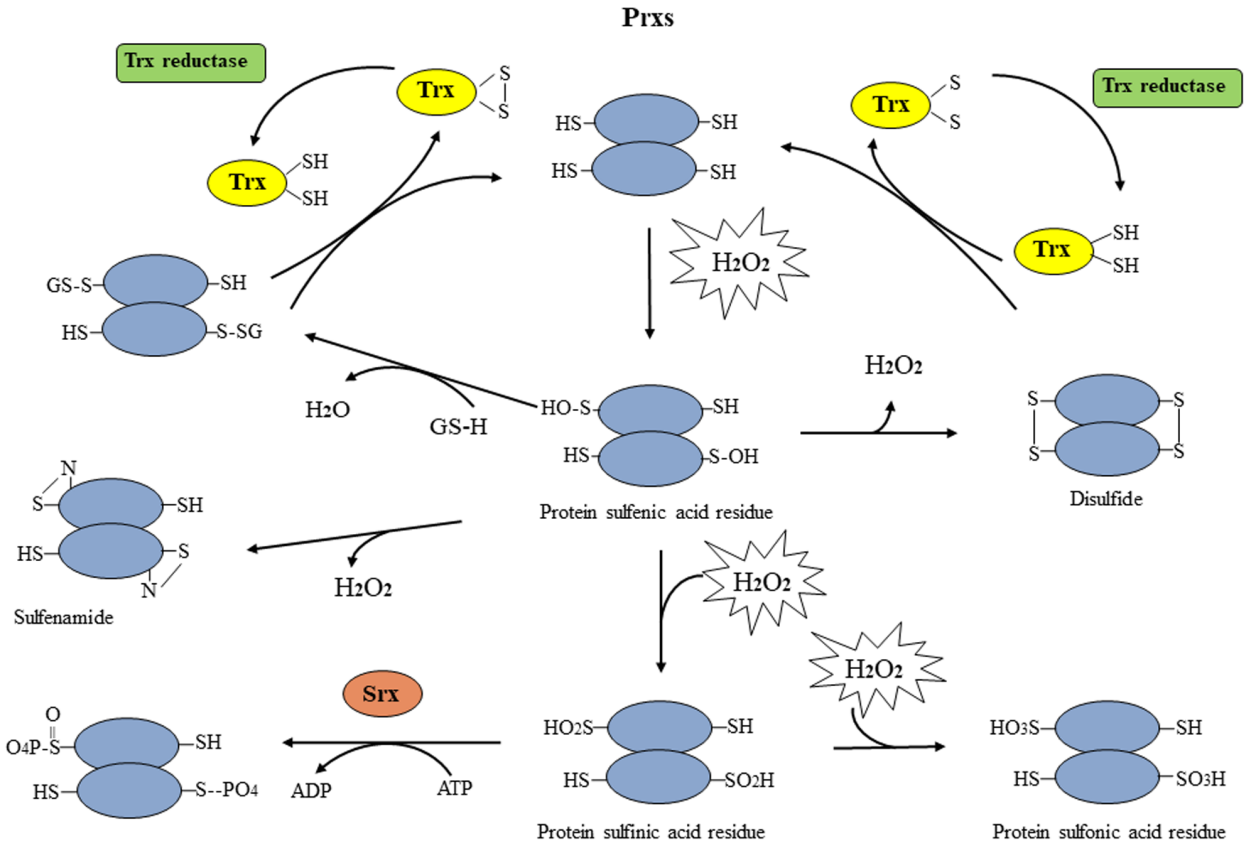

Figure 2. The involvement of the PRDX-TRDX system in the regulation of H_2O_2 metabolism.

significance. The resulting conformational changes promote further attack of cysteine with formation of disulfide bonds within Prxs subunits. Prx-disulfide is converted into the reduced form by Trx, which is regenerated by Trx-R. –SOH can interact intramolecularly with nitrogen of the nearest serine residue with formation of cyclic sulfenylamide, which is observed during oxidation of protein tyrosine phosphatases. The sulfenyl acid residue can interact with GSH with formation of a –SSG compound [8, 72].

