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Experimental Study of Combined Nootropic Drugs on Glucose Levels During the Development of Hemic Hypoxia

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Annotation. Worldwide, according to statistics (WHO), 47.5 million people suffer from dementia, and 7.7 million new cases are detected every year. By 2050, the world is expected to have 140 million patients, that is, approximately three times more than today. "...Much of the increase is due to an increase in the number of people with dementia living in low- and middle-income countries..." Dementia is considered the main cause of disability among the elderly and senile people worldwide. Despite the availability of a large number of nootropic drugs with different mechanisms of action, they are mostly imported at high cost, are aimed at a specific mechanism for the development of hypoxia and dementia, and are not available to the middle and lower strata of the population. In this regard, one of the urgent tasks that meets the standards of today's medicine is the creation of new complex nootropic drugs with combined effects, the study of specific and toxicological characteristics, as well as the molecular mechanisms of antihypoxic action.

Key words: Nootropic drugs, hypoxia, energy source

Introduction. Throughout the world, especially in regions with high fertility and life expectancy, special attention is currently being paid to a number of targeted scientific studies on the use of pharmacological compounds with various antihypoxic properties [6]. In this regard, despite the presence of a wide variety of nootropic drugs and the difference in their mechanisms of action, the effectiveness of existing nootropic drugs is considered insufficient. That is why an active search is being carried out not only for new synthetic nootropic drugs, but also for exploring the possibility of using a combination of several substances that meet the "price-quality" criterion in comparison with other drugs in which each active substance is contained separately. They have proven themselves due to their ability to reduce the number of medications a patient takes, thereby reducing the drug burden. Research aimed at simplifying such a treatment regimen, facilitating effective patient compliance with doctor's recommendations, has important scientific and practical significance.

Red blood cells lack mitochondria, so they can only use glucose as an energy source [3]. In erythrocytes, glucose catabolism ensures the preservation of the structure and function of hemoglobin, the integrity of membranes and the generation of energy for the operation of ion pumps. Glucose enters red blood cells through facilitated diffusion with the help of GLUT-2. About 90% of the incoming glucose is used in anaerobic glycolysis, and the remaining 10% is used in the pentose phosphate pathway.

The final product of anaerobic glycolysis, lactate, enters the blood plasma and is used in other cells, primarily hepatocytes [2]. ATP formed in anaerobic glycolysis ensures the operation of Na+, K+-ATPase and the maintenance of glycolysis itself, which requires the expenditure of ATP in the hexokinase and phosphofructokinase reactions.

Purpose of the study: Determination of glucose levels during the development of hemic hypoxia.

Material and research methods.

The antihypoxic activity of the drugs and some mechanisms of their action were studied in a model of hemic hypoxia, which was reproduced in 100 mature male rats by intraperitoneal administration of $NaNO_2$ at a dose of 50 mg/kg for 21 days. 14 rats died, which, in our opinion, is due to the toxic effect of the chemical. 10 rats made up the intact group. Experimental therapy began on the 7th day of the experiment, which lasted until the 21st day. The drugs were administered intraperitoneally for 7 and 14 days. On the 7th day of the experiment, the total number of surviving experimental animals was 76 rats, which were divided into 5 groups:

Group 1 – 16 rats, 0.9% NaCl solution was injected intraperitoneally in a volume of 3 ml (control);

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Group 2 – 15 rats, Citicoline solution was administered at a dose of 375 mg/kg intraperitoneally in a volume of 3 ml (comparison group);

Group 3 – 15 rats, were administered a solution of Cytargin at a dose of 780 mg/kg intraperitoneally in a volume of 3 ml (experiment 1);

Group 4 – 15 rats who were administered a solution of Cytcornit at a dose of 450 mg/kg intraperitoneally in a volume of 3 ml (experiment 2);

Group 5 – 15 rats who were administered Nootrotem solution at a dose of 337 mg/kg intraperitoneally in a volume of 3 ml (experiment 3).

Animals were decapitated on the 7th and 14th days from the start of treatment. The morphological composition of peripheral blood, hemoglobin content in erythrocyte hemolysate, methemoglobin (MetHb) level, methemoglobin reductase (MetHb-reductase) activity, HIF-1 content in the blood serum by enzyme immunoassay, and glucose level were determined.

Results and discussion.

It is well known that red blood cells do not have mitochondria, so only glucose is used as an energy source. Glucose catabolism preserves the structure and function of hemoglobin (Hb) and ensures the integrity of red blood cell membranes and provides energy for the ion pump. Thus, glucose comes to erythrocytes through facilitated diffusion of GLUT-1, approximately 90% of which is metabolized into anaerobic glycolysis, forming 2 lactate molecules and 2 ATP molecules, and approximately 10% in the pentose phosphate pathway [1] (Fig. 1).

