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SEARCH FOR NEW TARGET LINKS IN COMPLEX THERAPY OF PRENATAL CNS DAMAGE. PHARMACOLOGICAL MODULATION OF HSP70 – DEPENDENT MECHANISMS OF ENDOGENOUS NEUROPROTECTION

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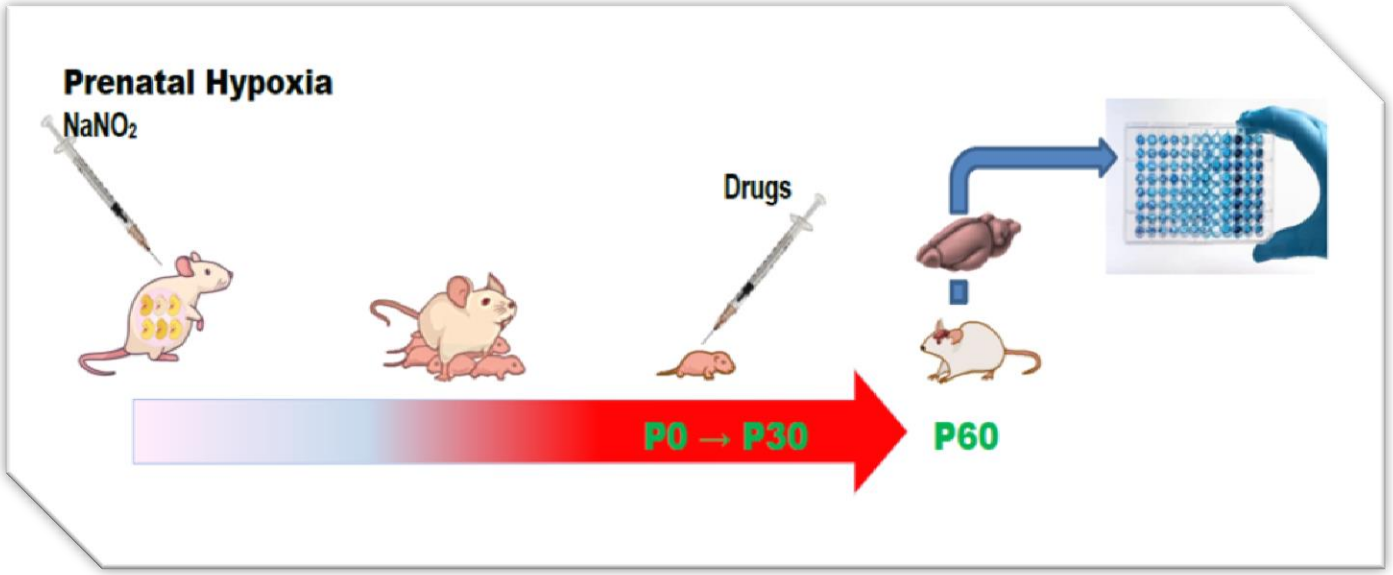
Search for New Target Links in Complex Therapy of Prenatal CNS Damage. Pharmacological Modulation of HSP70 – dependent Mechanisms of Endogenous Neuroprotection



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Abstract: Prenatal hypoxia (PH) is the main cause of prenatal pathologies of the central nervous system and neonatal mortality. The elaboration of new ways of pharmacological correction of nervous system disorders after the action of PH is a priority task for scientific and practical research.

The aim of this research was to establish the therapeutic efficacy of L-arginine, Tamoxifen, Cerebrocurin, Piracetam, Angiolin, RAIL, Glutoredoxin, Thiotriazoline and Mexidol by their ability to influence the expression and synthesis of HSP- and HIF-proteins as markers of endogenous neuroprotection under the conditions of modeling PH.

Hemic PH was modeled by the administration of sodium nitrite solution (50 mg/kg) to pregnant females from 16 to 21 days of pregnancy. From the first day of life, the rat pups were injected with the studied drugs in a course of 1 month. The material for the study was taken on the 60th day of life. Expression levels of HSP70 mRNA, HIF-1 mRNA, c-fos mRNA were determined by real-time PCR methods, and the concentration of HSP70 in the cytoplasmic and mitochondrial fractions of the brain was studied by enzyme immunoassay.

