Publication date: 01.06.2021
DOI 10.51871/2588-0500_2021_05_02_2
UDC 615.327:616-001.8

EFFECT OF SELENIUM-MODIFIED MINERAL WATER "KRASNOARMEYSKAYA NOVAYA" ON THE LEVEL OF ANTIOXIDANT PROTECTION OF THE LIVER AND BRAIN TISSUE CELLS DURING THE RECOVERY PERIOD AFTER EXPERIMENTAL NORMOBARIC HYPOXIA

V.F. Reps, A.V. Abramtsova
Pyatigorsk Scientific and Research Institute of Balneology, the branch of the FSBI “North Caucasus Federal Scientific and Clinical Center of the FMBA of Russia”, Pyatigorsk, Russia

Keywords: selenium, mineral water, antioxidant protection, liver, brain, hypoxia, experiment.

Annotation. The purpose of the study is to evaluate the antioxidant potential of liver and brain tissue in the posthypoxic period under the influence of a course of internal intake of selenium-modified mineral water (MW) from the spring "Krasnoarmeyskij Novyj" in the experiment. The multidirectional reaction of the liver and brain tissue to the interval hypoxic load lasting 17 days and in the long-term period 14 days after its completion are determined. The least resistance to hypoxia and rapid recovery are observed in the liver tissue. The intake course of native MW decreases the antioxidant protection of the liver, and the addition of selenium to MW leveled its stressful effect. In the brain tissue, the intake course of native and selenium-modified MW unidirectionally increases the reserve of antioxidant protection, reducing the intensity of spontaneous and induced lipid peroxidation.

Introduction. The effectiveness of using natural factors in therapeutic and rehabilitation purposes depends on the balance of pro- and antioxidant systems of an organism. It was established that generating reactive metabolites and reactive oxygen intermediates (ROI) in particular, plays a central role in cell’s life. These metabolites are always being controlled by endogenic antioxidant systems, which can be enzymatic and nonenzymatic. Change in the antioxidant status caused by exogenous or endogenous sources could disturb the cell’s reductive-oxidative balance and lead to pathological disorders, one of the main components of which is the oxidative stress [19].

However, more works started to appear stating that ROI could participate in various physiological processes as a specific signaling molecule, including the autophagy induction, which is considered as an effective defense mechanism from

cell stress [14, 15]. A high level of antioxidants is registered in the brain of many mammals, which allows them preserving the ROI balance in hypoxia and reoxygenation [16].

In this respect, the evaluation of changes in the balance between the level of lipid peroxidation (LP) caused by the increase in the ROI content in tissues and the change in resources of the antioxidant system is relevant to understanding mechanisms of sanogenetic potential of native and modified drinking mineral waters, which are natural adaptogens. Earlier it was shown that the intake course of drinking mineral water of the Caucasian Mineral Waters region decreases the level of LP in the liver tissue, provided that the mechanism of their action is different depending on mineralization and physical and chemical composition [9]. Modification of biological potential of low-salt and medium-salt waters would contribute to the extension of their use in conditions of spa treatment.

Earlier obtained data gives evidence of the presence of selenium's impact on the content of MDA-oxygenized low-density lipoproteins (LDL) in blood with selenium intakes in the interval of 20 μg/kg to 40 μg/kg, which could be the opposite depending on the level of glutathione peroxidase (selenium-containing enzyme of the antioxidant system). Physiological mechanisms of the intake course of the "Krasnoarmeiskaya novaya" mineral water modified by selenium nanoparticles involve various levels of the regulation of metabolic reactions, which are the endocrine testing (decrease of cortisol level), substrate profile (changes in the level of energy substrate in blood) and enzymatic profile (increase in capacity of the antioxidant system) [1].

Organic selenium is one of the important modifying components due to the fact that there are several selenoproteins participating in the regulation of reductive-oxidative homeostasis of cells of various tissues of an organism [22]. Glutathione peroxidase, selenprotein, which supports the ROI inactivation in tissues, are catalyzing recovery of lipid hydroperoxides and hydrogen peroxide to water.

The purpose of this study is to evaluate the antioxidant potential of the liver and brain tissue during the post-hypoxic period under the influence of the intake course of selenium-modified mineral water "Krasnoarmejskaya novaya" in the experiment.

Methods and organization. Thirty five white outbred male rats, comparable in age (3,5 months) and body mass (220-250 g), were included in the study. Animals were contained in standard conditions of the vivarium in the PSRIB, the branch of the FSBI "NCFSCC of the FMBA of Russia" regulated by the SER 2.2.1.3218-14 "Sanitary and epidemiological requirements to the arrangement, equipment and maintenance of experimental and biological clinics (vivarium)", GOST 33215-2014 "Guidelines on management and care of laboratory animals". Work with animals

was carried out according to principles of humane treatment to animals, in compliance with requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (ETS № 123, Strasbourg, 1986) with adjustments from June 22, 1998. All animals had access to drinking water and received standard laboratory food every day.

According to the experiment's design, two research blocks were carried out.

