

PHARMACOLOGICAL MODULATION OF HIF-1 α IN THE CEREBRAL CORTEX OF RATS AFTER CHRONIC PRENATAL HYPOXIA

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Introduction

Despite the significant advances in modern medicine, the problem of perinatal hypoxic CNS damage in children occupies one of the leading places in modern neonatology. Hypoxic damage to the fetal brain is the cause of delayed psycho-linguistic and motor development, mental insufficiency, movement disorders, cerebral palsy, disability and severe cases of neonatal mortality. Chronic prenatal hypoxia (PH) leads to biochemical and structural changes in the developing brain and, as a consequence, to the pathological development of the fetal brain, to the development of neurological deficit not only immediately after birth, but also in the late periods of postnatal ontogenesis. The protein factors identified in recent decades, which are involved in the mechanisms of urgent and long-term adaptation to hypoxia (HIF1), can serve as specific targets for pharmacological action, opening up promising opportunities for the search for new effective drugs for the treatment of hypoxic CNS lesions in children.

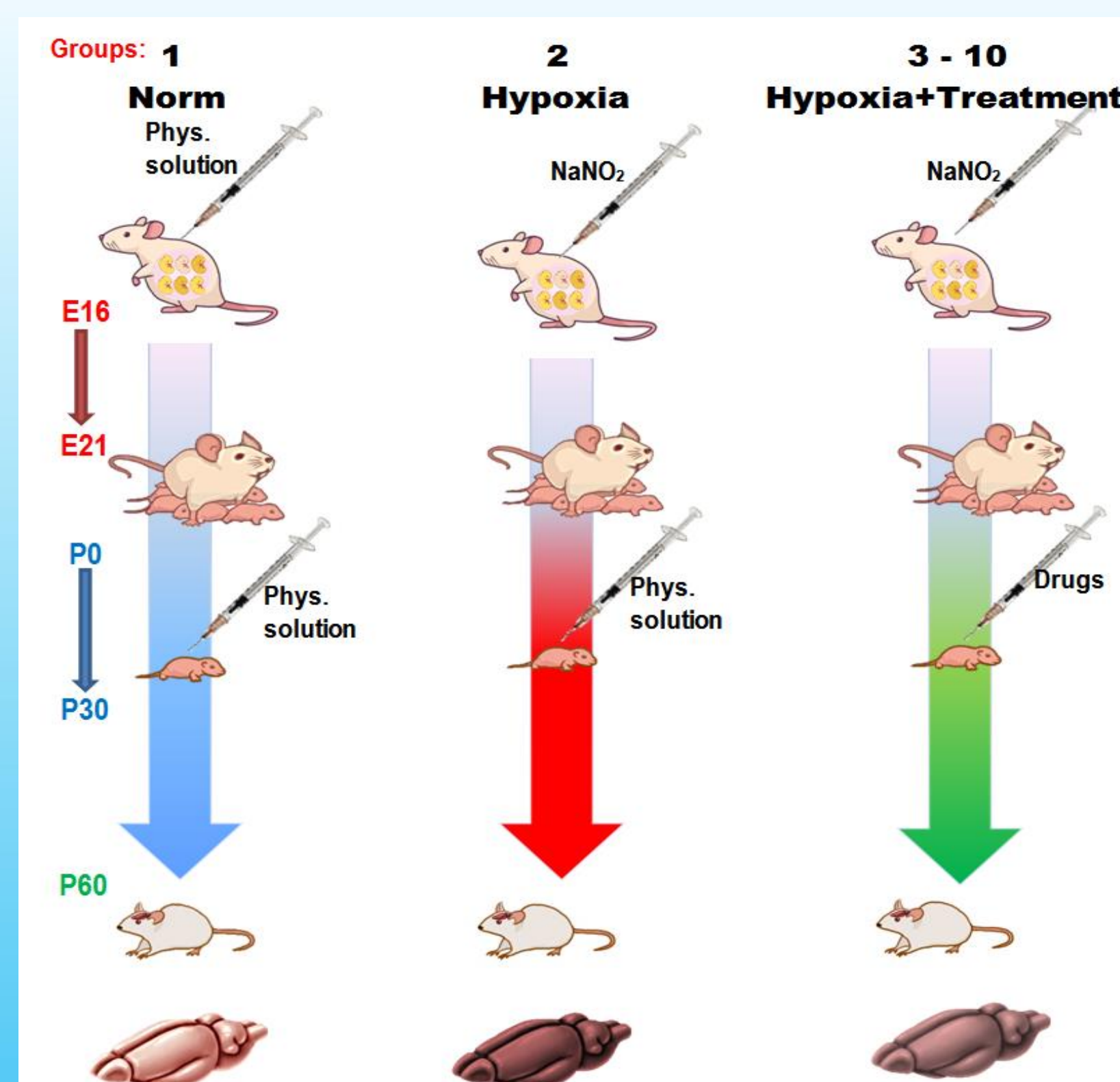
Statement of Purpose

