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MODULATION OF HSP70 IN THE PHARMACOLOGICAL CORRECTION OF NERVOUS SYSTEM DISORDERS AFTER PRENATAL HYPOXIA

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Introduction

The problem of pharmacological correction of CNS hypoxic disorders is one of the priority. The heat shock protein Hsp70 is an endogenous regulator of many physiological processes, demonstrating cytoprotective effects in modeling of ischemic, hypoxic, and neurodegenerative processes. The neuroprotective effect of HSP70 is realized due to chaperone activity, stabilization of active enzymes, and regulation of apoptosis and necrosis of nerve cells. The multifaceted mechanisms of HSP70 cytoprotection indicate that it can be an effective pharmacological target, and the modulation of the synthesis and activity of HSP70 is a promising direction in the development of neuroprotective drugs for the treatment of the consequences of hypoxic action.

The aim of this research was to study the ability of cerebrocurin, angiolin, glutoredoxin, tamoxifen, thiotriazoline, L-arginine, nikomex, HSF-1 and piracetam to modulate the level of HSP70 in the cerebral cortex and blood plasma of rats after prenatal hypoxia (PH).

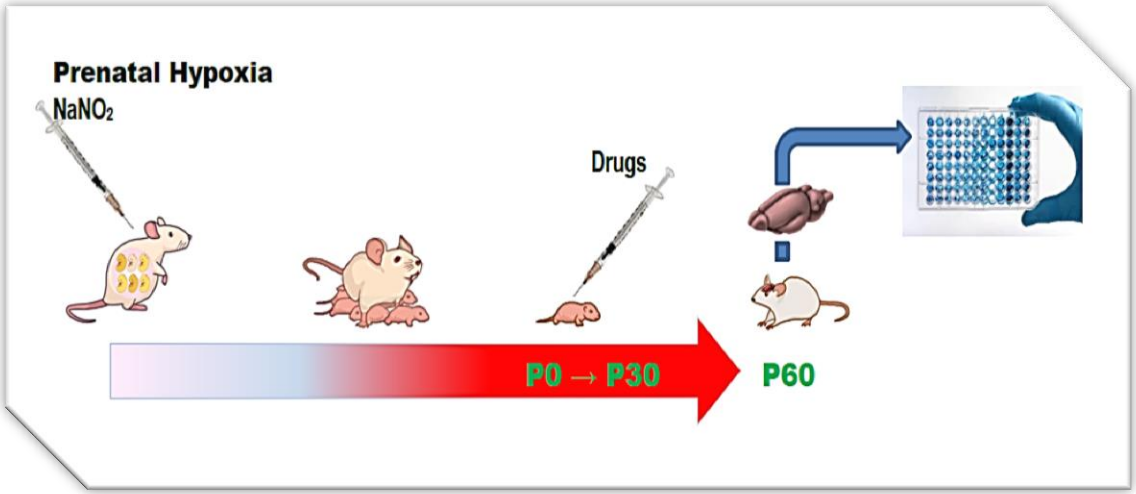
Materials and Methods

Hematic hypoxia modelling was performed in the prenatal development by daily intraperitoneal administration of sodium nitrite solution to pregnant female rats from day 16 to day 21 of the pregnancy at 50 mg/kg. Control pregnant rats received physiological solution in the same manner.
Newborns pups were divided into groups:
1- healthy pups from females with physiologically normal pregnancy which received physiological solution;
2- control group of pups after PH which received physiological solution daily;
3 - 12 groups of pups after PH that received drugs daily from postnatal day 1 to day 30.