The first block is the comparative evaluation of the LP intensity in the liver and brain tissues depending on the duration of hypoxic influence. Animals were divided into 4 groups, 5 specimen each: 1 – control group (CG), without influence; 2-4 groups – experimental groups with modeling of the interval normobaric hypoxic hypoxia with hypercapnia (INHHwH) 12 days long for the 1st Experimental group (EG1), 17 day long for the 2nd Experimental group (EG2) and 17 days long followed by a 14-day presence in the experiment without hypoxic influence for the 3rd Experimental group (EG3). The INHHwH modeling was carried out with time intervals of 24-48 hours by placing animals in a pressurized chamber (desiccator), 5 specimen each, until they appear to be in a preagonal state. Animal sacrificing was carried out on the 13th (EG1), 18th (EG2) and 33th (EG3) day by decapitation under brief ether anesthesia.

The second block – the examination of the effect of the intake course (14 days) of the native and modified by organic selenium "Krasnoarmejskaya Novaya" MW on the level of antioxidant protection reserves in various tissues (the liver and the brain) during the recovery period after the 17-day INHHwH.

Animals were divided into 3 groups, 5 specimen each: the 1st control group, animals with the modeling by the 17-day interval normobaric hypoxic hypoxia with hypercapnia followed by a 14-day presence in the experiment (INHHwH sep) without hypoxic influence (matches with the EG3 from the first block), the 2nd experimental group after the 17-day INHHwH with the intake course of the native "Krasnoarmejskaya novaya" MW (INHHwH+KN) and the 3rd experimental group after the 17-day INHHwH and the intake course of the selenium-modified "Krasnoarmejskaya Novaya" MW (INHHwH+KNSe).

The duration of the intake course of the native and modified "Krasnoarmejskaya novaya" MW from the Pyatigorsk Resort is 14 days. MW was administered per os every day at a rate 1,5 ml on 100 g of an animal's body mass, selenium in the form of the "Selenkor" substance was added to MW right before giving the water at the rate of 3 μg/kg for animal's body mass.

"Krasnoarmejskaya Novaya" mineral water (Kurlov's formula) is a low-carbon sulfate-bicarbonate-chloride calcium-sodium mineral water of medium mineralization (6-8 g/l):

$$CL^{*39*}\ HCO_3{}^{38*}SO_4{}^{*23}$$

$$CO_2\ 1{,}36\ M\ 5{,}0 \quad \text{———————————} \quad pH\ 6{,}1$$

$$(Na + K)^{*61}Ca^{*32}$$

During the experiment, body mass of rats was determined, tissues were retrieved from the liver and the brain (large hemispheres) in order to obtain tissue homogenates (500 mg in 5 ml 40 mmol tris/HCL buffer solution of pH 7,4 with 1,2% KCL), the level of malondialdehyde (MDA) and levels of spontaneous and induced by the spectrophotometric method (during calculating the MDA content in the samples, the molar extinction coefficient was used 1,56 × 10-5 mol^{-1} cm^{-1}) with preliminary standard sample preparation were also identified [10].

Statistical analysis of results of the study was carried out on a personal computer using methods of non-parametric variational statistics. Obtained data was assessed using the Newman-Keuls test for numerous intergroup comparisons of independent variables and the multifactor dispersive analysis. Indicators were presented in the form of median (Me) and quartiles (Q25-Q75). Differences were considered as significant when the minimal level of significance is $p<0{,}05$.

Results and discussion. The oxidative stress has a different effect on tissue metabolism in the liver and brain. Usage of antioxidants is a rational therapeutic strategy for prevention and therapy of liver diseases related to the oxidative stress in the liver [17].

In order to study the direction of pathological processes during modeling hypoxic hypoxia in animals, a comparative study of LP intensity in liver and brain hemispheres depending on hypoxia's duration was carried out.

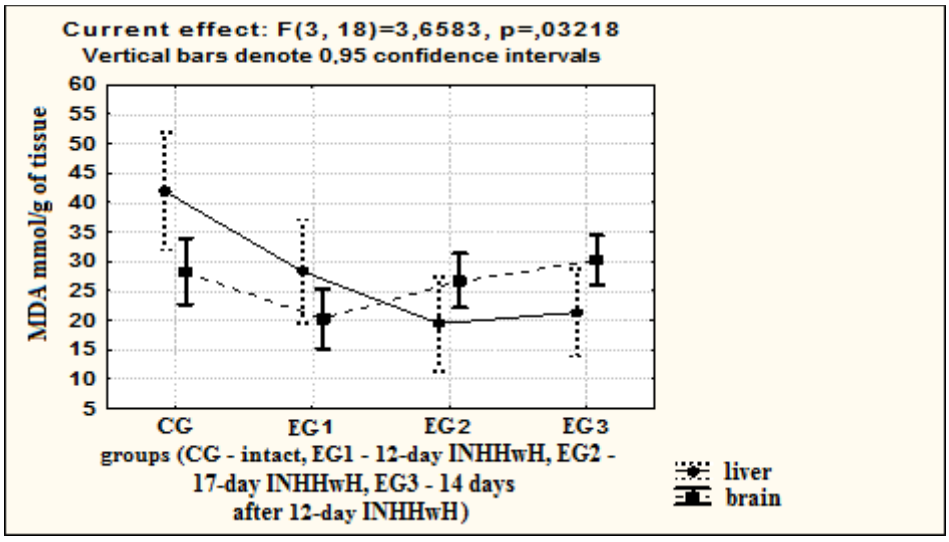

Fig. 1. Content of LP products (MDA) in the liver and brain tissues of rats with interval normobaric hypoxic hypoxia of various duration

