# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

**4,800**
Open access books available

**122,000**
International authors and editors

**135M**
Downloads

Our authors are among the

**154**
Countries delivered to

**TOP 1%**
most cited scientists

**12.2%**
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

## Interested in publishing with us?
## Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 23

# Use of CoA Biosynthesis Modulators and Selenoprotein Model Substance in Correction of Brain Ischemic and Reperfusion Injuries

Nina P. Kanunnikova, Natalya Z. Bashun and Andrey G. Moiseenok

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/46077

## 1. Introduction

Acute disruption in brain blood circulation is a widespread cause of death and the most frequent cause of health loss in most countries of the world. About 6 millions of people suffer from stroke every year and this number is constantly increasing. Stroke has a high mortality rate – up to 30% of patients die. Only about 20% of surviving patients manage to return to their previous occupation. Most of patients are unable to take care of themselves and need help of relatives or medical personnel [1, 2]. About 80-85% of all cases of stroke are ischemic strokes. Therefore protecting brain from ischemia-induced damage is in the focus of modern neuropathology and neurosurgery studies, especially due to the increase in the number of neurosurgical operations which might cause additional blood flow impairements.

The severity of injuries of physiological reactions and biochemical processes caused by blood flow impairements depends on the degree of blood flow disruption in brain (fig.1) [1, 3].

| Blood brain flow, ml/100 g/min | Parameters |
|---|---|
| 60-80 | Standard |
| 35-60 | Decrease of protein synthesis, selective gene expression |
| 20-35 | Lactate acidosis, cytotoxic edema |
| 10-20 | Energic deficiency, glutamate excitoxicity |
| 0-10 | Anoxic depolarization, necrosis, apoptosis |

**Figure 1.** Correspondence between brain tissue changes and blood flow disruption

Decline of partial pressure of oxygen, significant decrease of ATP and glucose levels, membrane depolarization, extremely high levels of extracellular glutamate and intracellular calcium ions - all these factors contribute to development of the aforementioned injuries in the nervous tissue [4, 5, 6]. For example, higher level of calcium ions leads to stimulation of phospholipases and proteases, and activation of glutamate NMDA-receptors which in turn increase activity of nNoS and eNOS isoforms. As the result, amplification of lipoperoxidation takes place.

Disruption of electron transfer and oxidative phosphorilation within mitochondria are the first manifestations of ischemia-induced damages in the brain [7, 8, 9, 10], and the basic object of the injuries are presumably mitochondrial membranes [11, 12, 13, 14]. On this basis, ability of the brain to restore its functions following ischemia and reperfusion depends mainly on three processes - depletion of energic resources, excessive accumulation of excitatory amino acids [15, 16, 17], and formation of reactive oxygen species caused by leakage of electrons from intermediate links of respiratory change [18, 19, 20].

## 2. Features of oxidative stress in brain tissue during ischemia-reperfusion

Brain ischemia causes formation of free radical forms of oxygen which induce damage of neuronal membranes and biomacromolecules, particularly nucleic acids and proteins. Brain tissue has heightened disposition to development of oxidative stress. Brain cell membranes have high concentrations of polyunsaturated fatty acids which are the main substrate of free radical reactions [21, 22, 23]. When a free radical appears in membrane chance for its interaction with fatty acid is increased as a number of unsaturated links is rised. Unsaturated fatty acids provide more fluidity for membranes, therefore their changes caused by more active lipoperoxidation lead to increase of their viscosity and injuries of their barrier functions. It is known that synapse plasmatic membranes contain higher level of polyunsaturated fatty acids than myelin membranes. Many functionally important neuronal proteins are membrane-bound and depend on lipid environment. Simultaneously, system of antioxidant protection in brain has obviously less capacity than in other tissues, and enzymatic components of the system in brain are more sensitive to oxidative action [24, 25].

The second danger of lipoperoxidative activation in brain lies in the fact that disruption of nerve membrane integrity leads to increasing release of “excitotoxic” transmitters, such as glutamate, aspartate, etc [15, 16, 26-28].High rate of biogenic amine metabolism in brain leads to formation of ROS [29]. For example, monoamine oxidase reaction is linked with $H_2O_2$ formation. This phenomenon may be an additional source for generation of active radical products which are able to initiate lipoperoxidation in the presence of metals with variable valence. Dopamine, its precursor L-DOPA, 5-hydroxytraptamine, and norepinephrine may generate $O^{2\bullet-}$ not only, but quinones/semiquinones, too, which may decrease GSH level and bound with protein SH-groups. Oxidation can be catalized by transitional metal ions. Maximal increase for free radical generation and following activation for lipoperoxidation takes place in postischemic time – during recovery of blood circulation in brain tissue [30-33]. Nevertheless, possibility for formation of free radicals at

earlier stage of brain damage exists during ischemia, too [34]. Enhancement of redox state of mitochondrial respiratory chain in these conditions gives an opportunity for oxygen to interact with intermediate components of the respiratory chain, for example ubisemiquinone [7]. This process takes the path of one-electron reduction of molecular oxygen and leads to formation of superoxide-anion. Consequently, heightened formation of free radicals may take place in tissues with insufficient blood circulation and decreased partial oxygen pressure [35]. Studies in mice and rats with genetic deficiency of superoxide dismutase confirmed the important role of free radicals in neuronal death/survival during brain ischemia [36, 37].In the postischemic period (during recirculation) when oxygen actively absorbs by brain tissue, oxygen radicals generation is caused by activation of enzymatic processes, too (arachidonic acid cascade, xantine oxydase system, activation of NADPH-oxydase in polymorphonuclear leucocytes) [38-40].

The fact that ischemia itself is unable to increase level of lipoperoxidation intermediate products is not surprising because during hypoxia amount of molecular oxygen is insufficient for observable activation of lipoperoxidation in brain tissue. Nevertheless, in these conditions the amount of hydroxyperoxides is increased and lag period for lipoperoxidation activation becomes shorter, which serves as evidence for decrease of antioxidant protection and increased formation of superoxide oxygen anion in brain tissue [41]. Herewith level of endogenic antioxidants in brain may be unchanged [42, 43]. For example, $\alpha$-tocoferol level in rat brain is unchanged following 80 min after occlusion of middle cerebral artery and subsequent reperfusion. Unchanged levels of antioxidants were observed following bilateral occlusion of arteria carotis and reperfusion in gerbils, too [44, 45].

Recently a concept on polyfunctional physiologic role of free radicals in organism and in brain especially, is declared [42, 43, 46-48]. On the one hand, they act on key cell enzymes and receptors inside cells and cause destructive processes in tissues. On the other hand, they play a role of second messengers and may help with cell adaptive reactions to changed environmental conditions. Therefore low efficiency of antioxidant therapy by substances which bound free radical excess during ischemic injury treatment is not surprising [49, 50, 51]. In addition, these drugs have low bioavailability and must be used for at least several weeks before any effect can be observed [52, 53, 54-56].

It is necessary to emphasize that the main defense from excessive amounts of free radicals formed within cells is the action of antioxidant protection enzymes, such as selenoproteins, but not the action of low molecular wieght antioxidants. Under normal conditions these enzymes are sufficient for maintenance of low safe levels of free radicals, but in reperfusional conditions their activity is insufficient for maintenance pro- and antioxidant balance. Earlier attempts to administer substances of superoxide dismutase and catalase enzymes to animals in experimental models were unsuccessful because they poorly penetrate blood-brain barrier and cell membranes [51, 53].

Further research of neuroprotection in this direction is not very promising because activation of lipoperoxidation in phospholipid structures of nerve cell membranes is

eliminated by the system of superoxide dismutase – catalase to a small degree [53]. Detoxication in these structures is primarily carried by enzymes of glutathione cycle, selenium-cystein-comprising glutathione peroxidases [49, 54, 55, 57-59].