It has been established that chronic PH suppresses the expression of HSP70 mRNA, HIF-1 mRNA, c-fos mRNA in brain neurons and, as a result, reduces the concentration of HSP70 in the neuronal mitochondrial and cytosolic fractions in the early postnatal period. The influence of most of the drugs selected for the study leads to the activation of the synthesis of HSP70, HIF-1, c-fos, increasing the expression of the corresponding mRNA and the content of HSP70 in the cytoplasmic and mitochondrial fractions. The most active modulators of HSP70/HIF-1 were Angiolin and Cerebrocurin. The results of the work can be a substantiation for the development of new approaches to rational neuroprotection after PH, the action of which is aimed at the activation of HSP70/HIF-1a-mediated mechanisms of endogenous neuro- and cytoprotection and, ultimately, at rehabilitation after neurological damages.

Keywords: CNS, prenatal hypoxia, endogenous neuroprotection, HSP70

Introduction

Prenatal hypoxia (PH) is the main cause of prenatal pathologies of the central nervous system and neonatal mortality. The elaboration of new ways of pharmacological correction of nervous system disorders after the action of PH is a priority task for scientific and practical research.

The **aim** of this research was to establish the therapeutic efficacy of L-arginine, Tamoxifen, Cerebrocurin, Piracetam, Angiolin, RAIL, Glutoredoxin, Thiotriazoline and Mexidol by their ability to influence the expression and synthesis of HSP- and HIF-proteins as markers of endogenous neuroprotection under the conditions of modeling PH.

Materials and Methods

Modelling hematic hypoxia was performed in the prenatal period of 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 regime.

The progeny was divided into groups:

1- healthy pups from females with physiologically normal pregnancy which received physiological solution;

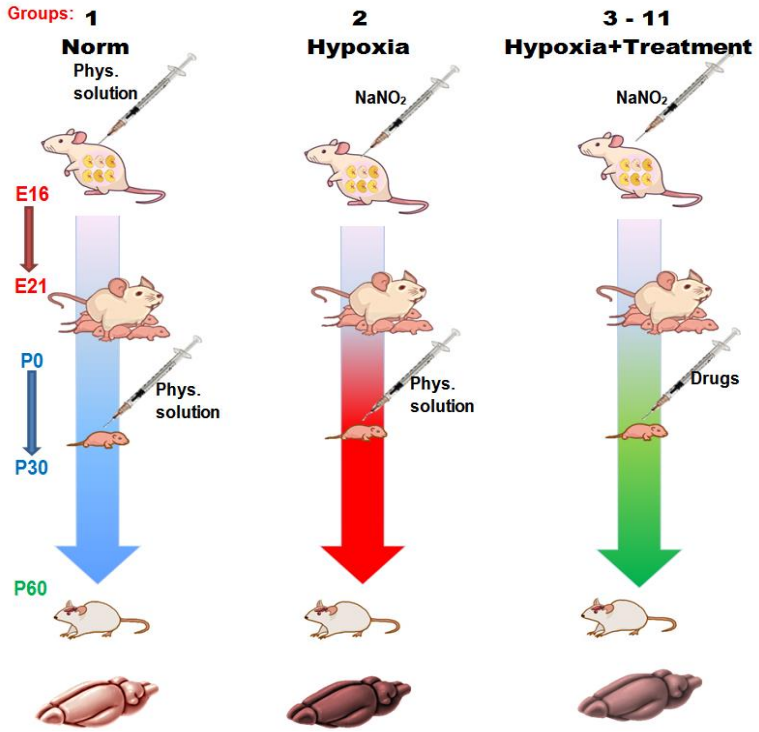
2- control group of pups after PH which received physiological solution daily;

3 - 11 groups of pups after PH that received drugs daily from postnatal day 1 to day 30.