The initial level of MDA in the liver tissue of the CG was 1,5 times significantly higher than in tissue of large hemispheres of the brain (LHB) (Fig. 1). At the 12 day of INHHwH (EG1), the MDA level in the liver tissue and LHB was decreased, but this change was not significant in comparison with the MDA level in tissues if the CG. It was revealed that after 17 days of INHHwH (EG2), the MDA level in liver tissue is 2 times lower in comparison with the CG, and it was registered on this level in animals within the long-term period after INHHwH (EG3). MDA content in the brain after 17 days (EG2) and within the long-term period after INHHwH (EG3) is almost on the same level as it is in the CG.

According to obtained results, LP processes in the liver tissue are more active in intact animals (CG). Earlier in other studies, it was also revealed that the level of LP products (diene and triene conjugates, as well as the end products of this process – Schiff bases) is higher in the liver of animals than in the brain [8]. Obtained results on different MDA content in the brain and liver tissue could be used as criteria for the assessment of the effect of antioxidant activity of tissues considering the fact that the MDA level is an integral indicator, which shows the intensity of free-radical oxidation, which is being controlled by systems of antioxidant protection, taking tissue specificity into account.

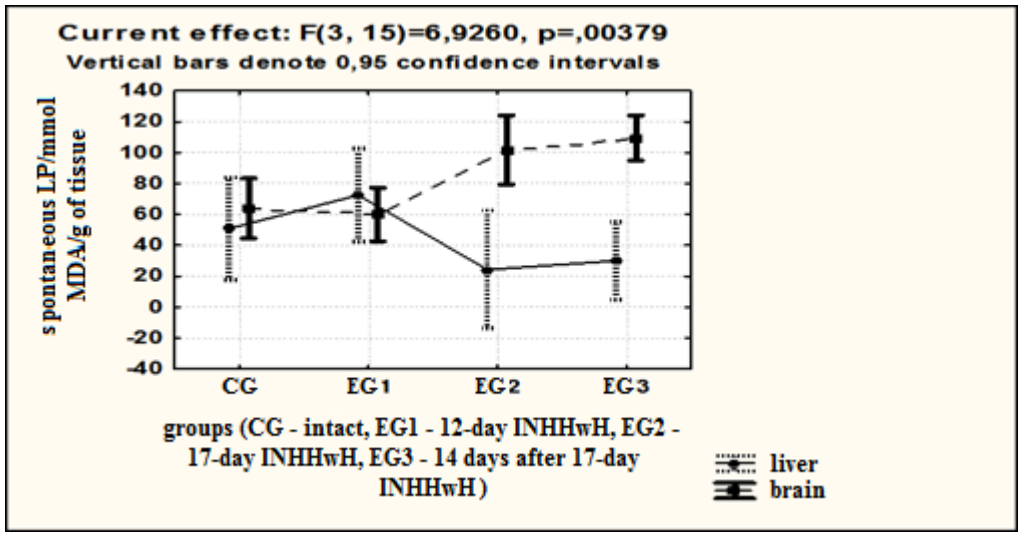

Fig. 2. MDA content in the spontaneously induced LP in the liver and brain tissue of rats (in vitro) during normobaric hypoxia of various duration

A change in the intensity of LP in many disorders of brain function in hypoxic conditions is registered. Thus, a moderate activation of LP is registered in patients with atherosclerosis of the internal carotid artery (brain ischemia) before surgery, which is related to the perpetuation of brain tissue ischemia [6]. In this experimental study, the intensity of spontaneous LP in vitro (during incubation of liver's homogenate for 15 minutes at 37^0 C), by which the level of reserves of the antioxidant protection system was evaluated both in the liver and the brain after the

12-day INHHwH (EG1), does not differ from values of the CG (Fig. 2). After the 17-day INHHwH (EG2) and within the long-term period after INHHwH (EG3), the level of spontaneous LP in the brain tissue was 2 times higher in comparison with values of the CG and the 12-day INHHwH (EG1). The level of spontaneous LP in vitro was 1,5 times lower in the EG2, 2 times lower in the EG3, in comparison with its level after the 12-day INHHwH (EG1), and was near the CG level.