## 3. Role of glutathione in mechanisms of antioxidant protection in brain

Glutathione cycle is the most important antioxidant system in brain cells [59-66]. Glutathione protects cells against reactive oxygen, nitrogen and other species. As an antioxidant it is involved in the detoxication of malonic dialdehyde, 4-hydroxy-2-nonenal and other products of lipoperoxidation. The glutathione couple GSH/GSSG takes part in maintaining cellular redox status [67, 68]. Glutathione is presumably a key participant of the defense system in brain cell [69-71].

Increased level of oxidized form of glutathione and changes of glutathione system activity occur at early stages of oxidative stress and may be marks of the severity of oxidative stress [71-75]. Hydroxyl radical and nitric oxide or peroxynitrite may interact directly with GSH leading to GSSG formation. Hydrogen peroxide may be removed by catalase or by glutathione peroxidase [76].

GSH is present in cytoplasma, endoplasmatic reticulum, nucleus, and mitochondria. In most of the compartments GSH is found predominantly in highly reduced state (about 99% of the total level of glutathione). Glutathione peroxidase is localized mainly in cytosol, too, whereas catalase is found mostly in peroxisomes. The affinity of glutathione peroxidase for $H_2O_2$ is one to two orders of magnitude higher than that of catalase, and catalase is less active in brain than in other tissues.

GSH is synthesized from cysteine, glutamate and glycine. Neurones have lower GSH level and use a more limited list of substrates for GSH synthesis, but they use glutamine for GSH synthesis more effectively than astrocytes because they have glutaminase for formation of glutamate from glutamine. Neurones can not absorb cystine but they actively carry off cysteine [65], so availability of cysteine influences at the GSH level inside neurones. At the same time maximal rate for GSH synthesis within astrocytes is observed in the presence of glutamate, cystine and glycine.

GSSG restores by glutathione reductase into GSH in the presence of NADPH (salvage cycle), which originated mainly from pentose phosphate pathway of metabolism. About 3-5% of oxygen in brain is consumed this way.

In physiological conditions GSSG level both in neurones and astrocytes reach no more than 1% of total content of glutathione in tissue but during oxidative stress it may be about 40% of total value of the glutathione in the astrocyte culture. One astrocyte cell may effectively protect 20 neurons from peroxides but lack of glucose greatly decreases capacity of astrocytes to bind peroxides. It has been shown that pentose phosphate pathway in astrocyte culture is very sensitive to peroxide action.

Decrease of total glutathione content and decline of GSH/GSSG ratio are indicators of the severity of oxidative stress in ischemic brain tissue [67]. It is known that decrease of GSH level leads to aggravation of ischemia-induced injuries, while increase of its level leads to opposite result. Glutamate may facilitate decrease of GSH level because it inhibits use of cysteine which is required for glutathione synthesis by cells [67]. Genetic failure of a cell glutathione peroxidase makes rats more susceptible to neurotoxins and brain ischemia [68]. Excessive glutathione peroxidase expression in transgenic mice leads to prevention of irreversible hypoxia-induced changes. Decline of GSH concentration may weaken the stability of an organism to hypoxia both by inactivation of pentose phosphate way enzymes as by inhibition of thioenzymes of tissue respiration chain [76, 77]. These disruptions cause development of energy deficiency which is the main chain of biochemical mechanism of tissue hypoxia. In addition thiol-disulfide metabolism changes may form the basis for mechanisms of disconnection of the oxidation and phosphorilation processes [78-80]. As a result, use of oxygen in biological oxidation processes may be broken and become a base for pathogenetic component of intiation and generalization of oxidative stress.

## 4. Role of energy metabolism changes in mechanisms of brain tissue ischemia-induced injuries

Brain is very sensitive to disruptions of energy metabolism processes beacause brain tissue requires constant supply of energy substrates whereas sources for energy formation in brain are rather limited, turnover of metabolism is high, and metabolism is dependent on aerobic oxidation of glucose and constant supply of oxygen in a great extent [81, 82] Maintenance for electric neuron activity and rate of impulse passage depend directly on presence and availability of energy substrates, too [83, 84].

Brain tissue cannot metabolize fatty acids therefore the main source for energy formation in brain is glucose. Nevertheless, during focal brain ischemia, increase of glucose level does not help cells to prevent ischemic injuries and also promotes their structural and functional damage [85]. Mechanisms of these changes include shift of pH to an acid side inside cell, increase of permeability of blood-brain barrier, infiltration of brain parenchyma by neutrophiles, accumulation of extracellular glutamate, and unfavorable corticosterone action. Intensive metabolism of glucose in the penumbra region may promote increasing acidic reaction of the medium, promote attraction of neutrophiles in the region.

Limitation of metabolic consumption of glucose in ischemic brain tissue may have protective effect, especially in such conditions when its metabolism will be faster or other source of fuel will be used. Possibilities for replacement of glucose in brain tissue are rather limited [86-89]. Lactic acid may be an alternative source for energy formation in brain in certain conditions because the glucose is metabolized presumably in glial cells whereas in neurones energy metabolism is based presumably on lactate oxidation [90, 91]. There is some evidence that the process is particularly important for maintenance of vital functions during postischemic time. For example, decrease of lactate transfer through plasmatic mebrane in brain following preliminary whole ischemia causes neurone injuries. From clinic

practice it is known that consumption of lactate or pyruvate during brain ischemia show neuroprotective actions of the substances [90, 91]. Presence of adequate concentrations of pyruvate facilitate for maintenance of stable level of membrane potentials and proton gradient on vesicular membranes [87, 92].

Brain ischemia is different from other types of ischemia because oxygen deficiency causes significant changes in the oxidating process of energy substrates which are present in brain in suffucient quantities [20, 42]. Anaerobic glycolisis as alternative way for energy supply is not substantial for supporting ATP stock in nerve tissue during compensated and decompensated stages of hypoxia [11].

Aerobic energy formation is the basic process for nerve tissue, but starts to fail before oxygen concentration falls below critical level, because hypoxia influences kinetic properties of respiratory chain enzymes. During early stages of ischemia energy functions of mitochondria already start changing: conjugacy of oxidative phosphorilation process and regulatory control by ATP becomes weaker, rate of inphosphorilated respiration increases. Shift of ratio NAD/NADH occurs to the side of NADH, as a result final stages of the Krebs' cycle are inhibited, and activation of succinate oxidase stage takes place. This way allows to maintain oxidative phosphorilation and respectively macroergic substance production at sufficient level for some time. "Oxygen hunger" already at early stages of hypoxia leads to beginning of relative "substrate hunger" - energy substrates are not being oxydated while they are still available. This is a characteristic property for ischemia [93].

There are only 2 ways of restoration of brain metabolism after stroke and hypoxia – restoration of NAD-dependent part of the Krebs' cycle and stimulation of alternative path of metabolism, succinate oxidation.

Succinic acid is an intermediate of the cytric cycle which supports formation of macroergic phosphates and reductive equivalents in the conditions with physical loadings and stress [94-97]. Oxidation of succinic acid is the most potent energy process inside mitochondria, and during stress this process becomes even more important due to succinate dehydrogenase activation. Depletion of endogenic succinic acid may be a reason explaining inability of tissue to maintain reaction of activation of energy processes for a long time [98]. If NADH and $CO_2$ are present in excess, conversion of reactions of second part of the cytrate cycle in which NADH is consumed takes place - from oxaloacetate to succinate, and that fact supports reactions of the first part of the cytrate cycle reactions which require oxidized NAD and promote for additional accumulation of succinate.

Another important result of the bioenergic hypoxia is damage of ion pump action and ion imbalance in the form of excessive accumulation of intracellular calcium, sodium, chlorine [99]. The intracellular calcium excess leads to activation of phospholipase A, damage of cell membranes and release of arachidonic acid take place. As a result, lipoperoxidation activates and causes following cell membrane damages, neuron depolarization and release of excitotoxic amino acids, especially glutamate, in extracellular space [99].

