NEUROTOXICANT EFFECTS ON ANTIOXIDANT SYSTEM INDICATORS AND SPECIFIC NEUROTROPHIC FACTORS IN THE REMOTE PERIOD AFTER SEVERE ACUTE POISONING

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Currently, biochemical mechanisms of neurotoxicant long-term effects on central nervous system (CNS) after acute severe poisoning remain largely unclear [2]. The number of neurological disorders is increasing steadily according to the type of asthenic syndrome, encephalopathy and organic disorders. However, most of these disorders are not associated with previous poisoning. Therefore, it is necessary to identify the pathogenetic mechanisms of long-term effects of the severe acute intoxication with neurotoxic substances and to determine the criteria for the effectiveness of pharmacological correction preparations. Thiopental sodium, a depressant, allows simulating severe poisoning which involves CNS damage. Cytotoxic action of neurotoxicants, in particular, manifests itself in the activation of free radical oxidation and disturbance of neurotrophic factor exchange in the brain. However, the antioxidant system reflects a general functional state of all organs and systems, not allowing assessing the CNS damage. It is known that active forms of oxygen cause disruption of intracellular homeostasis and trigger the induction of the mitochondrial signal pathway of the cell apoptosis [1]. Therefore, to assess the damage in nervous tissues, it is essential to determine both antioxidant system indices and the concentration of specific neurotrophic factors.

Materials and Methods. The study was performed with 30 white mongrel male rats. Animals were divided into two groups: control and experimental. The experimental group received thiopental sodium at a dose of 85 mg/kg body weight and the control group received a physiological saline solution. One month after the poisoning, the survived animals were euthanized to select a biological material. Concentrations of reduced glutathione, glutathione-S-transferase, products of lipid peroxidation - malonic dialdehydes, and diene conjugates were measured in erythrocyte hemolysates using modified spectrophotometric methods. The activity of superoxide dismutase, glutathione peroxidase, glucose-6-phosphate dehydrogenase was determined using a BioSystems A-25 biochemical analyzer and Randox reagents. The activity of the studied enzymes was calculated per gram of hemoglobin. Concentrations of neurotrophic markers, in particularly, myelin basic protein (MBP), calcium binding protein (S100), brain derived neurotrophic factor (BDNF), pigment epithelium derived factor (PEDF), and glial fibrillary acidic protein (GFAP) in the serum of laboratory animals were determined by ELISA. A statistical analysis was performed using Microsoft Excel. The mean and standard error (m ± sem) values were determined by Mann-Whitney U-test. Statistically significant differences were considered at p <0.05.

Results. The results obtained indicated a disturbance of the antioxidant system homeostasis. In particular, a significant 20% decrease in the activity of superoxide dismutase, a first link of the antioxidant protection, was registered one month after acute poisoning with sodium thiopental. Moreover, concentrations of diene conjugates increased by 20% compared to the control group, thus indicating the activation of lipid peroxidation processes, as one of the essential links in the pathogenesis of acute severe poisoning by neurotoxicants. It was also found that the S100 concentration reduced by 20% in the thiopental affected group, suggesting a general decrease in cell functions. S100 proteins are involved in numerous cellular activities, such as signal transduction, cell differentiation and motility, transcription, and cell cycle progression, through the regulation of Ca2+ exchange. At the same time, the concentration of PEDF, a protein with antiangiogenic, antitumorigenic, and neurotrophic properties, which was found to prevent the apoptotic death of neuronal cells under the peroxide stress, increased only by 15% (p<0.05) compared to the control [3]. The results obtained suggested that molecular-cellular changes in the organism during a long period after severe acute poisoning by neurotoxicants are characterized by an imbalance between pro- and antioxidant systems, as well as a disruption of the homeostasis of neurospecific factors. The study also showed the relevance of antioxidant system indicators in erythrocyte hemolysates coupled with specific biochemical markers of neurotoxicity-neuroprotection determined in the blood serum for assessing the effectiveness of neuroprotection and antioxidant therapy, which will allow predicting the outcome of treatment and the selection of appropriate curative strategy.

Prospects for further research. Our future research will aim at methodological approaches to the study of chemical neurotropic agent effects on CNS, which will allow solving urgent problems of the selection of pathogenetically valid diagnostic criteria and development of effective methods for prevention of long-term effects of neurotoxication.

References:


Key words: oxidative stress; neurotoxicants; antioxidant system; neurotrophic factors.

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