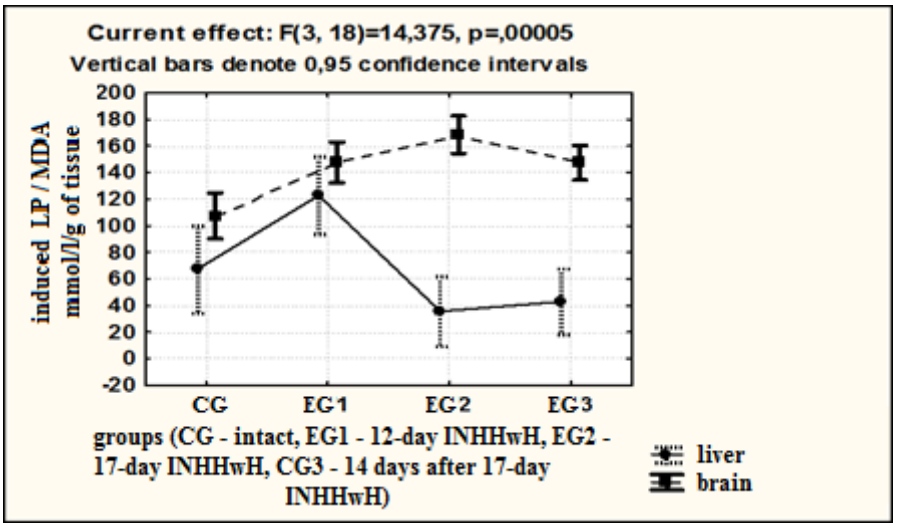

Fig. 3. Level of induced (by exogenous Fe^{2+}) LP in the liver and brain tissue of rats (in vitro) during normobaric hypoxia of various duration

The level of induced nonenzymatic LP is a “loading” test, which allows to assess indirectly the resource limits of the antioxidant system of examined tissue. Indicators of induced LP in vitro (when adding Fe^{2+} in the incubation medium) in animals of the CG and after the 12-day INHHwH both in the liber and brain are not significantly different (Fig. 3). However, after the 17-day INHHwH, the level of induced LP in the brain is rapidly increased (2 times) in comparison with the CG level, and such tendency in preserved in 14 days after the 17-day INHHwH. On the contrary, the level of induced LP in the liver is decreased after the 17-day INHHwH. (EG2) and in 14 days after the 17-day INHHwH (EG3) in comparison with the level after the 12-day INHHwH (EG1), but it is not significantly different than the CG level.

Various response made by the antioxidant defense system in examined tissues and registered by us is related to their morphological features and different formed strategies of adaptation to hypoxic states. The oxidative stress is considered as a systemic pathological mechanism contributing to initiation and progression of liver damage. The liver is a main organ, in which ROI are the most reactive, and violations of membrane integrity and metabolic exchange caused by them lead to stenosis, fibrosis and other liver diseases [21]. Parenchymal cells are the initial cells, which are subject to the oxidative stress caused by liver damage. Mitochondria,

microsomes and peroxisomes in parenchymal cells can produce ROI. Moreover, Kupffer cells, hepatic stellate cells and endothelial cells are potentially more susceptible to the effect and sensitive to molecules related to the oxidative stress [17].

Moreover, the systemic oxidative stress appearing with liver diseases could also cause damage of such extrahepatic organs as the brain and kidneys [12].

During repeat of 17-day INHHwH (EG2), the MDA level in the liver tissue (thiobarbituric acid products in vivo) is decreased 2 times and remains decreased during the long-term period in the EG3 animals. The obtained effect of decreased MDA in the liver tissue is necessary to interpret not from the point of the formation of antioxidant defense, but as a result of deep disorder of the parenchymal structure of the liver. Thus, on the 17th day of INHHwH (EG3), a total hydropic degeneration of hepatic cells and local necrosis happen (according to conducted histologic studies of analyzed tissues) [7]. The decrease of LP appearance in the liver tissue is the best demonstrated in case of acute experimental toxic liver damage, when after 2-3 days of intoxication the oxidation rate is increased leading to total damage of liver cells, and as a consequence to a decrease in the chemiluminescence indicators in the liver homogenate, the growth of thiobarbituric acid products is decreased [4].

It is important to note that within the long-term period 14 days after INHHwH LP products content was on the same level as in animals of the EG3. As it was shown earlier, according to data of histologic study in animals 14 days after the 17-day INHHwH, cytoarchitectonics of the liver tissue is not disturbed, hepatic cells are without signs of dystrophia. It indicates a total physiological recovery of liver microstructure after cancellation of pathological factors due to its high regenerative potency [5]. Therefore, in our experiment within the long-term period after the end of INHHwH, MDA content in the initial state (in vivo) and after the induction of LP processes into the liver tissue (in vitro), the antioxidant potency of tissue when it is almost fully recovered is registered (Fig. 2-3).

Thus, a multidirectional response of the liver and brain tissue to the 17-day long interval hypoxic load and within the long-term period after the 17-day INHHwH with the recovery of antioxidant defense of peripheral tissues (the liver). Studies on the intensity of LP of the liver and brain in the 17-day INHHwH and 14 days after the 17-day INHHwH could allow to assess differently reserves of the antioxidant protection of organs under the influence of examined balneological factors.