Materials and Methods

Groups:

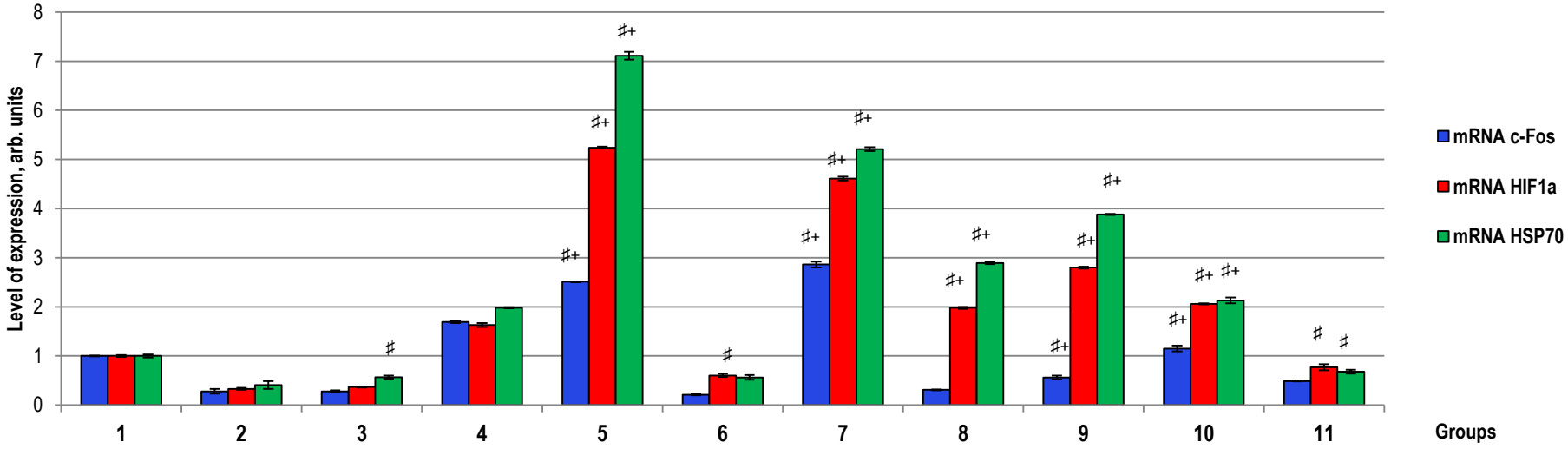
1 - healthy animals (intact), n = 10;
2 - animals subjected to PH (control), n = 10;
3 - PH + L-arginine (200 mg/kg), n = 10;
4 – PH + Tamoxifen (0.1 mg/kg), n =10;
5 - PH + Cerebrocurin (contains neuropeptides, S-100 proteins, reelin, nerve growth factor (NGF) (not less than 2 mg/ml) and amino acids) (150 µl/kg), n = 10;
6 - PH +Piracetam (500 mg/kg), n = 10;
7 - PH + Angiolin ((S)-2,6–diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate) (50 mg/kg), n = 10;
8 - PH + RAIL (selective IL-1b antagonist) (1 mg/kg), n = 10;
9 - PH + Glutoredoxin (200 µg/kg), n = 10;
10 – PH +Thiotriazoline (3-methyl-1,2,4-triazolyl-5-thioacetic acid morpholine) (50 mg/kg);
11 – PH + Mexidol (2-ethyl-6-methyl-3-hydroxypyridine succinate) (100 mg/kg), n = 10.



Expression levels of mRNA HSP70, HIF-1, c-fos and the content of HSP70 in the cytoplasmic and mitochondrial fractions of the brain of rat on the 60th day of life after PH were determined by real-time PCR and enzyme immunoassay.