In eukaryotic Prxs, the C-terminal domain stabilizes the –SOH region; this promotes further oxidation with formation of sulfinic acid Cys-SO_2H. This process is considered as hyperoxidation due to H_2O_2, and formation of $–SO_2H$ is considered as an irreversible reaction of cysteine oxidation. However, sulforedoxins (Srxs), identified as cysteine sulfinyl reductases, can reduce the Prx $–SO_2H$ structure and its functional activity [75]. It should be noted that the superoxidation process is not a privilege of only Prxs. It is also characteristic of reactive cysteine residues of other proteins [75]. Summarizing the structural and catalytic properties of Prxs, it should be noted that the Prx actions could be characterized as a catalytic cycle. Depending on the oxidation stage, changes in the conformational status of the protein are observed during these reactions [73, 76, 77].

Analyzing the thiol system involved in the regulation of cellular redox homeostasis one should take into consideration the localization of its isoforms in cell compartments. For example, GPx1 is involved in H_2O_2 reduction in the mitochondrial matrix, and GPx4 acts in the cytosol and mitochondria, protecting cells from lipid peroxidation. Depletion of mitochondrial GSH in both neurons and astrocytes is accompanied by an increase in H_2O_2, loss of mitochondrial membrane potential, and cell death through neurodegeneration. Trx1, localized in the cytosol, is translocated to the nucleus during OS [78]. However, cytosolic and nuclear Trx1 are regulated independently of each other. Trx2 is localized mainly in mitochondria and participates in mitochondrial redox homeostasis. The regulation of mitochondrial Trx2 differs from that of cytosolic and nuclear Trx1 [78, 79].

It should be noted that reduced and oxidized Trx (Trx-SH/Trx-SS), as well as GSH/GSSG, control the redox system, but exhibit differences in their actions independently of each other. The significance of these differences is currently not fully determined and, according to some researchers, the data obtained should be considered as a general paradigm in assessing redox control of cells during proliferation, differentiation and apoptosis [43, 78–80]. Prx3 and Prx5 are two isoforms that are actively involved in the destruction of not only H_2O_2, but also organic hydroperoxides and peroxynitrite. The effect of Prx in mitochondria is significantly more pronounced compared to GSH/GPx.

A significant decrease in Prx3 expression was found in AD [8, 80, 81]. Prxs were shown to act as general sensitive transducers of H_2O_2-dependent oxidized equivalents in redox signaling. Prx1 accelerates ASK1 oxidation due to the transit formation of Prx1-ASK1 disulfide [69, 82]. Prx can participate in the oxidation of transcription factor STAT3, which is converted into oxidized dimers and tetramers with weakened activity [65, 83–85].

Analyzing the effect of H_2O_2 on the redox balance, it should be noted that most thiol groups of cysteine residues of proteins are characterized by a high pK_a value (about 8.5), which makes them resistant to oxidation by H_2O_2. However, some cysteine residues are located near positively charged amino acids, and then pK_a fluctuates within 4–5. Under these conditions, the disulfide group exists as the thiolate anion $Cys–S^-$, which is very sensitive to oxidation. It is believed that the thiolate anion is more prone to oxidation by ROS than reduced thiols [41, 86, 87]. These reactions result in the formation of oxidation products such as sulfenic (SOH), sulfinic (SO_2H), and sulfonic (SO_3H) acids, external or internal (inter or intra) protein disulfides. In the presence of oxidants, protein thiols can form a mixed form of disulfides with reduced GSH. As a result of these reactions, GSH can form reactive intermediates including glutathione sulfenic acid (GSOH), glutathione disulfide (GSSG), and glutathiol radicals. They all can react with other GSH or protein thiols thus forming mixed disulfides [86].

Sensitivity to oxidative modification may depend on the reactivity of individual oxidants that affect the protein structure and, first of all, neighboring amino acid residues or the location of metal ions. Additionally, cysteine residues can be modified through alternative (so-called “redox-base”) modifications (SNO, SOH, SSC, S–S), which can have a differential effect on different protein functions. In fact, cysteine is considered a unique molecular switch for the processing of various signals in the cell [88–90].

