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Changes In the Course of Energy and Oxidative Processes of The Brain During Its Ischemia

Lizaveta I. Bon*, MAKSIMOVICH N. Ye., Dremza I.K., Portonenko A.M.

Candidate of biological science, assistant professor of pathophysiology department named D.A. Maslakov, Grodno State Medical University, 80, Gorky St., 230009, Grodno, Belarus

***Corresponding Author**: Lizaveta I. Bon., Candidate of biological science, assistant professor of pathophysiology department named D.A. Maslakov, Grodno State Medical University, 80, Gorky St., 230009, Grodno, Belarus

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Abstract

Energy deficiency and oxidative stress are stages of the biochemical cascade in brain damage of ischemic origin. There is information in the literature about their changes in certain types of ischemia, but there are no data on the features and comparative characteristics in cerebral ischemia of varying severity. It was found that the most pronounced disturbances in the prooxidant-oxidant balance and energy metabolism were observed in total cerebral ischemia. Similar, however, less pronounced disorders were found in daily subtotal ischemia and in the subgroup of stepped subtotal ischemia with an interval between ligation of the common carotid arteries of 1 day. The least pronounced disorders were in the subgroup with an interval between ligation of the common carotid arteries 7 days

The aim of the work is to assess the state of the energy and oxidative processes of the brain during its ischemia of varying severity.

Keywords: *energy metabolism, mitochondria, oxidative stress.*

Introduction

Energy deficiency and oxidative stress are stages of the biochemical cascade in brain damage of ischemic origin [3, 4]. There is information in the literature about their changes in certain types of ischemia, but there are no data on the features and comparative characteristics in cerebral ischemia of varying severity.

The aim of the work is to assess the state of the energy and oxidative processes of the brain during its ischemia of varying severity.

Materials and research methods

The experiments were carried out on 60 male outbred white rats weighing 260 ± 20 g in compliance with the requirements of the Directive of the European Parliament and of the Council No. 2010/63/EU of September 22, 2010 on the protection of animals used for scientific purposes.

The studies used models of partial, total, subtotal and stepped subtotal cerebral ischemia [2,6,10]. Partial cerebral ischemia (PCI) was modeled by ligation of one CCA on the right. Total cerebral ischemia (TCI) was modeled by decapitation of animals. Subtotal cerebral ischemia (SCI) was modeled by simultaneous ligation of both common carotid arteries (CCA). Stepwise subtotal cerebral ischemia (SSCI) was performed by successive ligation of both CCAs with an interval of 7 days (subgroup 1), 3 days (subgroup 2), or 1 day (subgroup 3). The control group consisted of sham operated rats of similar sex and weight [1, 2,10].

Modeling of cerebral ischemia (CI) was performed under conditions of intravenous thiopental anesthesia (40-50 mg/kg). The material was taken 1 hour after decapitation. Energy and oxidative processes have been studied, and the severity of morphological changes in brain neurons during its ischemia of varying severity has been assessed [6,8].

The state of energy was assessed by the activity of mitochondrial respiration using succinate and the malate/glutamate complex as substrates, which makes it possible to assess the degree of functional activity of the electron transport chain (ETC) in mitochondria as a whole, in particular, I and II of the ETC complex [1,6]. The following indicators of

mitochondrial respiration were recorded: V1 – basal respiration rate; V2 – substrate-dependent respiration rate; V3 –respiration rate associated with phosphorylation (after ADP addition); V4 –the respiratory rate after completion of phosphorylation of the added ADP. The indicators characterizing the conjugation of the processes of oxidation and phosphorylation in mitochondria were determined: the coefficient of acceptor control (AC= V3/V2), the coefficient of respiratory control (RC= V3/V4) and the coefficient of phosphorylation - ADP/O. The study of mitochondrial respiration of the brain was carried out after its homogenization in the isolation medium according to the modified method [1,2,6,10].

To assess the severity of oxidative processes in brain homogenates, the level of antioxidant protection (indicators of total SH-groups, GSH concentrations, glutathione peroxidase activity), and the state of lipid peroxidation (the content of products that react with thiobarbituric acid) were determined on a spectrophotometer PV 1251C (Solar, Belarus) [5].

In order to study the consequences of energy disorders and changes in oxidative stress activity, a morphological study of neurons in the parietal cortex of the rat brain was carried out using an Axioscop 2 plus microscope (Zeiss, Germany), a digital video camera (LeicaDFC 320, Germany) and ImageWarp image analysis program (Bitflow, USA). In histological studies, the size and shape of the perikaryons of rat brain neurons were determined, and changes in cytoplasmic chromatophilia were studied using conventional methods [1,2,4].

Statistical research

Since the experiment used small samples that had a non-normal distribution, the analysis was performed by nonparametric statistics using the licensed computer program Statistica 10.0 for Windows (StatSoft, Inc., USA). The data are presented as Me (LQ; UQ), where Me is the median, LQ is the value of the lower quartile; UQ is the value of the upper quartile. Differences between groups were considered significant at p<0>

Research results

The study of the respiration of the mitochondrial fraction of brain homogenates in rats with PCI for 1 hour did not reveal any changes in the parameters of mitochondrial respiration and prooxidant-antioxidant balance compared with the control (p>0.05). There were no morphological changes either [3,6].