Thereby adaptive effects of succinate derivatives are related to their property to induce compensatory metabolic flows in mitochondrial respiratory chain ("succinate oxidase" way) in extreme conditions, to provide replenishment for cytoplasmatic pool by reduced forms of NAD and NADP, to accelerate ATP formation, change over energy formation from NAD-dependent to FAD-dependent way, eliminate an excess of acetyl-CoA, support activity of the Krebs' cycle in hypoxic conditions, stabilize membrane potential of mitochondria and cell membranes. Advantage of succinate oxidase way versus NAD-dependent substrates in competition for respiratory chain is amplified in the hypoxia conditions because flavines (flavoproteins) continue in oxygenated form longer than pyridine nucleotides.

Disruption of energy metabolism can be mainly observed at the stage of succinate formation. That may be caused by oxidative stress-induced changes of stable state of plasmatic and mitochondrial membranes and changes in activity of membrane-bound enzymes of the Krebs cycle and GABA bypass [100, 101]. Significant activation of the GABA bypass enzymes takes place during ischemia-reperfusion which not only causes raise of succinate formation, but also leads to increasing formation of gamma-hydroxybutyric acid through reductase reaction. GHBA has protective effect against changes of energy formation processes in brain tissue during hypoxia [102]. As activity of glutamate dehydrogenase in brain is rather low compared with other tissues, GABA bypass plays a key role in compensatory maintenance of succinate level sufficient for adequate metabolism in "succinate oxidase" way in different extremal situations, for example in brain ischemia-reperfusion conditions.

Succinic acid derivatives are effective modern antioxidants in the brain because succinate regulates activity of SDH in the Krebs' cycle and restores activity of respiratory mitochondrial chain not only, but increases microcirculation in tissues.

## 5. Role of CoA in mechanisms of neuroprotection in brain ischemia-reperfusion conditions

Beneficial effects of precursors of CoA biosynthesis, such as pantothenic acid and its derivatives, include protection from lipoperoxidation and supporting membrane structure, and these effects have been observed in radiation injury, miocard ischemia, diabetes mellitus, $CCl_4$ -intoxication, heavy hypothermia, etc [103-106]. Protective action of pantothenate derivatives have been reported in situations accompanied by oxidative stress, for example, in experimental ischemia-reperfusion of myocardium. It has been shown that antioxidative and membrane-protective effects of the pantothenate derivatives are accompanied by an activation of biosynthesis CoA system and increasing of intracellular level of a free CoA [108, 109]. Presumably, the mechanism of cell protection is CoA-dependent or realized through CoA-(acyl-CoA)-dependent biochemical reactions, including rise of intracellular glutathione level and maintenance of its redox status.

It is believed that the physiological function of CoA system is participation in formation of redox potential of glutathione and proteins, redox signaling and maintenance of biological membrane stability, especially in brain tissue [104, 105, 106].

The CoA biosynthesis system is a group of very stable continuously active self-regulated processes focused on maintaining stability of intramitochondrial CoA-SH (up 70-80% of the total cell value). This function maintains constant flow of oxidative substrates and their effective using for ATP formation in the citric acid cycle [109, 110, 111].

The lesser CoA pool in cytosol where acyl-CoA is used in biosynthetic processes (biosynthesis of phospholipids, fatty acids) is studied to a lesser extent. "Turnover" pool of the coenzyme takes part in reactions of carnitine-dependent transfer of fatty acid residues and acetate through mitochondrial membranes [105]. The main events for interrelations between specifically bound cytosolic CoA-S-S-protein, CoA-S-S-glutathione, free and proteidized glutathione take place within cytosolic compartment (including endoplasmatic reticulum) presumably due to thiol-disulfide-exchange reactions which provide stability during limited variations of redox potential and support a realization of redox sygnaling. Based on this hypothesis, the capability of CoA biosynthesis precursors in low concentrations (0.1-1 мМ) or in vivo experiments prevents lipoperoxidation activation, damages of membrane integrity initiated by different physical or chemical factors. The obligatory condition of the above-mentioned defensive effect is biotransformation of pantothenate derivatives into CoA and significant increase of intracellular GSH level. The process is highly specific because homopantothenic acid which is similar to pantothenic one in terms physical and chemical properties can not transform into CoA, does not increase intracellular glutathione level and does not protect plasmatic membrane stability in cell culture [112].

Additional effects of the CoA precursors in defense of lipoperoxidative activation have also been observed. These include rapid initiation of lipid biosynthesis from labeled precursors, positive influence on mitochondrial energy parameters, as well as protection against apoptosis activation caused by free radical oxidation products [113, 114]. Redox sygnaling process controls the initiation and direction of these processes. The redox potential is determined by the glutathione system predominantly [105, 115]. This data may confirm that the CoA biosynthesis system is the most important factor of intracellular stability of GSH level [103, 105].

Maintenance of sufficiently high CoA biosynthesis activity has an important role in brain because acetyl-CoA is used not only as the main way for glucose intake into the Krebs cycle but is also a substrate for acetylcholine synthesis. The relationship between ability for CoA biosynthesis and activity of acetylcholine metabolism within cholinergic neurones may be an important factor in modulation of their sensitivity to damaging influences [103].

Among the necessary conditions for successful biosynthesis of acetyl-CoA, are presence of CoA precursors inside mitochondria, and also the presence of carnitine which transfers acetyl radicals into mitochondria. Under oxidative stress conditions when a lot of lipoperoxide products are released from membranes as a result of phospholipase activation, the potential for CoA sequestration increases, which includes appearance of hard to metabolize acyl-CoA derivatives. Under these conditions the role of carnitine increases. CoA and L-carnitine are among the key factors of intramitochondrial metabolism of fatty and

organic acids, and relationship between their levels represents an essential mechanism for cytosol-mitochondrial process of acyl residue activation and transfer [110, 116]. Based on the main localization of a total CoA within mitochondrial matrix, while carnitine is located in cytosol, the molar ratio of CoA/carnitine may have significant functional role for decrease of long-chain acyl-CoA in cytosol and their accelerated utilization in a β-oxidation process.

Generation and use of succinyl-CoA in mitochondria have a special role for mitochondrial oxidation regulation during oxidative stress caused by ischemia-reperfusion [107, 108]. Chances for alternative succinyl-CoA biosynthesis increase significantly when CoA biosynthesis processes are activated in cytosol. In view of this, data on the effects of carnitine on the activity of the key enzyme of CoA biosynthesis, namely patothenate kinase, has high significance. It has been shown that L-carnitine cancels out inhibitory action of physiological concentrations of dephospho-CoA, CoA-SH, and acetyl-CoA on pantothenate kinase. This enables directed regulation of CoA-dependent metabolic processes following simultaneous injection of carnitine substances and pantothenate derivatives - precursors of CoA biosynthesis - namely, panthenol [117, 118].

Study of changes of CoA level during ischemia or ischemia-reperfusion showed markedly stable ratio and levels of free CoA, short-chain acyl-CoA, and on the whole the acid-soluble fraction of CoA, in hemispheres during ischemic damage [117]. Following 2-3 h of brain ischemia, the free CoA level declines. This diminishment with simultaneous decrease of the acid-soluble CoA fraction achieves maximal reduction within 24 h under continued conditions of reperfusion (reoxygenation). These results confirm significance of the CoA system in pathogenic mechanisms of reoxygenation-reperfusion syndrome development.

CoA is one of the fundamental metabolism factors, and its biosynthesis and catabolism are subject to rigid control on the cell level. Therefore, as a rule, changes of particular CoA forms may happen only under extreme conditions and after prolonged period of time, sufficient to cause imbalance in metabolism regulation systems in the cell. Such imbalance starts to influence the CoA system during ischemia no earlier than one hour after occlusion of arteria carotis.