Numerous studies of Cys modification and redox regulation suggest that redox-sensitive regulatory cysteine residues of proteins play a critical role in cell signaling and control as a part of the redox network structure. They can be involved in numerous signaling pathways through direct or indirect interaction with various protein traps controlled by GSH and Trx redox systems [8, 57, 59].

Although sulfhydryl groups of proteins play the main role in redox regulation in addition to the thiol system, one cannot exclude the influence of other amino acid residues of these proteins, which under conditions of increased ROS generation during information transfer, can also be subjected to oxidation. This is especially true for structural proteins involved in the construction of cell membranes and the formation of active ligand-receptor complexes [42, 90].

3. THE STATE OF THE REDOX SYSTEM (H_2O_2 AND THIOL SYSTEM) DURING NEURODEGENERATION PROCESSES

It is known that cells have a balanced defense system that allows the organism to maintain its ability to survive in constantly changing conditions. The processes of synaptic plasticity and the functioning of neurotrophins as growth factors are closely related to the redox signaling system and, consequently, to ROS and the thiol system. This is determined, in particular, by H_2O_2 involvement in the control of many cellular processes, including proliferation, apoptosis, and aging of brain cells.

Normally, during mild stress, the defense systems of the body maintain the vital activity of cells and subsequently develop tolerance. In the case of severe stress effects accompanying any pathological process, cell growth may stop, followed by adequate restoration of damage. If the inhibition of proliferation processes is permanent, the cell enters the aging stage. All this ultimately leads to cell death, which can manifest itself either in a slower, highly regulated process of programmed cell death (apoptosis), or in catastrophically rapidly developing necrosis. In nervous tissue, this is associated with the initiation and progression of neurodegeneration processes under conditions of OS and the development of neurodegenerative diseases (AD, PD, vascular dementia, depressive state, cognitive impairment against the background of dystrophic syndrome, etc.) [5, 91–94].

During neurodegeneration processes associated with occurring OS development, the organized system of ROS maintenance at the physiological level is impaired; first of all, this imbalance affects H_2O_2, as one of the second messengers of the sequential transmission of any signals to the cell. This is manifested in the intensive generation of ROS, oxidative destruction of lipids, proteins, carbohydrates, and impairment of the functioning of the enzymatic and non-enzymatic AOD, thiol status. The degree of expression of these changes depends on the intensity and duration of pathological effects [93–95].

Our previous studies in AD patients at different stages of the disease revealed not only an increase in the degree of oxidation of lipids and proteins, but also an imbalance in the enzymatic system; this contributes to additional generation of H_2O_2, an impaired ratio of the thiol system components [96, 97].

Intensive generation of ROS in nervous tissue during neurodegeneration is associated with disorders of the mitochondrial tissue respiration system, metabolism of arachidonic acid, catecholamine and xanthine oxidase, and an inflammatory response in microglia [3]. Thus, peroxidation of membrane phospholipids leads to the formation of hydroperoxides, which can not only inactivate proteins, but also change the physical properties of the membrane. It is believed that cleavage of phospholipids in cell membranes is an early sign of developing neurodegeneration [98].

We have found a decrease in the concentration of arachidonic acid, which is part of the omega-6 acids, in the blood plasma of patients at the initial stages of AD. This may be due to formation an “uncontrolled cascade” of arachidonic acid, followed by its sharp depletion, impaired structures of the cell membrane itself. This is of great importance for nervous tissue characterized by a high level of PUFAs [99].

Thus, during neurodegeneration processes under conditions of OS development, the finely organized system of maintaining the redox status at the physiological level is altered and this leads to profound disturbances in the structure of the nervous tissue.

CONCLUSIONS

The thiol system and associated ROS (particularly H_2O_2) play the central role in the redox status of the cells. Normally, a dynamic balance is maintained between the thiol system and H_2O_2. This is ensured by maintaining the physiological level of individual components of the thiol system, H_2O_2 and their concerted interaction at all stages of information transfer. This is one of the determining factors of the functioning of H_2O_2 as a second messenger, participation in the regulation of phosphorylation/dephosphorylation, glutathionation/deglutathionation, activity of transcription factors, hydrolysis of phospholipids, etc. Accordingly, this leads to the activation of the main links of the cell cycle and activation of proliferation processes, triggering apoptosis and establishment of a dynamic balance between proliferation and apoptosis (Fig. 3).