The aim of the research: to study the ability of a number of drugs (Cerebrocurin, Angiolin, Glutoredoxin, Thiotriazoline, L-arginine, Mexidol, Tamoxifen and Piracetam) to modulate the level of HIF-1 α expression in the cerebral cortex of rats after chronic PH.

Materials and Methods

The studies were carried out on 100 male rats of two months of age, obtained from females, in which, chronic PH was modeled in the offspring. Modelling of 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 a dose of 50 mg/kg.

Newborn animals were divided into 10 groups: 1st – intact animals obtained from females with normal physiological pregnancy, which received 1 ml of physiological solution; 2nd – control animals after PH, 3-10 groups – animals after PH, which after birth were intraperitoneally injected with the drug in an effective dose: 3 – L-arginine (200 mg/kg); 4 – Tamoxifen (0.1 mg/kg); 5 – Cerebrocurin (contains neuropeptides, S-100 proteins, reelin, nerve growth factor (NGF) (not less than 2 mg/ml) and amino acids) (150 μ l/kg); 6 – Piracetam (500 mg/kg); 7 – Angiolin ((S)-2,6-diaminohexanoic acid 3-methyl-1,2,4-triazolyl-5-thioacetate) (50 mg/kg); 8 – Glutoredoxin (200 μ g/kg); 9 – Thiotriazoline (3-methyl-1,2,4-triazolyl-5-thioacetic acid morpholine) (50 mg/kg); 10 – Mexidol (2-ethyl-6-methyl-3-hydroxypyridine succinate) (100 mg/kg).