Data on the key role of the CoA biosynthesis system in maintaining redox potential of the glutathione system, neuronal membrane stability and defense of nitroperoxide acyl-CoA gives rationale to the use of CoA precursors in treatment of ischemia and ischemia-reperfusion-induced damages in the brain tissue.

## 6. Role of selenium in mechanisms of antioxidant protection for brain

Selenium is an essential microelement in different brain functions [119-124]. Neuroprotective potential of selenium is realized through the expression of selenoproteins: glutathione peroxidase, thioredoxine reductases, methionine sulfoxide reductases, selenoproteins P and R, which participate in regulation of the oxidation-reduction state of the neurones and glial cells under both physiologic conditions, and during oxidation stress [125, 126, 128]. Selenium regulates antioxidative processes in the CNS, protects brain tissue

from neurodegenerative injuries during Alzheimer and Parkinson diseases, prione diseases, has antiischemic and angiogenic actions, etc. Insufficient level of selenium intensifies damages of neuron functions and structure caused by different endogenic and exogenic affections and leads to some neurodegenerative pathologies [122, 129-132].

The biological role of selenium is explained by the selenium presence in active sites of selenium-related enzymes [121, 133], which protect brain tissue during oxidative stress. Expression extremely diverse Se-containig proteins is observed in the brain. Selenoprotein P is required for transfer of selenium into the brain, and the brain selenium level is strictly dependent from an expression of selenoprotein [129]. Activity of Se-dependent enzymes in the brain is maintained at rather stable levels even during profound selenium deficiency, owing to the presence of unique Se-transport system in the brain (proteins containing selenium-cysteine, Se-transported protein of a Golgi apparatus). This system achieves its maximum value in hypothalamus.

Injections of selenium-containing compounds lead to an increase of activities of glutathione peroxidase and thioredoxin reductase, decrease of lipoperoxidation processes, cell defense from apoptosis [122, 126, 127]. Selenium ions activate oxidative-reductive enzymes of mitochondria and microsomes, take part in ATP synthesis, in electron transfer from hemoglobin to oxygen, maintain cysteine turnover, enhance $\alpha$-tocoferol action.

## 7. Metabolic approaches to correction for brain ischemia-reperfusion-caused injuries

Steady advances in the neurosciences have elicidated the pathophysiological mechanisms of brain ischemia and have suggested many therapeutic approaches to achieve neuroprotection in the acutely ischemic brain that are directed at specific injury mechanisms [134-136]. Nevertheless, methods of protection of ischemia and reperfusion-induced damages are still lacking [ 51, 137, 138]. Search for new ways of neurodefense during brain ischemia-reperfusion is necessary due to the absence of sufficient protective activity in the most substances with specific focus in clinical conditions: controlling excitotoxic effects of neurotransmitter amino acids (modulators of glutamic acid receptor activity and Ca-channels), regulating redox status of cells, as well as presence of high toxicity in the most anti-ischemic medicines [51, 139-141]. In the past two decades, numerous attempts were made to use different substances with the effect on Ca level in a cell and glutamate extracellular level, aiming to apply these as drugs for ischemia-induced injuries treatment, but they have not been successful in men [51, 139-141]. For example, in experimental models, blockators of NMDA- and AMPA-receptors of glutamate exhibit high protective action, but they have strong side-effects and weak protective effects in humans, especially blockators of NMDA-receptors. The role of glutamate in neurotoxic phenomena during ischemia is known to be significant, but usage of glutamate receptor antagonists is rather problematic [51]. There are ongoing studies of Mg substances which block NMDA-receptors, as well as with blockators of AMPA-receptors. There have been recent proposals to combine usage of several drugs with different mechanisms of action. All of the above

drugs have a common property – rather high toxicity. Therefore, usually a certain combination of drugs is applied in order to minimize their toxicity and maximize effectiveness [140].

Substances for metabolic therapy may be particularly useful during treatment of brain blood circulation injuries in the case of their simultaneous application with specific medicines because they have no toxic effects and may be used safely for prolonged period [51, 142, 143]. Apart from these drugs, compounds for so-called restoration therapy may be used. Their effects include restoration of metabolism and blood flow in damaged region. Application of the metabolic substances that help to maintain energy metabolism and redox status of glutathione system may be useful for remedying damages to the brain after ischemia-reperfusion [51, 143]. Previously we have shown high efficacy of pantothenic acid derivatives – CoA precursors, as a means of protecting cell membranes from different types of oxidative stress [117, 118, 144]. D-panthenol presents an important substance in this respect because it penetrates into the brain through blood-brain barrier easily and is converted into pantothenic acid, 4-phosphopantothenic acid, CoA, and after that into acyl-CoA (acetyl-, malonyl-, succinyl-CoA), which have high metabolic activity. These effects create the preconditions for stabilization of CoA-dependent processes of membrane phospholipid biosynthesis, neurotransmitter biosynthesis, regulation of energic processes, etc [118].

The efficacy of panthenol as a neuroprotector within a stroke model in rats has been demonstrated [117, 118, 144]. Panthenol not only decreased the volume of infarction, but also diminished neurological deficiency in animals [103]. Fairly high protector activity of D-panthenol was observed in respect to changes of energic metabolism and glutathione system activity during brain ischemia-reperfusion. Protective effects of pantothenic derivatives is not related to their action as free radical scavengers, however. They act primarily as CoA precursors, whereas CoA accelerates various metabolic pathways, such as biosynthesis of glutathione, which constitutes one of the main systems of cell protection against oxidative stress.

Succinic acid is essential for keeping energy formation processes stable in the brain under extreme conditions [94-97]. Consequently, injections of panthenol and succinate following brain ishemia-reperfusion stabilize levels of lipoperoxidation in blood and in brain hemispheres, stabilize levels of protein SH-groups in blood, lead to significant decrease of the GSSG level and normalization of glutathione enzyme activities, as well as glutamate and glutamine metabolism in the brain to control values [118]. D-panthenol and succinate ammonium injection served to partially remedy the injuries and restore these parameters to their normal levels, especially if administered together. These effects are likely linked to activation of succinyl-CoA biosynthesis.

Attempts were made to use selenium-containing compounds for prevention of ischemia-indused injuries, such as ebselen (2-phenyl-1,2-benzisoselenozol-3), which imitated glutathione peroxidase activity [146-148]. However, under clinical conditions the ebselen was not effective. Di-(3-methylpyrazolil-4)-selenide (selecor) imitates effects of

selenoproteins, has low toxicity, and satisfactory bioavailability. Additional injections of selecor increase effects of the panthenol and succinate, especially on the lipoperoxidation parameters and activities of glutathione system and selenium-bound enzymes, on ischemia-reperfusion- induced injuries [149].

Effects of D-panthenol and succinate on decrease of lipoperoxidation activities contribute to the overall protective effects of the composition. However, it is evident that metabolic actions of the substances are related to their capasity for regulation of energy metabolism and mitochondrial respiration activity, restoration of the CoA-SH level and cell redox status, membrane-protective activity of the panthenol [118]. Addition of di-(3-methylpyrazolil-4)-selenide (selecor) to D-panthenol and succinate does has limited effect on protective antioxidant properties of the composition. It is likely that this provides additional evidence for significance of specifically metabolic effects of the composition. Increase of selenium level in blood plasma, which may contribute in maintaining of antioxidant activity of glutathione system, takes place in the absence of selenoprotein substrates, after injections of panthenol and succinate. Nevertheless, addition of a selenium source to panthenol and succinate strengthened protective potential of the substances with respect to changes for enzyme activities of glutamate and glutamine which play an important role in maintaining of energy supply and detoxication in ischemic brain tissue and confirms the antiischemic effect of the substances. Effects of di-(3-methylpyrazolil-4)-selenide may be explained less by selenium supply as a selenoprotein component rather than by its modeling of selenoprotein activity, as is known to be the case with ebselen [146-148].

