medical sciences forum

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Abstract

Modulation of Hsp70 in the Pharmacological Correction of Nervous System Disorders after Prenatal Hypoxia †

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† Presented at the 2nd International Electronic Conference on Biomedicines, 1–31 March 2023. Available online: https://ecb2023.sciforum.net.

Abstract: The problem of pharmacologically correcting CNS hypoxic disorders is one of priority. HSP70, an endogenous regulator of cytoprotective processes, can be considered as an effective pharmacological target. 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). We studied the effect of the drugs on the content of HSP70 in the plasma and neurons (cytoplasmic and mitochondrial fractions) of rat pups on the 30th and 60th day of life in model of chronic hemic PH using the enzyme immunoassay method. It was found that PH leads to the suppression of HSP70 synthesis and to the decrease in its intra- and extracellular levels, with the most significant decrease during the 1st month of life. Drugs course administration 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 HSP70 fractions was the least of all the drugs studied. Here, we show that 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 hypoxic disorders. HSP70 can serve as a target and marker of hypoxia pharmacological correction.

Keywords: CNS; prenatal hypoxia; HSP70; modulators of HSP70; pharmacological correction; pharmacological target; neuroprotection; neuroprotective drugs; cerebrocurin; angiolin

Citation: Aliyeva, O.; Belenichev, I.; Popazova, O. Modulation of Hsp70 in the Pharmacological Correction of Nervous System Disorders after Prenatal Hypoxia. *Med. Sci. Forum* **2023**, *21*, 39. https://doi.org/10.3390/ECB2023-14091

Academic Editor: Masaru Tanaka

Published: 1 March 2023

The problem of pharmacologically correcting CNS hypoxic disorders is one of priority. HSP70, an endogenous factor of cytoprotective processes, can be considered as an effective pharmacological target. The heat shock protein Hsp70 is an endogenous regulator of many physiological processes, demonstrating cytoprotective effects in models of ischemic, hypoxic, and neurodegenerative processes. The neuroprotective effect of HSP70 is realized due to chaperone activity, the stabilization of active enzymes, and the regulation of nerve cell apoptosis and necrosis. The multifaceted mechanisms of HSP70 cytoprotection indicate that it can be an effective pharmacological target and that 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).

Hematic hypoxia modelling was performed during prenatal development by the daily intraperitoneal administration of a sodium nitrite solution to pregnant female rats between day 16 and day 21 of pregnancy at 50 mg/kg. Control pregnant rats received a physiological solution in the same manner.

Newborns pups were divided into groups:

1. Healthy pups from females with physiologically normal pregnancy, which received a physiological solution;
2. Control group of pups after PH, which received a physiological solution daily;
3. Groups three through twelve after PH that received drugs daily from postnatal day 1 to day 30.

The drugs received by groups 3-12 included 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, and 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); and 12—mildronate (50 mg/kg).

The content of HSP70 in the blood plasma and in the cytoplasmic and mitochondrial fractions of the brain of the rats on the 1st, 30th and 60th day of life after PH were determined using an enzyme immunoassay.

It has been established that PH leads to the suppression of HSP70 synthesis and to the 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. The 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.

PH leads to oxidative and nitrosative stress when neurons are damaged in newborns. The effect of the hyperproduction of ROS and cytotoxic forms of nitrogen monoxide during antioxidant deficiency is persistent impairment of the higher functions of the CNS due to the oxidative modification of receptors' protein structures, neuron ion channels, and the disruption of transmitter reuptake mechanisms. An excess of ROS and NO during the antenatal period can lead to the formation of primary mitochondrial dysfunction, to the disruption of the energy metabolism of the brain, to the low bioavailability of oxidation substrates, to the energy deficiency and, as a rule, to transmitter autokoidosis and to the initiation of apoptotic and ferroptotic reactions.

PH causes the intrauterine programming of the HSP70 gene, which leads to the inhibition of its response to heat stress and the loss of endogenous cytoprotection at a later age. HSP70 is involved in the regulation of cell-response signaling pathways to hypoxic stress at the level of HIF protein stability regulation. Thus, the normalization of HSP70 expression may be one of the therapeutic strategies to reduce CNS damage that develops after PH.

Here, we show that cerebrocurin and angiolin were the most effective modulators of HSP70, and their neuroprotective effect deserves further comprehensive study in order to develop methods for the effective treatment of hypoxic disorders. HSP70 can serve as a target and marker of hypoxia pharmacological correction.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ECB2023-14091/s1.

Author Contributions: Conceptualization, methodology, I.B. and O.A.; conducting an experiment, O.A., O.P.; data curation, O.P.; writing and editing, O.A.; project administration, I.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The experimental studies were carried out in accordance with the "Regulations on the Use of Animals in Biomedical Research" and with the European Convention on the Protection of Animals Used for Scientific and Other Purposes. The experiment was approved by the Bioethics Committee of Zaporizhzhia State Medical University.

Informed Consent Statement: Not applicable.

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

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