Materials and Methods

Experimental groups:

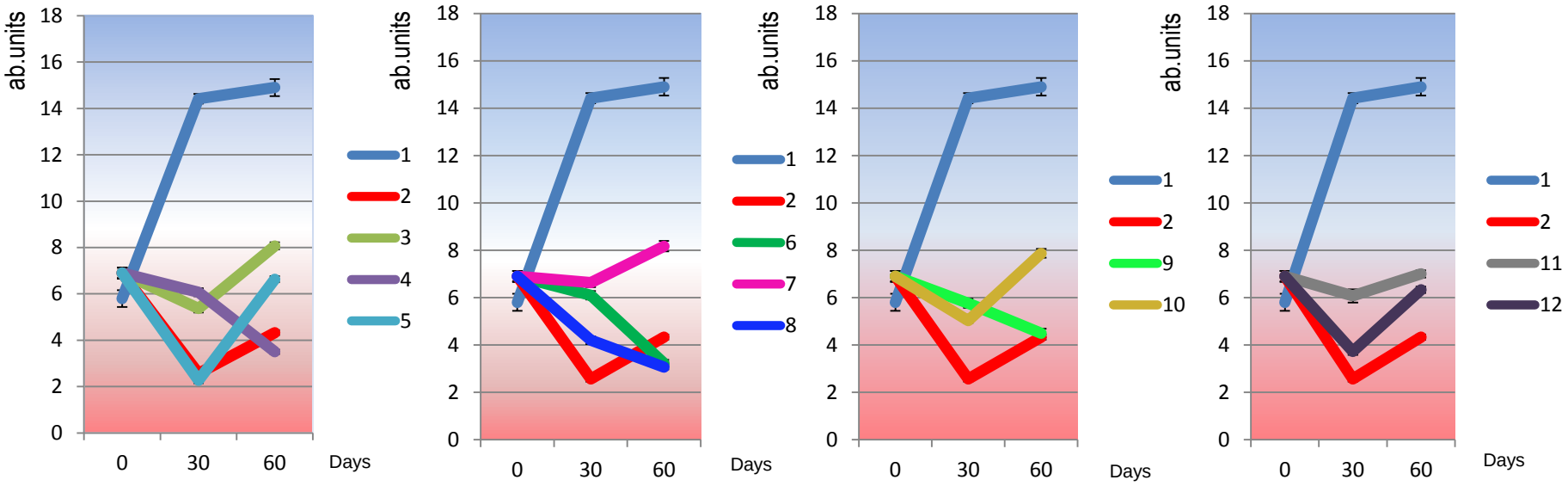
3 - PH + Angiolin ((S)-2,6–diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate) (50 mg/kg);
4 - PH +Piracetam (500 mg/kg);
5 - PH +Thiotriazoline (3-methyl-1,2,4-triazolyl-5-thioacetic acid morpholine) (50 mg/kg);
6 - PH + Mexidol (2-ethyl-6-methyl-3-hydroxypyridine succinate) (100 mg/kg);
7 - PH + Cerebrocurin (contains neuropeptides, S-100 proteins, reelin, nerve growth factor (NGF) (not less than 2 mg/ml) and amino acids) (150 µl/kg);
8 - PH + Tamoxifen (0.1 mg/kg);
9 - PH + L-arginine (200 mg/kg);
10 - PH + Glutoredoxin (200 µg/kg);
11 – HSF1 (50 mg/kg);
12 – Mildronate (50 mg/kg)



The content of HSP70 in the blood plasma and in the cytoplasmic and mito-chondrial fractions of the brain of rat on the 1st, 30th and 60th day of life after PH were determined by enzyme immunoassay.