Therefore it is expected that the tested substances, such as panthenol, succinic acid, selecor, and potentially other metabolic therapy drugs may have high efficacy as neuroprotectors in brain ischemia and reperfusion-induced damages.

## Author details

Nina P. Kanunnikova and Natalya Z. Bashun
*Department of Zoology and Physiology of Men and Animals,*
*Yanka Kupala's Grodno State University, Grodno, Republic of Belarus*

Andrey G. Moiseenok
*National Center for Foodstuffs, National Academy of Sciences of Belarus, Minsk, Republic of Belarus*

## 8. References

[1] Gusev EI, Skvortsova VI (2001) Brain ischemia. Moscow. Medicina. 328 p (rus).
[2] Breton RR, Rodriguez JCG (2012) Excitoxicity and oxidative stress in acute ischemic stroke. Acute ischemic stroke. Ed.JCG Rodriguez: 29-58.
[3] Heiss WD (1983) Flow threshold of functional and morphological damage of brain tissue. Stroke. 14: 329-331.

[4] Choi DW (1995) Calcium: still center stage in hypoxic-ischemic neuronal death. Trends Neurosci. 18: 58-60.
[5] Rayevsky KS, Bashkatova VG (1996) Oxidative stress, apoptosis and brain damage. Neirokhimia 13(1): 61-64 (rus).
[6] Rothman SM, Olney JW (1987) Excitotoxicity and the NMDA receptor // Trends Neurosci. 10: 299-302.
[7] Doubinina EE (2003) Role of oxidative stress in pathological states of nervous system. Uspekhi Funkc.Neirokhimii.Ed. Dambinova SA, Arutiunian AV. StPetersburg.: 285–301 (rus).
[8] Lazarewicz J, Strosznajder J, Gromek A (1972) Effects of ischemia and exogenic fatty acids on the energy metabolism in brain mitochondria. Bull.Acad.Pol.Sci.Biol. 20: 599-606.
[9] Strosznajder J (2005) Czynniki biochemiczne inicjuace niedokrwienie. Mozg a niedokrwienie. Pod red. J. Strosznajder, Z. Czernicki. Wydawnictwo PLATAN. Krakow: 7-15.
[10] Zavalishin IA, Zakharova MN (1996) Oxidative stress is a general mechanism of damages in nerve system diseases. Zh. Neurol. Psychiatr. 96(2): 111–114 (rus).
[11] Lin MT, Beal MF (2006) Mitochondrial disfunction and oxidative stress in neurodegenerative diseases. Nature. 443: 787-795.
[12] Andreyev AYu, Kushnareva YuE, Starkov AA (2005) Mitochondrial metabolism of reactive oxygen species. Biochemistry. 70 (2): 200–214.
[13] Beal MF (1996) Mitochondria, free radicals, and Neurodegeneration. Curr. Opin. Neurobiol. 6: 661–666.
[14] Shinder AF, Olson EC, Spitzer NC, Montal M (1996) Mitochondrial disfunction is a primary event in glutamate neurotoxicity. J.Neurosci. 16: 6125-6133.
[15] Sopala M, Danysz W (2005) Rola ukladu glutaminianergicznego w ischemicznym uszkodzeniu mozgu // Mozg a niedokrwienie / Pod red. J. Strosznajder, Z. Czernicki // Wydawnictwo PLATAN. Krakow: 47-65.
[16] Benveniste H et al (1984) Elevation of extracellular concentrations of glutamate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. J.Neurochem. 43: 1369-1374.
[17] Choi DW (1988) Glutamate neurotoxicity and diseases of the nervous system. Neuron 1: 623-634.
[18] Pelligrini-Giampietro DE, Cherici G, Alesiani M, Carla V, Moroni F. Excitatory amino acid release and free radical formation may cooperate in the genesis of ischemia-induced neuronal damage. J.Neurosci. 10: 1035-1041.
[19] Boldyrev AA (2003) Role of active species of oxygen in neuron vital functions. Uspekhi physiol.nauk. 34(3): 21–34 (rus).
[20] Boldyrev AA, Kukley ML (1996) Free radicals in normal and ischemic brain. Neirokhimia. 13(4): 271–278 (rus.).

[21] Kinuta Y, Kikuchi H, Ishikawa M, Kimura M, Itokawa Y (1989) Lipid peroxidation in focal cerebral ischemia. J.Neurosurg. 71: 421-429.
[22] Boldyrev AA (1998) Mechanisms of brain defense from oxidative stress. Priroda. 3: 26-34 (rus).
[23] Hayashi M. (2009) Oxidative stress in developmental of brain disorders. Neuropathology. 29(1): 1–8.
[24] Yamamoto M [et al.] (1983) A possible role of lipid peroxidation in cellular damages caused by cerebral ischemia and the protective effect of alpha-tocopherol administration. Stroke. 14: 977-982.
[25] White BC et al (2000) Brain ischemia and reperfusion: molecular mechanisms of neuronal injury. J.Neurol.Sci.179(S1-2): 1-33.
[26] Siesjo BK, Zhao Q, Pahlmark K, Siesjo P, Katsura K, Folbergrova J (1995) Glutamate, calcium and free radicals as mediators of ischemic brain damage. Ann.Thorac.Surg. 59: 1316-1320.
[27] Dugan LL, Choi DW (1994) Exitotoxicity, free radicals and cell membrane changes. Ann. Neurol. 35: 17-21.
[28] Oh SM, Betz L (1991) Interaction between free radicals and excitatory amino acids in the formation of ischemic brain edema in rats. Stroke 22: 915-921.
[29] Zeevalk GD, Bernard LP, Nicklas WJ (1998) Role of Oxidative Stress and the Glutathione Systems in Loss of dopamine Neurons Due to Impairment of Energy Metabolism. J. Neurochem. 70(4): 1421–1429.
[30] Fiodorova TN, Boldyrev AA, Gannushkina IV (1999) Lipoperoxidation in experimental brain ischemia. Biokhimia. 64(1): 94–98 (rus).
[31] Kukley ML, Stvolinsky SL, Shavratsky VCh (1995) Lipoperoxidation in rat brain during ischemia. Neirokhimia. 12(2): 28–35 (rus).
[32] Rafols JA, Krause GS (2000) Brain ischemia and reperfusion: molecular mechanisms of neuronal injury. J.Neurol.Sci.179(S1-2): 1-33.
[33] Sakamoto A, Ohnishi ST, Ohnishi T, Ogawa R (1991) Relationship between free radical production and lipid peroxidation during ischemia-reperfusion injury in the rat brain. Brain Res. 554: 186-192.
[34] Kitagawa RM [et al.] (1990) Free radical generation during brief period of cerebral ischemia may trigger delayed neuronal death. Neuroscience. 35: 551–558.
[35] Fridovich I (1995) Superoxide radical and superoxide dismutases. Annu.Rev. Biochem. 64: 97-112.
[36] Chan PH (2004) Oxidant stress as a molecular switch in neuronal death/ survival after stroke. J.Neurochem. 88(Suppl): S6-4.
[37] Murakami K, Kondo T, Kawase M, Sato S, Chen SF, Chan PH (1998) Mitochondrial susceptibility to oxidative stress exacerbated cerebral infarction that follows permanent focal cerebral ischemia in mutant mice with manganese superoxide dismutase deficiency. J Neurosci. 18: 205-213.