During the intake course of MW within the regeneration period, 14 days after the 17-day INHHwH, the tolerance of tissues to oxidation in animals of the INHHwH+KN group is decreased, which is registered according to the increase in the MDA level and the intensity of induced LP in the liver tissue to 20% in

comparison with values of animals of the INHHwH sep group (Fig. 4). Addition of selenium into MW in some way manages the appearance of LP products in the liver of animals of the INHHwH+KNSe group, the LP products level appears to be near the high level of values in the INHHwH sep group. It is known, that stressing factors can also influence the antioxidant potential of the liver within the regeneration period. Number of studies showed that if animals during the rehabilitation period after partial hepatectomy are exposed to immobilizing stress, then the MDA level in the liver tissue will be increased, and the activity of antioxidant enzymes is decreased [4].

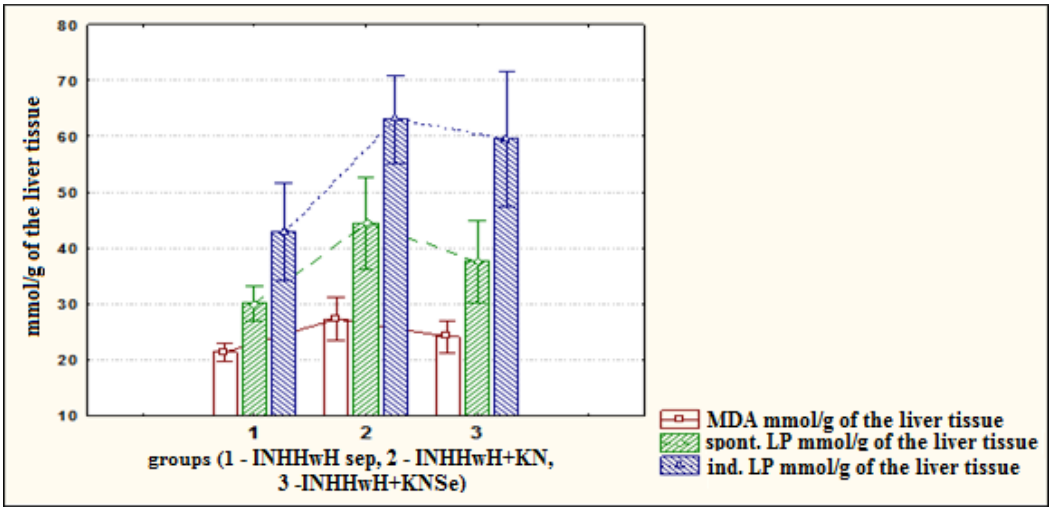

Fig. 4. LP products content in the liver tissue 14 days after the 17-day normobaric hypoxic hypoxia with hypercapnia (INHHwH sep) after the intake course of native mineral water from the "Krasnoarmejskij novyj" spring (INHHwH+KN) and selenium-modified version (INHHwH+KNSe)

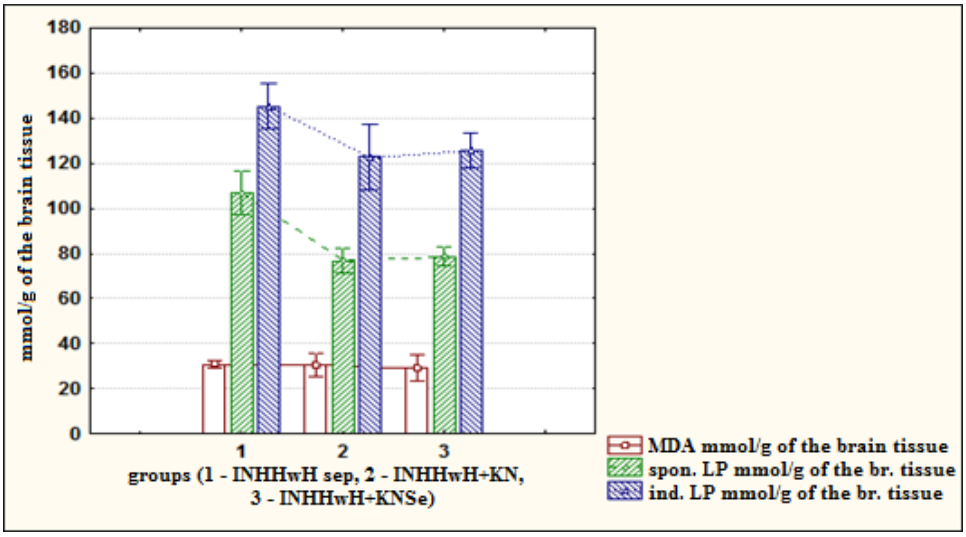

Fig. 5. LP products content in the brain tissue 14 days after the 17-day normobaric hypoxic hypoxia with hypercapnia (INHHwH sep) after the intake course of native mineral water from the "Krasnoarmejskij novyj" spring (INHHwH+KN) and selenium-modified version (INHHwH+KNSe)

During the intake course of the “Krasnoarmejskaya novaya” MW in the brain tissue, a decrease in the intensity of both spontaneous and induced LP was registered (Fig. 5). Modification of the “Krasnoarmejskaya novaya” MW by selenium led to insignificant decrease in the LP intensity in the liver tissue (Fig. 4) and almost did not affect reserves of the antioxidant enzyme system in the brain tissue (Fig. 5).

Various metabolic reaction of examined tissues on both pathogenic and therapeutical influence is connected to different mechanisms of regulation on physiological and cellular level [13, 20].