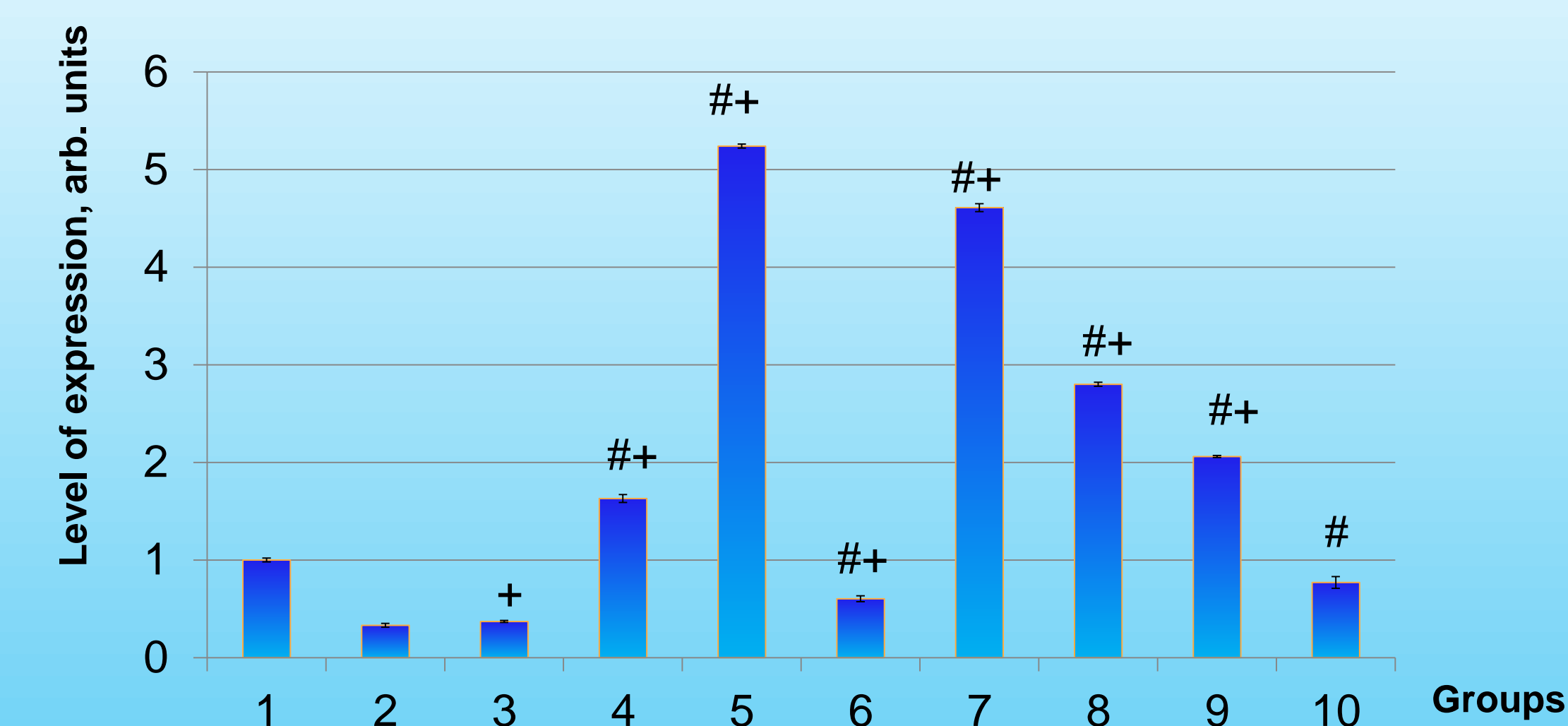


Real-time reverse transcription polymer chain reaction (RT-PCR) was used to assess the state of HIF-1 α expression. The results of the study were processed using the statistical package of the licensed program "STATISTICA for Windows 12.0". The significance of differences between the experimental groups was assessed using the nonparametric Mann-Whitney U-test. Differences with a significance level of more than 95% ($p < 0.05$) were considered significant.

Results

It was found that in animals after PH, the expression level of HIF-1 α mRNA is 3 times lower than in intact animals. Analysis of the results of the prolonged action of the studied preparations on the level of HIF-1 α mRNA expression shows that the use of the studied preparations led to an increase in the level of HIF-1 α mRNA expression, except for animals receiving L-arginine. Cerebrocurin increased this indicator by 15.8, Piracetam – by 82%, Angiolin – by 13.9 times, Glutoredoxin – 8.5 times, Thiotriazoline – 6.2 times, Mexidol – 2, 3 times.

Expression of mRNA of HIF1 α n 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, $p < 0.05$.

The indices of HIF-1 α mRNA expression in rats after administration of Cerebrocurin and Angiolin are maximal and significantly exceed those of all experimental groups.

The conducted studies show that modeling of prenatal hypoxia and its pharmacological correction change the pattern of HIF-1 α mRNA expression. An increase in the expression of HIF-1 α mRNA directly indicates the activation of certain genes of the cellular genome associated with the action of stimulating signals on the activation of adaptive-compensatory intracellular mechanisms in cells in response to the harmful effects of PH.

Conclusions

Thus, HIF-1 α is a promising target for neuroprotection after prenatal hypoxia exposure. Cerebrocurin and Angiolin can be considered as promising agents for correcting the negative consequences of chronic prenatal hypoxia in newborns.