medical sciences forum

MDPI

Abstract

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

Olena Aliyeva *, Igor Belenichev and Olena Popazova

Zaporizhzhia State Medical University, Zaporizhzhia, Ukraine
* Correspondence: aliyeva1eg@gmail.com
† Presented at the 2nd International Electronic Conference on Biomedicines, 1–31 March 2023; Available online: https://ecb2023.sciforum.net.

Abstract: The problem of pharmacological correction of CNS hypoxic disorders is one of the 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 drugs on the content of HSP70 in plasma and neurons (cytoplasmic and mitochondrial fractions) of rat pups on the 30th and 60th days of life in model of hemic chronic PH using the enzyme immunoassay method. It was found 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. 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**, *3*, x. https://doi.org/10.3390/xxxxx

Published: 1 March 2023

The problem of pharmacological correction of CNS hypoxic disorders is one of the 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 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).

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:

(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 mitochondrial fractions of the brain of rat on the 1st, 30th and 60th day of life after PH were determined by enzyme immunoassay.

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.

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

PH causes intrauterine programming of the HSP70 gene, which leads to inhibition of its response to heat stress and loss of endogenous cytoprotection at a later age. HSP70 is involved in the regulation of signaling pathways of cell response to hypoxic stress at the level of regulation of HIF protein stability. Thus, 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 effective treatment of hypoxic disorders. HSP70 can serve as a target and marker of hypoxia pharmacological correction.