Moreover, different structures of the brain are differently resistant to hypoxia of the dame degree and duration. Firstly, functions of younger (in a phylogenetic way) segments of the brain, which are the cerebral cortex and cerebellum, are being damaged. Our study was carried out on the tissue of large hemispheres of the brain – area of the brain, which is less tolerant to hypoxia in comparison to other areas. The liver in the normal state, as well as the brain, is characterized by the high oxygen consumption, however, hepatic cells are more adapted to changes in oxygen tension in the liver tissue due to prevalent blood supply from the system of portal vein [18].

It is also important to note that the liver and the brain are different in the strategy of forming tolerance to hypoxia and the oxidative stress. Anatomical and physiological conditions are formed in the brain to adapt to changes in the level of oxygenation [11].

Conclusion. Therefore, using selenium-modified MW increases resources of the antioxidant system of tissues and organs of the gastrointestinal tract (GIT) and is practicable in prevention and rehabilitation of GIT diseases, however, it should be done at the stage of remission, as it was noted earlier in clinical guidelines [2]. In case of disorders of the brain functions related to ischemia or hypoxia of various genesis, including diseases of contagious nature (post-COVID syndrome), a use of drinking mineral waters from the Pyatigorsk Resort is possible, but this type of rehabilitation requires further study both in the experimental form and in the practice of therapeutic and preventive institutions of the resort.

References

1. Abramtsova A.V. The possibilities of using selenium in balneology / A.V. Abramtsova // Resort medicine. – 2017. – №1. – P.35-44.

2. Efimenko N.V. Mechanisms of action of drinking mineral waters and their role in resort gastroenterology / N.V. Efimenko // Resort medicine. – 2015. –№ 3. – P.2-6.

3. Kantyukov S.A. The state of free radical oxidation processes in acute liver damage / S.A. Kantyukov, L.V. Krivokhizhina, R.R. Farkhutdinov // Bulletin Of The South Ural State University. – 2011. – № 39. – P.107- 112.

4. Lukash V.A. Interaction of LPO and phospholipid metabolism in subcellular fractions of regenerating liver under stress and pre-exposure to epinephrine in the age aspect / V.A. Lukash, V.N. Meshchaninov // Hospital Bulletin. – 2007. – №2(15). – P.33.-39.

5. Nalobin D.S. The regenerative capacity of the liver of mammals / D.S. Nalobin, S.I. Alipkina, M.S .Krasnov // Advances in modern biology. – 2016. – V.136. – №1. – P.13-24.

6. Neumann M.I. Effect of the anesthesia method on the activity of lipid peroxidation in carotid endarterectomy / M. I. Neumann, V.V. Shmelev, A.A. Shaidurov, V.A. Shalimov // Bulletin of Anesthesiology and Resuscitation. – 2018. – V.15. – №4. – P.34-41.

7. Patent for an invention RU 2609281 C, 01.02.2017. Application № 2015151845 от 02.12.2015. Abramova A.V., Migunova L. A., Demeshko N. I., Reps V. F.

8. Petrukhin A. S. The effect of propofol on lipid peroxidation in the brain and liver of rats / A. S. Petrukhin, N. D. Eshchenko, A. A. Dizhe, A. A. Vilkova, A. I. Ivanov // Vestnik SPbU. – 2007. – 3(2). – P.108-111.

9. Reps V.F. Metabolic action mechanisms of modified balneal drugs/ V.F. Reps // Resort medicine. – 2013. – №4. – P.18-21.

10. Reps V.F. Intensity of lipid peroxidation in the liver tissue as a metabolic criterion of the biological effect of native and modified mineral waters of the jententous type / V.F. Reps, A.V. Abramtsova // Modern issues of biomedicine. – 2020. – V.4(2). – P.1-16.

11. Angelova P.R. Functional Oxygen Sensitivity of Astrocytes / P.R. Angelova, V. Kasymov, I. Christie, S. Sheikhbahaei, E. Turovsky, M. Nephtali, A. Korsak, J. Zwicker, A.G. Teschemacher, G.L. Ackland, G.D. Funk, S. Kasparov, A.Y. Abramov, A.V. Gourine // Journal of Neuroscience. – 2015. – V.35 (29). – P.10460-10473; DOI: https://doi.org/10.1523/JNEUROSCI.0045-15.2015

12. Bosoi C.R. Systemic oxidative stress is implicated in the pathogenesis of brain edema in rats with chronic liver failure / C.R. Bosoi, X. Yang, J. Huynh, C. Parent-Robitaille, W. Jiang, M. Tremblay, C.F. Rose // Free Radic. Biol. Med. – 2012. – №52. – P.1228-1235.

13. Chen R.Reactive Oxygen Species Formation in the Brain at Different Oxygen Levels: The Role of Hypoxia Inducible Factors / R. Chen, U.H. Lai, L. Zhu, A. Singh, M. Ahmed, R. Nicholas // Forsyth Front. Cell Dev. Biol. – 10 October 2018. DOI: https://doi.org/10.3389/fcell.2018.00132

14. Dodson M.V. Cellular metabolic and autophagic pathways: traffic control by redox signaling / M.V. Dodson, V. Darley-Usmar, J. Zhang // Free Radical Biology and Medicine. – 2013. – V.63. – P.207-221.