Results and discussion

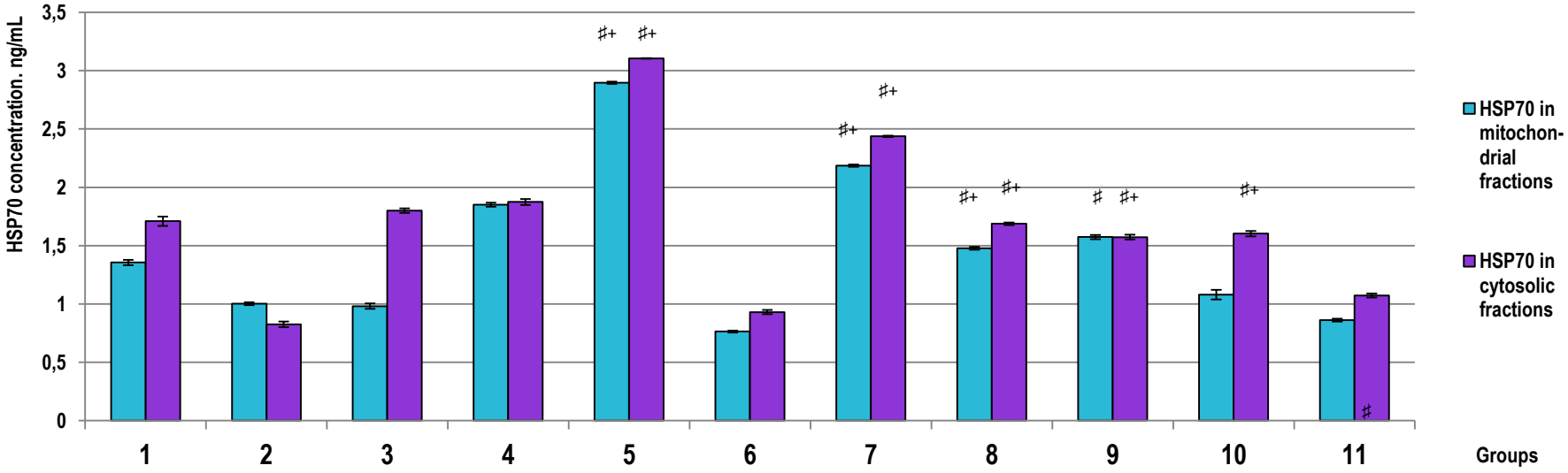
Expression of mRNA of c-fos, HIF1α and HSP70 in the sensorimotor cortex of rats after PH



♯ - statistically significant differences compared to the control group (PH), $p < 0.05$;
+ - statistically significant differences compared to the Piracetam control group, $p < 0.05$.

Results and discussion

HSP70 Concentration in Mitochondrial and Cytosolic Fractions of Rat Brain Homogenate



♯ - statistically significant differences compared to the control group (PH), p < 0.05;
+ - statistically significant differences compared to the Piracetam control group, p < 0.05.

Results and discussion

A decrease in the expression of mRNA of HSP70 and c-fos and a decrease in the concentration of HSP70 in mitochondria and in the cytosol of the brain in rat pups after PH indicate the inhibition of transcriptional processes in neurons and the suppression of HSP70 - dependent mechanisms of endogenous neuroprotection.

A 30-day course of treatment with the selected drugs resulted in various effects on the expression of HIF-α, HSP70, and c-fos mRNAs, as well as the concentration of HSP70 in the brain of pups subjected to PH. The highest significant ($p < 0.05$) values of HIF-α mRNA and HSP70 mRNA expression were observed in animals after Cerebrocurin and Angiolin. The drugs studied, except L-Arginine, RAIL and Piracetam, led to an increase in the level of c-fos mRNA expression.

The HSP70 concentration in the cytosol fraction of the brain homogenate in the experimental groups generally correlated with the values of its mRNA expression. The changes in HSP70 concentration in the mitochondrial fraction in the groups of animals subjected to PH that received treatment were different after the drugs studied (no changes after administration of L-Arginine and Thiotriazoline, a decrease after courses of Piracetam and Mexidol, an increase after treatment with other drugs with maximum effect of Cerebrocurin and Angiolin).

Conclusions

Chronic prenatal hypoxia suppresses the expression of HSP70 mRNA, HIF-1 mRNA, c-fos mRNA in brain neurons and, as a result, reduces the concentration of HSP70 in the neuronal mitochondrial and cytosolic fractions in the early postnatal period. The influence of most of the drugs selected for the study leads to the activation of the synthesis of HSP70, HIF-1, c-fos, increasing the expression of the corresponding mRNA and the content of HSP70 in the cytoplasmic and mitochondrial fractions. The most active modulators of HSP70/HIF-1 were Angiolin and Cerebrocurin. The results of the work can be a substantiation for the development of new approaches to rational neuroprotection after PH, the action of which is aimed at the activation of HSP70/HIF-1a-mediated mechanisms of endogenous neuro- and cytoprotection and, ultimately, at rehabilitation after neurological damages.