Indicators of impaired blood oxygen supply to tissues are considered as indicators of the severity of pathological processes and changes in the metabolism of erythrocytes and the body, since the erythrocyte is responsible for providing oxygen for all processes occurring in it. Compared to other tissues, during glycolysis a significant amount of 2, 3-diphosphoglyceric acid (2, 3-DPG) 1, 3-diphosphoglyceric acid appears, which combines with the β-chains of globin and contributes to the release of Hb to tissues [5].

The pentose phosphate cycle is especially important in the carbohydrate metabolism of erythrocytes. If in other cells (nucleated) it is needed for the formation of ribulose-5-phosphate, which is converted into ribose-5-phosphate, used for the synthesis of nucleotides and nucleic acids, then in erythrocytes it is necessary for the formation of NADPH.H+ and the subsequent reduction of glutathione. The active hydrogen of the sulfhydryl group of glutathione is a “trap” of free radicals and is used to neutralize peroxides with the participation of glutathione peroxidase (GPO) formed in the erythrocyte membrane and violating its integrity [4].

The main energy source for red blood cells is glucose, which is oxidized through the anaerobic and pentose phosphate pathways. Therefore, this theory prompted us to decide to determine the content of the energy source in the hemolysate.

We found that in intact rats the glucose content was 4.75±0.31 and 4.9±0.29 mg/g Hb on the 14th and 21st days from the start of the experiment (see Fig. 1). In rats with hemolytic anemia, the glucose content in bioassays decreased at both times by 1.4 times ($P<0.01$), i.e. the energy substrate in erythrocytes decreased, possibly due to the appearance of pathological forms and their lysis.

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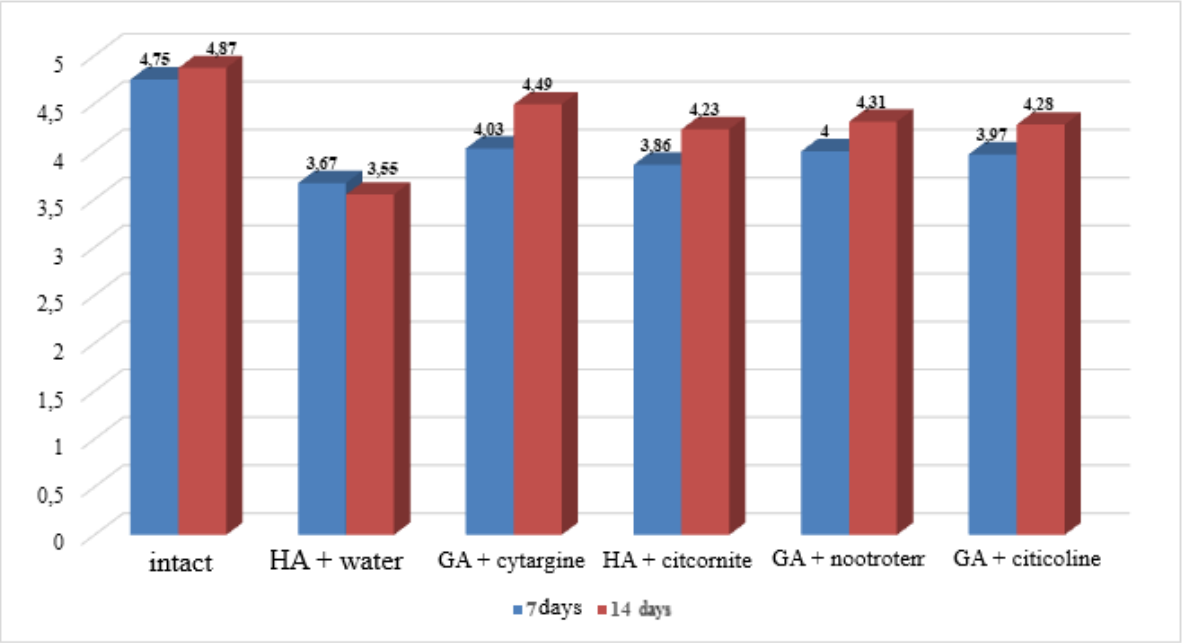

Rice. 1. Glucose content in the hemolysate of experimental animals, (mg/g Hb)

Experimental pharmacotherapy with nootropic drugs slightly increased the glucose content in biological objects, especially Cytargin, but not to the values of the intact group.
Based on the data obtained, the following conclusions can be drawn:
- with hemolytic hypoxia, hypoglycemia develops
- the use of nootropic drugs slightly increases glucose levels, but complete recovery is not observed.

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