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Abstract

Prognostic Significance of Neurodegradation/Neuroplasticity Markers and Endothelial Dysfunction Indicators in Assessing the Efficiency of Therapy for Children with CNS Disorders after Prenatal Hypoxia

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Abstract: Prenatal hypoxia (PH) is a leading factor in the disorders of fetal CNS development, potentially leading to death or significant neuropsychiatric pathologies in children. The aim of our study is to identify and evaluate the prognostic role of markers related to neurodegeneration/neuroplasticity and indicators of endothelial dysfunction in the assessing the efficiency of therapy of PH damage consequences. In the experimental model of chronic nitrite-induced PH, we studied the dynamics of markers of neurodegradation/neuroplasticity and indicators of endothelial dysfunction in offspring in the early postnatal period. We also investigated the relationship between neurodegradation/neuroplasticity and endothelial dysfunction indicators, and the clinical characteristics of children with cerebral insufficiency following PH exposure. Our findings reveal that neurotrophic factors, heat shock proteins, and factors induced by hypoxia are key neurochemicals with the potential to counteract neurodestruction mechanisms. Dysfunction in the synthesis of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) may contribute to impaired neuroplasticity during brain development, ultimately resulting in the development of cerebral insufficiency in children after PH. Here, we demonstrate the neuroprotective role of HSP70 and HIF-1a under PH conditions. We have established a direct correlation between HSP70 concentration, intensity of neurological disorders, and the levels of specific markers of neurodegeneration. HSP70 modulators could be considered as promising neuroprotectors in the complex therapy of children after PH.

Keywords: CNS, prenatal hypoxia, HSP70, markers of neurodegeneration/neuroplasticity, endothelial dysfunction, modulators of HSP70, neuroprotection

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Prenatal hypoxia (PH) is a leading factor contributing to fetal central nervous system (CNS) development disorders and can result in death or significant neuropsychiatric pathologies in children. Our studies, alongside that of other authors, has established that the development of cerebral insufficiency in children who have undergone pre- and perinatal hypoxia is based on the processes of neurodegradation. These processes are associated with the activation of transmitter autocoidosis, oxidative and nitrosative

stress and impaired energy metabolism, occurring against the backdrop of mitochondrial dysfunction. In both experimental and clinical settings, a direct correlation has been established between the concentration of several neurospecific proteins, their antibodies, molecular markers of oxidative stress, and mitochondrial dysfunction in the blood of newborns and the severity of their clinical condition. Presently, we are actively investigating the correlations between the processes of neurodegradation/neuroplasticity and endothelial dysfunction factors, which might be involved in the mechanisms underlying the development of cerebral insufficiency in children who have experienced pre- and perinatal hypoxia. Given the above, we believe that the identifying the relationship between neuromolecular and neurochemical markers of neurodegradation/neuroplasticity and indicators of endothelial dysfunction in children who have undergone pre- and perinatal hypoxia without receiving neuroprotective therapy is relevant and important in the subsequent organization of neuroprotective therapy.

The aim of our study is to identify and evaluate the prognostic role of markers of neurodegeneration/neuroplasticity and indicators of endothelial dysfunction in assessing the efficiency of therapy for PH-induced damage consequences.

We induced hematic hypoxia during the prenatal period by daily intraperitoneal administration of a sodium nitrite solution to pregnant female rats from day 16 to day 21 of the pregnancy at a dose of 50 mg/kg, which causes moderate hypoxia. The experiments were conducted using 50 outbred white female rats and 10 males, with weights ranging from 220 to 240 grams and aged 4.5 months, obtained from the vivarium of the Institute of Pharmacology and Toxicology of the National Medical Academy of Ukraine. We examined the dynamics of neurodegeneration/neuroplasticity markers and indicators of endothelial dysfunction in the early postnatal period. We investigated the relationship between neurodegeneration/neuroplasticity, endothelial dysfunction indicators and clinical characteristics of children in the early postnatal period. We sought to establish the prognostic significance of neurodegradation-neurorepair and endothelial dysfunction indicators in children with cerebral insufficiency following pre- and perinatal hypoxia, specifically regarding the assessment of pharmacotherapy's effectiveness in terms of neurological recovery.

It has been established that neurotrophic factors, heat shock proteins, and factors induced by hypoxia are among the few neuromolecules known to possess the capability to counteract neurodegradation mechanisms. Our accumulated preclinical data indicate that dysfunction in the synthesis of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) may contribute to impaired neuroplasticity during brain development, ultimately resulting in the development of cerebral insufficiency in offspring born to pre- and perinatal hypoxia survivors.

The study uncovered the neuroprotective role of HSP70 and HIF-1a in conditions of cerebral ischemia and hypoxia. A direct correlation was established between HSP70 concentration, the severity of neurological disorders and the level of specific markers of neurodegeneration. It was demonstrated that lower concentrations of HSP70 are

associated with the progression of neurodegeneration. The more pronounced increase in nitrotyrosine levels in the hippocampus can account for the reduced presence of HSP70 protein and higher scores on the stroke-index scale C. R. McGraw. Cortical neurons exhibited relatively more moderate nitrosative stress responses. Under these conditions, there was an observed increase in the level of HSP70. This is explained by its chaperone activity, which is aimed at intensification of reserve-adaptation capabilities under hypoxia conditions. Through statistical analysis of the data, a correlation was established between the obtained parameters. Pearson's coefficient was employed to assess the strength and statistical significance of this correlation. The results revealed a close relationship between the neurological deficit index and the level of heat shock proteins 70, both in the cerebral cortex ($r = -0.91$) and in the hippocampus ($r = -0.81$).

The observed relationship between the studied parameters and the increasing neurological deficit is linked to the development of oxidative and nitrosative stresses and the diminished compensatory capacity of the organism. Moreover, in the presence of excessive oxidative modification, HSP70 proteins themselves undergo oxidative alterations, leading to a decrease in the expression activity of genes responsible for chaperone synthesis. This disruption impairs the functional activity of HSP proteins and curtails their protective properties under ischemic conditions.

The data on shifts in the thiol-disulfide system under brain hypoxia and the increase of its oxidized intermediates in blood were obtained from one-month-old baby rats after HSP treatment.

Additionally, through statistical analysis, a correlation between the concentration of HSP70 and GSH was established in both the cerebral cortex (Pearson's coefficient $r=0.71$) and the hippocampus (Pearson's coefficient $r=0.80$).

Furthermore, it was found that PH, in conjunction with an increase in neurospecific markers of CNS lesions (S-100, NSE), is accompanied by an increase in blood inflammatory mediators leading to endothelial dysfunction (IL-1b, iNOS, serine proteases, nitrotyrosine, and products of oxidative protein modification).

We assume that there is a conjugated NO/SH system in the CNS, which plays a role in the mechanisms of neurodegradation/neuroprotection. We have found that in norm, the ratio of nitrotyrosine/GSH is around 1.3 units, while in mild neurology, it increases to 5.0, and in severe cases, it can reach up to 130. The administration of HSP70 modulators as neuroprotectants to children after PH resulted in a positive change in the studied markers, confirming the prospectiveness of our studies. Here we show the neuroprotective role of HSP70 and HIF-1a under conditions of PH. A direct correlation between HSP70 concentration, intensity of neurological disorders and the level of specific markers of neurodegeneration has been established. HSP70 modulators can be considered as promising neuroprotectors in the complex therapy of children after PH.

Supplementary Materials:

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Informed Consent Statement: Informed consent was obtained from all subjects in-volved in the study.

Data Availability Statement: The data are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.