15. Fang C. The Interrelation between Reactive Oxygen Species and Autophagy in Neurological Disorders / C. Fang, L. Gu, D. Smerin, S. Mao, X. Xiong // Oxidative Medicine and Cellular Longevity. – 2017. DOI: https://doi.org/10.1155/2017/8495160.

16. Larson J. No oxygen? No problem! Intrinsic brain tolerance to hypoxia in vertebrates / J. Larson, L.D. Kelly, L.P. Folkow, S.L. Milton, T.J. Park // J Exp Biol. – 2014. – 217. – P.1024-1039. DOI: 10.1242/jeb.085381.

17. Li S. The Role of Oxidative Stress and Antioxidants in Liver Diseases / S. Li, H.Y. Tan, N. Wang, Z.J. Zhang, L. Lao, C.W. Wong, Y. Feng // Int J Mol Sci. – 2015. – Nov.2. – V.16(11). – P. 26087-26124. DOI: 10.3390/ijms161125942.

18. Ngwenya L.D. Brain Tissue Oxygen Monitoring and the Intersection of Brain and Lung: A Comprehensive Review / L.D. Ngwenya, J.F. Burke, T. Geoffrey, G.T. Manley // Respiratory Care. – 2016. – V.61(9). – P. 1232-1244; DOI: https://doi.org/10.4187/respcare.04962

19. Noori S. An Overview of Oxidative Stress and Antioxidant Defensive System. / S. Noori // 2012. – 1:413. DOI: 10.4172/scientificreports.

20. Olguín-Albuerne M. Redox Signaling Mechanisms in Nervous System Development / M. Olguín-Albuerne, J. Morán // Antioxid Redox Signal. – 2018. – 20;28(18). – P.1603-1625. DOI: 10.1089/ars.2017.7284.

21. Sanchez-Valle V. Role of oxidative stress and molecular changes in liver fibrosis: A review / V. Sanchez-Valle, N.C. Chavez-Tapia, M. Uribe, N. Mendez-Sanchez // Curr. Med. Chem. – 2012. – 19(28). – P.4850–4860.

22. Zhang Y. Role of Selenoproteins in Redox Regulation of Signaling and the Antioxidant System: A Review / Y. Zhang, Y.J. Roh, S-J. Han, I. Park, H.M. Lee, Y.S. Ok, B.C. Lee, S.R. Seung-Lee // Antioxidants. – 2020. – 9. – 383; DOI:10.3390/antiox9050383.

Spisok literatury

1. Abramtsova A.V. Vozmozhnosti primeneniya selena v bal'neologii / A.V. Abramtsova //Kurortnaya meditsina. – 2017. – №1. – S. 35-44.

2. Efimenko, N.V. Mekhanizmy dejstviya pit'evykh mineral'nykh vod i ikh rol' v kurortnoj gastroenterologii / N.V. Efimenko // Kurortnaya meditsina. – 2015. – № 3. – S.2-6.

3. Kantyukov S.A. Sostoyanie protsessov svobodno-radikal'nogo okisleniya pri ostrom porazhenii pecheni / S.A. Kantyukov, L.V. Krivokhizhina, R.R. Farkhutdinov // Vestnik YUUrGU. – 2011. – № 39. – S.107- 112.

4. Lukash V.A. Vzaimodejstvie POL i fosfolipidnogo obmena v subkletochnykh fraktsiyakh regeneriruyushchej pecheni v usloviyakh stressa i pri predvozdejstvii adrenalinom v vozrastnom aspekte / V.A. Lukash, V.N. Meshchaninov // Gospital'nyj vestnik. – 2007. – № 2(15). – S.33.-39

5. Nalobin D.S. Regenerativnye sposobnosti pecheni mlekopitayushchikh / D.S. Nalobin, S.I. Alipkina, M.S. Krasnov // Uspekhi sovremennoj biologii. – 2016. T.136. – № 1. – S.13-24

6. Nejman M.I. Vliyanie metoda anestezii na aktivnost' perekisnogo okisleniya lipidov pri karotidnoj endarterektomii / M.I. Nejman, V.V. Shmelev, A.A. Shajdurov, V.A. Shadymov // Vestnik anesteziologii i reanimatologii. – 2018. – T 15. – №4. – S.34-41.

7. Patent na izobretenie RU 2609281 C, 01.02.2017. Zayavka № 2015151845 ot 02.12.2015. Abramtsova A.V., Pigunova L.A., Demeshko N.I., Reps V.F.

8. Petrukhin A.S. Vliyanie propofola na perekisnoe okislenie lipidov v golovnom mozge i pecheni krys / A.S. Petrukhin, N.D. Eshchenko, A.A. Dizhe, A.A. Vilkova, A.I. Ivanov // Vestnik SPbGU. – 2007. – Ser.3. , vyp.2. – S.108-111.