In the "TCI" group, with a complete cessation of blood circulation, the most pronounced changes in the studied parameters were noted. In the study of respiration of the mitochondrial fraction of brain homogenates, in comparison with the indicators in the control group, in the presence of malate/glutamate, V1 decreased by 65(58;67) %, p<0 xss=removed>V2 – by 41(38;48) %, p<0 xss=removed>V3 – by 25(22;38) %, p<0>0.05). In the presence of succinate, V1 decreased by 44(38;52) %, p<0 xss=removed>V2 – by 60(48;64) %, p<0 xss=removed>V3 – by 59(38;65) %, p<0 xss=removed>V4 – by 32(28;46) %, p<0 xss=removed>V1 was more pronounced when using the succinate substrate (by 21%, p<0>0.05), due to the complete absence of oxygen necessary for their production. Violations of energy and oxidative processes were reflected at the morphological level: hyperchromic wrinkled neurons made up a large proportion of the cell population, both normochromic and hyperchromic neurons were absent, a decrease in the size of neuronal perikaryons was observed (by 74 (68; 78) %, p <0>

In the " SCI " group, which provides for the shutdown of 90% of the blood flow, compared with the "control" group, in the presence of malate / glutamate, an increase in V2 by 24 (18; 27) %, p < 0 xss=removed>ETC [3,4,6,7].

However, changes in a number of indicators of mitochondrial respiration (V1, V2 and V3) with 1-hour SCI and 1-hour TCI were multidirectional. Their increase in SCI is associated with uncoupling of oxidation and phosphorylation, while their decrease in TCI is associated with a lack of substrates for mitochondrial respiration, in both cases leading to a decrease in energy production [3,7,10]. Energy disorders in the “SCI " group were accompanied by a decrease, compared with the "control" group, in the indicators of non-enzymatic mechanisms of antioxidant defense - total SH-groups of proteins and glutathione by 56 (49; 61) %, p<0>

Compared with the "control" group, in the 1st subgroup of SSCI with an interval between ligation of both common carotid arteries of 7 days, in the presence of malate/glutamate in the 1st subgroup of SSCI, an increase in V2 by 46 (39;56) % was observed, p<0>

In the 2nd subgroup of SSCI with an interval between dressings of 3 days, compared with the "control" group in the presence of the "malate/glutamate" substrate, there was only a decrease in V4 by 49(32;54) %, p<0>

In the 3rd subgroup of SSCI with a minimum interval between dressings of both CCAs of 1 day, compared with the control group in the presence of succinate, there was a decrease in the rates of V2, V3 and V4

by 52(43;65) %, p<0>

In general, the greatest disturbances in the energy and oxidative processes of the brain were observed in the 2nd and 3rd subgroups of SSCI, which indicates the highest activity of oxidative stress. At the same time, the indicators of mitochondrial respiration and prooxidant-antioxidant balance in these subgroups were the closest to those in the SCI group, while in the 1st SSCI subgroup with an interval between ligation of both common carotid arteries of 7 days, they were the same as in the PCI group. At the morphological level, step-by-step SCI with an interval of 1 and 3 days between dressings of both CCAs led to neuronal damage, which manifests itself in a decrease in their size, deformation of perikaryons, and an increase in the number of shrunken neurons and shadow cells. The most pronounced changes were observed in the subgroup with an interval between dressings of 1 day. These changes were similar to those in SCI (p>0.05). SSCI with an interval between CCA ligations of 7 days, on the contrary, is manifested by a lesser severity of histological changes: the size of the neuronal perikaryons and the ratio of neurons in terms of the degree of cytoplasmic chromatophilia differed slightly from those in the "PCI" group [5,7,9].

Thus, the most pronounced morphological and functional disorders (depression of mitochondrial respiration, suppression of antioxidant protection, shrinkage of neurons) occur during the simulation of TCI [10]. Subtotal ischemia, modeled by simultaneous ligation of both CCAs, and stepwise ligation of both CCAs with an interval of 1 day also led to severe irreversible neuronal damage: an increase in the number of hyperchromic shriveled neurons corresponded to inhibition of respiration of the mitochondrial fraction of brain homogenates and activation of peroxide processes [10]. When modeling SCI, the blood circulation in the circle of Willis is compensated, which explains a slight, compared with TCI and SCI, decrease in respiratory rates of the mitochondrial fraction of brain homogenates, as well as maintaining the prooxidant-antioxidant balance [1,2,8,10]. When the CCA was ligated with an interval of 7 days, the ratio of neurons according to the degree of chromatophilia of the cytoplasm and the size of the pericaryons of neurons did not differ from the values of the indicator in the control group. In the same animals, the respiratory parameters of the mitochondrial fraction of brain homogenates and the prooxidant-antioxidant balance were insignificant [1,2,8]. It was noted that the antioxidant protection of the brain was preserved as a manifestation of the activation of compensatory mechanisms: an increase in the efficiency of the processes of utilization of oxygen and oxidation substrates and their delivery to the mitochondria of neurons due to the effects of neuroglobin, an increase in the synthesis of nucleic acids and proteins, the transport of O2 and metabolic substrates, the dominance of the activity of anabolic processes over catabolic [4], which reduces the severity of oxidative stress.

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