Results

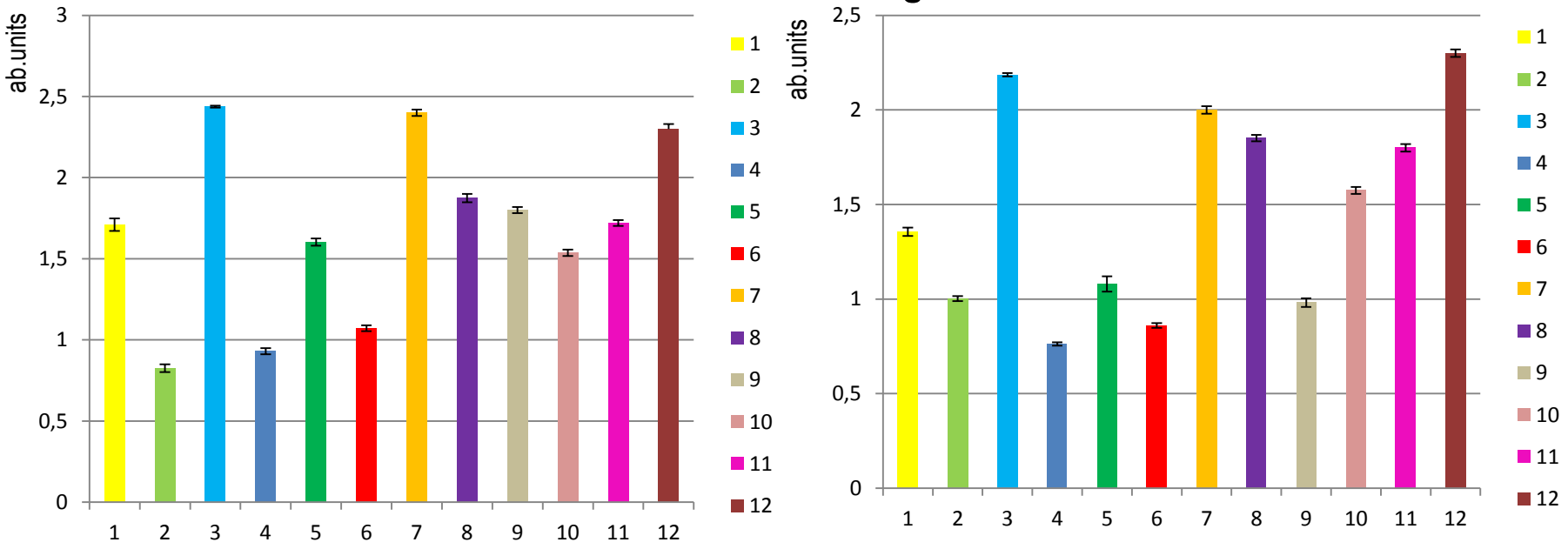
The content of HSP70 proteins in blood plasma after the use of drugs



Groups: 1 - intact, 2 – PH (control), 3 - PH + Angiolin); 4 - PH +Piracetam; 5 - PH +Thiotriazoline; 6 - PH + Mexidol; 7 - PH + Cerebrocurin; 8 - PH + Tamoxifen; 9 - PH + L-arginine; 10 - PH + Glutoredoxin; 11 – HSF1; 12 – Mildronate.

Results

HSP70 Concentration in Mitochondrial and Cytosolic Fractions of Rat Brain Homogenate



Groups: 1 - intact, 2 – PH (control), 3 - PH + Angiolin); 4 - PH +Piracetam; 5 - PH +Thiotriazoline; 6 - PH + Mexidol; 7 - PH + Cerebrocurin; 8 - PH + Tamoxifen; 9 - PH + L-arginine; 10 - PH + Glutoredoxin; 11 – HSF1; 12 – Mildronate.

Results

It has been established that PH leads to suppression of HSP70 synthesis and to decrease in its intra- and extracellular levels with the most significant decrease during the 1st month of life. By the end of the 2nd month, a 2-fold increase in the content of HSP70 in the blood plasma is observed, but it remains 3.5 times lower than the intact values. Course administration of drugs demonstrates an increase in intracellular and extracellular levels of HSP70 with a prolonged effect. Cerebrocurin, angiolin, and tamoxifen were the most active modulators of intracellular HSP70. Cerebrocurin, angiolin, and piracetam had the most active effect on the HSP70 content in blood plasma, but the effect of piracitam on the cytosolic and mitochondrial fractions of HSP70 was the least of all the drugs studied.

Conclusions

- PH leads to a significant and long-term decrease in intracellular and extracellular levels of HSP70 after birth.
- The introduction of drugs increases the content of HSP70 in blood plasma and intracellular fractions.
- Cerebrocurin and angiolin were the most effective modulators of HSP70, and their neuroprotective effect deserves further comprehensive study in order to develop methods for effective treatment of the PH consequences.
- HSP70 can serve as a target and marker of hypoxia pharmacological correction.