[38] Clemens JA (2000) Cerebral ischemia: gene activation, neuronal injury, and the protective role of antioxidants. Free Rad.Biol.Med. 28: 1526-1531.
[39] Nita D Al et al. (2001) Oxidative damage following cerebral ischemia depends on reperfusion – a biochemical study in rat. Journal Cell. Mol. Med. 5(2): 163–170.
[40] Skvortsova VI [et al.] (2007) Oxidative stress and oxygen status in ischemic stroke. Zh. Nevrol. Psikhiatr. Im. S.S. Korsakova. 107(1): 30–36 (rus).
[41] Turrens JF (1997) Superoxide production by the mitochondrial respiratory chain. Biosci.Rep. 17: 3-8.
[42] Boldyrev AA (1995) Dual role of free radical species of oxygen in ischemic brain. Neirokhimia. 12(3): 3–13 (rus).
[43] Gulyaeva NV, Yerin AN (1995) Role of free radical processes in development of neurodegenerative diseases. Neirokhimia. 13(2): 3–15 (rus).
[44] Hall ED, Braughler JM, Pazak KE (1993) Hydroxyl radical production and lipid peroxidation parallels selective post-ischemic vulnerability in gerbil brain. J. Neurosci. Res. 45(1): 107–112.
[45] Oliver CN [et al.] (1990) Oxidative damage to brain proteins loss of glutamine synthesis activity and production of free radicals during ischemia–reperfusion induced injury to gerbil brain. Proc. Natl. Asad. Sci. USA. 87: 5144–5147.
[46] Halliwell B (1992) Reactive oxygen species and the central nervous system. Free Radical in the brain. Aging. Neurological and Mental Disorders/ Eds Packer L, Christen Y. Springer – Verlag. Berlin, N.–Y., London: 21–41.
[47] Halliwell B (2006) Oxidative stress and neurodegeneration: where are we now? J. Neurochem. 97: 1634–1658.
[48] Halliwell B (2001) Role of free radicals in the neurodegenerative diseases: therapeutic implications for antioxidant treatment. Drugs Aging. 18(3): 685–716.
[49] Gupta R, Singh M, Sharma A (2003) Neuroprotective effect of antioxidants on ischaemia and reperfusion-induced cerebral injury. Pharmacol. Res. 48(Is.2): 209–215.
[50] Halliwell B. (1996) Antioxidants in human health and disease. Ann. Rev. Nutr. 16: 33–50.
[51] Grieb P (2005) Szanse na skuteczne neuroprotekcyjne leczenie udaru niedokrwiennego mozgu. Mozg a niedokrwienie. Pod red. J. Strosznajder, Z. Czernicki. Wyd. PLATAN. Krakow: 237-260.
[52] Gruener N [et al.] (1994) Increase in superoxide dismutase after cerebrovascular accident. Life Sci. 54(11): 711–713.
[53] Kumari NK, Panigrahi M, Prakash Babu P (2007) Changes in endogenous antioxidant enzymes during cerebral ischemia and reperfusion. Neurol. Res. 29(8) 877–883.
[54] Suslina ZA et al (2000) Antioxidant therapy in ischemic insult. Zh. Neurol. Psychiatr. 100(10): 34-38 (rus).
[55] Shapoval GS, Gromovaya VF (2003) Mechanisms of antioxidant protection during action of reactive oxygen species. Ukr.Biokhim.Zh. 75(2): 5–13 (rus).

[56] Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J (2007) Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem.Cell Biol. 39: 44-84.

[57] Kalinina EV et al. (2010) Modern conceptions on antioxidant role of glutathione and glutathione-dependent enzymes. Vestnik RAMN. 3: 46–54 (rus).

[58] Sies H (1997) Oxidative stress: oxidants and antioxidants. Exp. Physiology. 82: 291-295.

[59] Sies H (1999) Glutathione and its role in cellular functions. Free Radical Biology and Medicine. 27(Iss.9–10): 916–921.

[60] Schulz JB Lindenau J, Seyfried J, Dichgans J (2000) Glutathione, oxidative stress, and neurodegeneration. Eur. J. Biochem. 267(16): 4904–4911.

[61] Lorenc-Koci E. (2003) Neuroprotekcyjne wlasciwosci glutationu I ich znaczenie w schorzeniach neurodegeneracyjnych. Neuroprotekcji. XX Zimowa Szkola Instytutu Farmakologii PAN. Pod red. M.Smialowskiej. – Mogilany: 169-185.

[62] Cooper AJL, Kristal BS (1997) Multiple roles of glutathione in the central nervous system. J.Biol.Chem. 378: 793-802.

[63] Cruz R, Almaguer Melian W, Bergado JA Rosado J (2003) Glutathione in cognitive function and neurodegeneration. Rev. Neurol. 36(9): 877–886.

[64] Dringen R (2000) Metabolism and functions of glutathione in brain. Prog. Neurobiol. 62: 649-671.

[65] Dringen R, Hirrlinger J (2003) Glutathione pathways in the brain Biol. Chem. 384(4): 505–516.

[66] Lushchak VI (2012) Glutathione homeostasis and functions: potential targets for medical interventions. J Amino Acids. 2012: http://www.hindawi.com/journals/jaa/2012/736837/

[67] Jones DP (2002) Redox potential of GSH/GSSG couple: assay and biological significance. Methods in enzymology. 348: 93-112.

[68] Makarov P, Kropf S, Wiswedel I, Augustin W, Schild L (2006) Consumption of redox energy by glutathione metabolism contributes to hypoxia/reoxygenation-induced injury in astrocytes. Mol. Cell Biochem. 286 (1-2): 95-101.

[69] Bains JS, Shaw CA (1997) Neurodegenerative disorders in humans: The role of glutathione in oxidative stress-mediated neuronal death. Brain Res. Rev. 25: 335–358.

[70] Townsend DM, Tew KD, Tapiero H (2003) The importance of glutathione in human disease. Biomed.Pharmacotherapy. 57(3): 145-155.

[71] Mari M, Morales A, Colell A, Garcia-Ruiz C, Fernandez-Checa JC (2009) Mitochondrial glutathione, a key survival antioxidant. Antioxidants and Redox Signalling. 11(11):2685-2700.

[72] Beer SM, Taylor ER, Brown SE et al. (2004) Glutaredoxin 2 catalyzes the reversible oxidation and glutathionylation of mitochondrial membrane thiol proteins: implications

for mitochondrial redox regulation and antioxidant defense. J Biol Chem. 279(46): 47939-47951.

[73] Kumar C, Igbaria A, D'Autreaux B et al. (2011) Glutathione revisited: a vital function in iron metabolism and ancillary role in thiol-redox control. EMBO J. 30(10): 2044-2056.

[74] Kramer K et al. (1992) Glutathione mobilization during cerebral ischemia and reperfusion in the rat. Gen. Pharmacol. 23(1): 105–108.

[75] Bessonova LO, Verlan NV, Kolesnichenko LS ΛC (2008) Role of glutathione system in antioxidant protection during complex pathology of hypoxic genesis. Sibirskij Med.Zh. 6: 19–21 (rus).

[76] Mizui T, Kinouchi H, Chan PH (1992) Depletion of brain glutathione by buthionine sulfoximine enhances cerebral ischemic injury in rats. Am. J. Physiol. 262(2): 313–317.

[77] Islecel S [et al.] (1999)Alterations in superoxide dismutase, glutathione peroxidase and catalase activities in experimental cerebral ischemia-reperfusion. Res. Exp. Med. 199: 167–176.

[78] Anderson MF, Sims NR (2002) The effects of focal ischemia and reperfusion on the glutathione content of mitochondria from rat brain subregions. J. Neurochem. 81: 541–549.

[79] Holmgren A (2000) Antioxidant function of thioredoxin and glutaredoxin systems. Antioxidant Redox Signal.2: 811-820.

[80] Shivakumar BR, Kolluri SV, Ravindranath V (1995) Glutathione and protein thiol homeostasis in brain during reperfusion after cerebral ischemia. J. Pharmacol. Exp. Ther. 274(3): 1167–1173.