Long-term stress exposure and the development of pathological conditions are accompanied by impaired functioning of evolutionarily formed processes. Compounds playing key role in the sequential transmission of information begin to exhibit a toxic effect. These include, in particular, the components of the POS, H_2O_2, 4-HNE. Under certain conditions, their toxic effect can be aggravated by individual components of the AOS, such as SOD, GSH, etc., exhibiting prooxidant activity. Under certain conditions, GSH can be a source of highly reactive thiyl radical [88, 100, 101].

Thus, in pathological conditions of the body, a number of chemical compounds that play a key role in metabolic processes can exhibit a toxic effect at the level of first, second messengers third link of information transmission and, accordingly, lead, first of all, to a impairments in the ratio of proliferation and apoptosis with predominance of apoptosis.

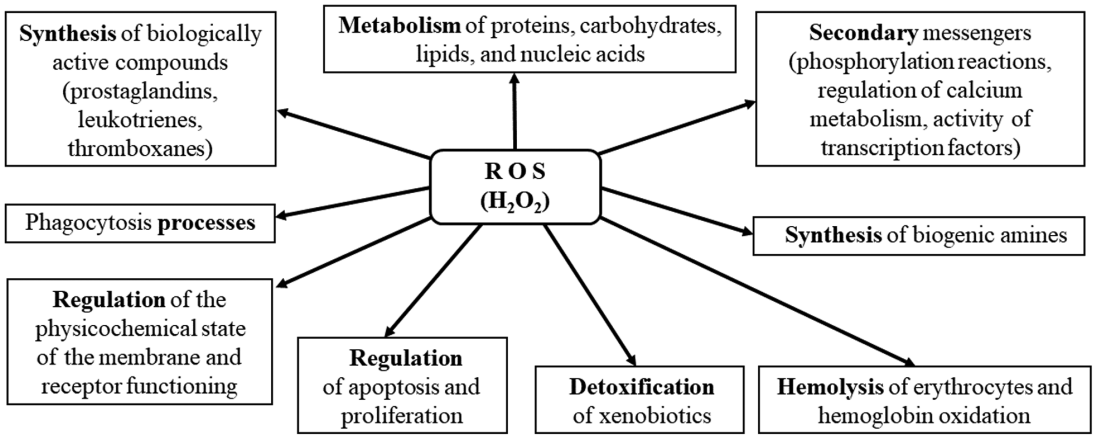

Figure 3. The effect of hydrogen peroxide on the functional activity of cells.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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РОЛЬ СИГНАЛЬНОЙ РЕДОКС-СИСТЕМЫ (H_2O_2 И ТИОЛОВАЯ СИСТЕМА) В РЕГУЛЯЦИИ ФУНКЦИОНАЛЬНОЙ АКТИВНОСТИ НЕРВНОЙ ТКАНИ В НОРМЕ И ПРИ ПАТОЛОГИИ

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Обзорная статья посвящена роли активных форм кислорода (АФК) и тиоловой системы в регуляции функциональной активности нейронов. Проанализирована их контролирующая функция в процессах синаптической пластичности и функционирования нейротрофинов, участие в таких клеточных процессах как пролиферация, апоптоз и старение клеток. Подробно рассмотрена роль отдельных компонентов тиоловой системы, их связь с H_2O_2 в регуляции сигнальной редокс-системы клеток. Обобщены литературные данные, отражающие участие H_2O_2 в регуляции ключевых метаболических каскадов нервной ткани. Анализ литературных и собственных данных позволил прийти к выводу о двойственной природе компонентов стресс-системы в зависимости от функционального состояния организма. Проявление их токсического действия, в первую очередь, зависит от их концентрации и химической структуры.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: оксидативный стресс; активные формы кислорода; пероксид водорода; сигнальная тиоловая редокс система; нервная ткань

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