9. Reps V.F. Metabolicheskie mekhanizmy dejstviya modifitsirovannykh bal'neosredstv / V.F. Reps // Kurortnaya meditsina. – 2013. – № 4. – S.18-21.

10. Reps V.F. Intensivnost' perekisnogo okisleniya lipidov v tkani pecheni kak metabolicheskij kriterij biologicheskogo effekta nativnykh i modifitsirovannykh mineral'nykh vod essentukskogo tipa / V.F. Reps, A.V. Abramtsova // Sovremennye voprosy biomeditsiny. – 2020. – T. 4(2). – S.1-16.

11. Angelova P.R. Functional Oxygen Sensitivity of Astrocytes / P.R. Angelova, V. Kasymov, I. Christie, S. Sheikhbahaei, E. Turovsky, M. Nephtali, A. Korsak, J. Zwicker, A.G. Teschemacher, G.L. Ackland, G.D. Funk, S. Kasparov, A.Y. Abramov, A.V. Gourine // Journal of Neuroscience. – 2015. – V.35 (29). – P.10460-10473; DOI: https://doi.org/10.1523/JNEUROSCI.0045-15.2015

12. Bosoi C.R. Systemic oxidative stress is implicated in the pathogenesis of brain edema in rats with chronic liver failure / C.R. Bosoi, X. Yang, J. Huynh, C. Parent-Robitaille, W. Jiang, M. Tremblay, C.F. Rose // Free Radic. Biol. Med. – 2012. – №52. – P.1228-1235.

13. Chen R.Reactive Oxygen Species Formation in the Brain at Different Oxygen Levels: The Role of Hypoxia Inducible Factors / R. Chen, U.H. Lai, L. Zhu, A. Singh, M. Ahmed, R. Nicholas // Forsyth Front. Cell Dev. Biol. – 10 October 2018. DOI: https://doi.org/10.3389/fcell.2018.00132

14. Dodson M.V. Cellular metabolic and autophagic pathways: traffic control by redox signaling / M.V. Dodson, V. Darley-Usmar, J. Zhang // Free Radical Biology and Medicine. – 2013. – V.63. – P.207-221.

15. Fang C. The Interrelation between Reactive Oxygen Species and Autophagy in Neurological Disorders / C. Fang, L. Gu, D. Smerin, S. Mao, X. Xiong // Oxidative Medicine and Cellular Longevity. – 2017. DOI: https://doi.org/10.1155/2017/8495160.

16. Larson J. No oxygen? No problem! Intrinsic brain tolerance to hypoxia in vertebrates / J. Larson, L.D. Kelly, L.P. Folkow, S.L. Milton, T.J. Park // J Exp Biol. – 2014. – 217. – P.1024-1039. DOI: 10.1242/jeb.085381.

17. Li S. The Role of Oxidative Stress and Antioxidants in Liver Diseases / S. Li, H.Y. Tan, N. Wang, Z.J. Zhang, L. Lao, C.W. Wong, Y. Feng // Int J Mol Sci. – 2015. – Nov.2. – V.16(11). – P. 26087-26124. DOI: 10.3390/ijms161125942.

18. Ngwenya L.D. Brain Tissue Oxygen Monitoring and the Intersection of Brain and Lung: A Comprehensive Review / L.D. Ngwenya, J.F. Burke, T. Geoffrey, G.T. Manley // Respiratory Care. – 2016. – V.61(9). – P. 1232-1244; DOI: https://doi.org/10.4187/respcare.04962

19. Noori S. An Overview of Oxidative Stress and Antioxidant Defensive System. / S. Noori // 2012. – 1:413. DOI: 10.4172/scientificreports.

20. Olguín-Albuerne M. Redox Signaling Mechanisms in Nervous System Development / M. Olguín-Albuerne, J. Morán // Antioxid Redox Signal. – 2018. – 20;28(18). – P.1603-1625. DOI: 10.1089/ars.2017.7284.

21. Sanchez-Valle V. Role of oxidative stress and molecular changes in liver fibrosis: A review / V. Sanchez-Valle, N.C. Chavez-Tapia, M. Uribe, N. Mendez-Sanchez // Curr. Med. Chem. – 2012. – 19(28). – P.4850–4860.

22. Zhang Y. Role of Selenoproteins in Redox Regulation of Signaling and the Antioxidant System: A Review / Y. Zhang, Y.J. Roh, S-J. Han, I. Park, H.M. Lee, Y.S. Ok, B.C. Lee, S.R. Seung-Lee // Antioxidants. – 2020. – 9. – 383; DOI:10.3390/antiox9050383.

Information about the authors: Valentina Fyodorovna Reps – Doctor of Biological Sciences, Associate Professor, Lead Researcher of the Department of Research of Physical Factors' Mechanisms of Action Factors of the PSRIB, the branch of the FSBI "NCFSCC of the FMBA", Pyatigorsk, e-mail: v.reps@mail.ru; **Anna Viktorovna Abramtsova** – Candidate of Medical Sciences, Senior Researcher of the Depratment Research of Physical Factors' Mechanisms of Action of the PSRIB, the branch of the FSBI "NCFSCC of the FMBA", Pyatigorsk, e-mail: abramtsovaav@ngs.ru.