[81] Shivakumar BR, Kolluri SR, Ravindranath V (1992) Glutathione homeostasis in brain during reperfusion following bilateral carotid artery occlusion in the rat. Moll. Cell. Biochem. 111(1–2): 125–129.

[82] Suh SW, Shin BS, Ma H, Van Hoecke M, Brennan AM, Yenari MA, Swanson RA (2008) Glucose and NADPH oxidase drive neuronal superoxide formation in stroke. Ann.Neurol. 64: 654-663.

[83] Zauner A, Daugherty WP, Bullock MR, Warner DS (2002) Brain oxygenation and energy metabolism. Neurosurgery 51: 289-301.

[84] Erecinska M, Nelson D, Chance B. (1991) Depolarization induced changes in cellular energy production // Proc. Natl Acad.Sci.USA. 88: 7600–7604.

[85] Kozuka M (1995) Changes in brain energy metabolism, neurotransmitters, and choline during and after incomplete cerebral ischemia in spontaneously hypertensive rats. Neurochem. Res. 20(1): P. 23–30.

[86] Martin RL, Lloyd HG, Cowan AI (1994) The early events of oxygen and glucose deprivation: setting the scene for neuronal death? Trends Neurosci 17: 251-257.

[87] Elman I. et al. (1999) The effects of pharmacological doses of 2-deoxyglucose on cerebral blood flow in healthy volunteers. Brain Res. 815: 243-249.

[88] Gonzalez-Falcon A. et al. (2003) Effects of pyruvate administration on infarct volume and neurological deficits following permanent focal cerebral ischemia in rats // Brain Res. 990: 1-7.

[89] Suzuki M et al.(2001) Effect of of beta-hydroxybutyrate, a cerebral function improving agent, on cerebral hypoxia, anoxia and ischemia in mice and rats. Japan J.Pharmacol. 87: 143-150.

[90] Wey J, Cohen DM, Quast MJ (2003) Effects of 2-deoxy-d-glucose on focal cerebral ischemia in hyperglicemic rats // J.Cereb.Blood Flow Metab. 23: 556-564.

[91] Bouzier-Sore AK et al (2003) Lactate is a preferential oxidative energy substrate over glucose for neurons in culture. J.Cereb.Blood Flow Metab. 23: 1298-1306.

[92] Chih CP, Lipton P, Roberts EL (2001) Do active cerebral neurons really use lactate rather than glucose? Trends Neurosci. 24: 573-578.

[93] Hsueh-Meei Huang [et al.] (2003) Inhibition of the $\alpha$-ketoglutarate dehydrogenase complex alters mitochondrial function and cellular calcium regulation. Biochim. Biophys.Acta.1637: 119–126.

[94] Niizuma K, Endo H, Chan PH (2009) Oxidative stress and mitochondrial disfunction as determinants of ischemic neuronal death and survival. J.Neurosci. 109 (Suppl.1): 133-138.

[95] Kondrashova MN (1991) Cooperation for processes of transaminations and oxidation of carbonic acids in different cell functional states. Biokhimia. 56(3): 388-405 (rus).

[96] Kondrashova MN, Grigorenko EV, Babski AM, Khazanov VA (1987) Homeostasis of physiologic functions at the level of mitochondria. In: Mol.mechanisms of cell homeostasis. Novosibirsk: 40–66 (rus).

[97] Khazanov VA (2004) Past, present, and future of bioenergic pharmacology. In: Regulators of energic metabolism. Clinical and pharmacologic aspects. Tomsk: 3-7 (rus).

[98] Khazanov VA (1997) Oxidation of succinic acid in brain mitochondria. In: Succinic acid in medicine, food industry, agriculture. Ed. Kondrashova MN. Pushchino: 74–78 (rus).

[99] Mayevsky EI, Rosenfeld AS, Vazatashvili MV, Tchilaya SM (1997) Possibility for oxidation of exogenic succinic acid in vivo. In: Succinic acid in medicine, food industry, agriculture. Pushchino: 52–57 (rus).

[100] Lazarewicz J, Salinska E (2005) Udzial ionow wapnia w pathologii niedokrwiennej mozgu. Mozg a niedokrwienie. Pod red. J. Strosznajder, Z. Czernicki // Wydawnictwo PLATAN. Krakow: P.16-46.

[101] Villa RF, Gorini A, Hoyer S (2009) Effect of aging and ischemia on enzymatic activities linked to Krebs' cycle, electron transfer chain, glutamate and amino acids metabolism of free and intrasynaptic mitochondria of cerebral cortex. Neurochem.Res. 28: P.347–351.

[102] Kanunnikova NP, Omeyanchik SN, Bashun NZ, Shalavina EG, Doroshenko EM, Zolotukhin MM, Karayedova LM, Artiomova OV, Moiseenok AG (2003) Metabolism of

GABA abd glutamate in the rat brain in experimatnal ischemia and reperfusion. Neirokhimia. 20(3): 196-200 (rus).

[103] Mutuskina EA, Zarzhetski YuV, Trubina IE, Avrushchenko MA, Volkov LV, Onufriev MN, Lazareva NA, Stepanichev My, Gulyaeva NV, Gurvich AM (1997) Influence of ammonium succinate on functional, biochemical, and morphologic parameters of the central nervous system recovery in rats after 10 min break of blood flow. In: Succinic acid in medicine, food industry, agriculture. Pushchino: 145-150 (rus).

[104] Moiseenok AG, Komar VI, Khomich TI, Kanunnikova NP, Slyshenkov VS (2000) Pantothenic acid in maintaining thiol and immune homeostasis. Biofactors. 1: 53-55.

[105] 104] Brass EP (1994) Overview of Coenzyme A metabolism and its role in cellular toxicity. Chem. Biol. Interact. 90(3): 203-214.

[106] Moiseenok AG et al. (2004) CoA biosynthesis is an universal mechanism for conjugation of exogeneity and multiplicity of pantothenic acid functions. Ukr. Biokhim.Zh. 76(4): 68–81 (rus).

[107] Moiseenok AG (2003) Pantothenic acid: from universal distribution to universal functions. In: Biochemistry, pharmacology, and clinical use of pantothenic acid derivatives. Grodno: 107-114 (rus).

[108] Omelyanchik SN, Kanunnikova NP, Bashun NZ (2007) Changes of CoA pool structure in experimental brain ischemia and reperfusion and their correction by CoA biosynthesis precursors. Vestnik GrDU. 2(2): 89-93 (rus).

[109] Rabin O [et al.] (1997) Changes in cerebral acyl–CoA concentrations following ischemia–reperfusion in awake gerbils. J.Neurochem. 68: 2111–2118.

[110] Leonardi R, Zhang Yong-Mei, Rock ChO., Jackowski S (2005) Coenzyme A: Back in action. Progress in Lipid Res. 44: 125-153.

[111] Moiseenok AG, Rolevich IV, Kanunnikova NP, Khomich TI, Slyshenkov VS, Omelyanchik SN (1998) Simultaneous use of D-pantothenic acid substances and carnitine: foundation, and perspectives of use in prophylactic and therapeutic treatment. In: Panthenol and other derivatives of pantothenic acid: biochemistry, pharmacology, and medical use. Grodno: 130-137 (rus.).

[112] Grishina EV et al. (2007) Inhibition of mitochondrial energetics by CoA derivatives. Toxic effects of saturated fatty acids. In: Reception and intracellular signalling. Pushchino: 215-218 (rus).

[113] Slyshenkov VS, Rakowska M, Moiseenok AG, Wojtczak L. (1995) Pantothenic acid and its derivatives protect Ehrlich ascites tumor cells against lipid peroxidation. Free Rad. Biol. Med.19(66): 767-772.

[114] Slyshenkov VS, Piwocka K, Sikora E, Wojtczak L (2001) Pantothenic acid protects jurkat cells against ultraviolet light-induced apoptosis. Free Rad. Biol. Med. 30(11): 1303-1310.

[115] Slyshenkov VS, Dymkowska D, Wojtczak L (2004) Pantothenic acid and pantothenol increase biosynthesis of glutathione by boosting cell energetics. FEBS Letters 569: 169-172.

[116] Etensel B. et al. (2007) Dexpanthenol attenuates lipid peroxidation and testicular damage at experimental ischemia and reperfusion injury. Pediatr. Surg. 23(2): 177-181.

[117] Kanunnikova NP, Bashun NZ, Raduta EF, Slyshenkov VS, Omelyanchik SN (2007) Influence of panthenol and carnitine on parameters of lipoperoxidation and glutathione in experimental brain ischemia-reperfusion. In: Ecolog.Antropologia. Minsk: 154-156 (rus).

[118] Omelyanchik SN, Kanunnikova NP, Slyshenkov VS, Bashun NZ (2003) Role of panthenol in correction of some damages caused by experimental brain ischemia-reperfusion. In: Biochemistry, pharmacology, and clinical use of pantothenic acid derivatives. Grodno: 144-150 (rus).

[119] Bashun NZ, Raduta HF, Balash ZhI, Kirvel PCh, Sushko LI, Kanunnikova NP, Moiseenok AG (2007) Correction of postischemic disturbances in the hemispheres of the brain using precursors of succinyl-CoA biosynthesis. Neurochemical Journal. 1(3): 249-252.

[120] Schweizer U, Brauer A, Kohrle J, Nitsch R, Savaskan NE (2004) Selenium and brain function: a poorly recognized liaison. Brain Res. Rev. 45: 164–178.

[121] Brauer AU, Savaskan NE (2004) Molecular actions of selenium in the brain: neuroprotective mechanisms of an essential trace element. Rev.Neurosci. 15: 1-19.

[122] Gromova OA, Rebrov VG, Solupayeva LV (2004) Biological role of selenium. In: Selenium substances and health. Ed. Sanockij IV. Moscow: 12–42 (rus).

[123] Arteel GE, Sies H (2001) The biochemistry of selenium and the glutathione system. Environmental Toxicol.Pharmacol. 10: 153–158.

[124] Whanger PD (2001) Selenium and the brain: a review. Nutr. Neurosci. 4(2): 81–97.

[125] Baraboj VA (2004) Selen: biological role and antioxidant activity. Ukr.Biokhim.Zh. 76(1): 23-31(rus).

[126] Tapiero H, Townsend DM, Tew KD (2003) The antioxidant role of selenium and seleno–compounds. Biomedicine and Pharmacoterapy. 57: 134–144.

[127] Chen J, Berry MJ (2003) Selenium and selenoproteins in the brain and brain diseases. J. Neurochem. 86(1): 1–12.

[128] Steinbrenner H [et al.] (2006) Involvement of selenoprotein P in protection of human astrocytes from oxidative damage. Free Radical Biol. Med. 40(9): 1513–1523.

[129] Ozbal S [et al.] (2008) The effects of selenium against cerebral ischemia-reperfusion injury in rats. Neurosci. Lett. 438(Is.3): 265–269.

[130] Holmgren A, Lu J (2010) Thioredoxin and thioredoxin reductase: current research with special reference to human disease. Biochem. Biophys. Res.Communs. 396(1): 120-124.

[131] Ansari M.A. [et al.] (2004) Selenium protects cerebral ischemia in rat brain mitochondria. Biol. Trace Elem. Res. 101(1): 73–86.

[132] Yousuf S [et al.] (2007) Selenium plays a modulatory role against cerebral ischemia-induced neuronal damage in rat hippocampus. Brain Res. 114(25): 218–225.

[133] Huang K., Lauridsen E, Clausen J (1994) The uptake of Na-selenite in rat brain. Localization of new glutathione peroxidases in the rat brain. Biol. Trace Elem.Res. 46(Is.1–2): 91–102.

[134] Moiseenok AG (2004) Efficiency of sodium selenite and dimethyldiprosolilselenid (selecor) in protection of development of oxidative stress during endogenic intoxication. In: Selenium substances and health. Ed. Sanotsky. Moscow: 79–88 (rus).

[135] Moustafa RR, Baron J-C (2008) Pathophysiology of ischaemic stroke: insights from imaging, and implications for therapy and drug discovery. Br J Pharmacol 153: S44-S54.

[136] Adamek D (2003) Neuroprotekcja w urazach mozgu I rdzenia. Neuroprotekcija. XX Zimova Szkola Farmakol. PAN. Pod red. Smialowskiej M. Mogilany: 107-125.

[137] Zaleska MM, Mercado MLT, Chavez J, Feuerstein GZ, Pangalos MN, Wood A (2010) The development of stroke therapeutics: promising mechanisms and translational challenges. Neuropharmacol. 56: 329-341.

[138] Ginsberg MD (1995) Neuroprotection in brain ischemia: an update (Part II). The Neuroscientist. 1(3): 164-175.

[139] Cheng YD, Al-Khoury L, Zivin JA (2004) Neuroprotection for ischemic stroke: two decades of success and failure. NeuroRes1:36-45.

[140] Zhang ZG, Chopp M (2009) Neurorestorative therapies for stroke: uderlying mechanisms and translation to the clinic. Lancet Neurol 8: 491-500.

[141] Mehta SL, Manhas N, Raghubir R (2007) Molecular targets in cerebral ischemia for developing novel therapeutics. Brain Res. Rev 54: 34-66.

[142] Bacigaluppi M, Hermann DM (2008) New targets of neuroprotection in ischemic stroke. Scientific World Journal. 13(8): 698–712.

[143] 142] Szczudlik A (2003) Neuroprotekcja jako kierunek leczenia niedokrwienia mozgu. Neuroprotekcji. XX Zimowa Szkola Instytutu Farmakologii PAN. Pod red. M.Smialowskiej. - Mogilany: 99-105.

[144] Kanunnikova NP (2009) Role of metabolic therapy in complex treatment of ischemic and reperfusion injuries in brain. Zh. Grodn.Gos.Med.Univ. 4: 16-19 (rus).

[145] Slyshenkov VS, Shevalye AA, Moiseenok AG (2007) Pantothenate Prevents Disturbances in the Synaptosomal Glutathione System and Functional State of Synaptosomal Membrane under Oxidative Stress Conditions. Neurochem. J. 1(3): 235–239.

[146] Onufriev MV, Stepanichev MYu, Lazareva NV, Katkovskaya IN, Tishkina AO, Moiseenok AG, Gulyaeva NV (2010) Panthenol as neuroprotectant: study in a rat model of middle cerebral artery occlusion. Neurochem.J. 4(2): 148-152.

[147] Imai H, Graham DJ, Masayasu H, Macrae IM (2003) Antioxidant ebselen reduces oxidative damage in focal cerebral ischemia. Free Rad.Biol.Med. 34: 56-63.

[148] Parnham M, Sies H (2000) Ebselen: prospective therapy for cerebral ischaemia. Expert Opin.Invest.Drugs. 9: 607-619.

[149] Yamagata K [et al.] (2008) Protective effect of ebselen, a seleno-organic antioxidant on neurodegeneration induced by hypoxia and reperfusion in stroke-prone spontaneously hypertensive rat. Neuroscience. 153(2): 428–435.

[150] Kanunnikova NP, Raduta EF, Yelchaninova VA, Katkovskaya IN, Kovalenchik IL, Lukiyenko EP, Pehovskaya TA, Bashun NZ, Moiseenok AG (2010) Influence of panthenol, succinate ans selecor on changes of activities of lipoperoxidation and glutathione system in rat brain and blood after brain ischemia and reperfusion. Novosti med.-biol.nauk. 2(4): 156-162 (rus).