DESCRIPTION FOR THE GENERAL PUBLIC (IN ENGLISH)

The main goal of the proposed research is to determine the mechanisms of neuroprotective effect of group II the metabotropic glutamate receptors (mGluR2/3) agonists in an animal model of birth asphyxia.

Perinatal hypoxic-ischemic states, known as asphyxia, often lead to the death of the newborn, whereas 25% of infants, which survive these episodes, display permanent structural and functional disabilities (such as cerebral palsy, epilepsy, pseudobulbar and extrapyramidal palsy as well as spastic paresis) known as postischemic encephalopathy.

The pathomechanisms of a number of neurodegenerative diseases include, as a common secondary element, excessive or prolonged stimulation of glutamate receptors, known as excitotoxicity. Therefore, it seems reasonable to search for pharmacological substances and therapeutic strategies that inhibit this process and/or modulate the physiological level of glutamate transmission.

It has been shown that activation of group II receptors (mGluR2 /3) results in an inhibition of glutamate release and the activation of the production of trophic factors by glial cells, which may exert a neuroprotective effect. Based on these considerations administration of mGluR2/3 agonist may result in neuroprotective after cerebral ischemia (Bruno et al., 2001).

Therefore in proposed project we plan to check the effect of two specific agonists - LY 379268 (mGluR2) and NAAG (mGluR3) on neuroprotection in an animal model of perinatal hypoxia. We want to explore the mechanisms of their action, concentrating on potential inhibition of apoptosis and the role in induction of neurotrophic factors synthesis.

Proposed experiments will be conducted on an established, widely used model of hypoxic-ischemic brain injury, induced on 7-day old rats. The model is based on the unilateral interruption of blood flow to the brain by the left common artery ligation followed by a 75 minute hypoxia (7.5% oxygen in nitrogen). Hypoxia-ischemia results in a unilateral brain damage (ipsilateral hemisphere). The opposite hemisphere (contralateral) will be treated as an inner control.

Chosen mGluR2/3 agonists (LY 379268 and NAAG) will be applied before (24 h or 1 h) or (1h or 6 h) hypoxia-ischemia and the effect of agonists on the process of neuroprotection will be examined. The first stage of the proposed experiments includes the determination of the effects of agonists on the degree of brain damage (morphological evaluation and brain weight deficit). The next stage includes the analysis of activity of enzymes and expression of factors engaged in apoptotic processes s: caspase 3 and 9, Omi/HtrA2 , endonuclease G, cytochrome C, AIF, SMAC/Diablo, Apaf-1 and HIF-1 alpha. The analysis will also assess selected growth factors: brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), transforming growth factor β (TGF-β. The neuroprotection will be also examined in behavioral open field test. The results of proposed experiments will be published in international journals. In case of confirmation of neuroprotective effects of mGluR2/3 agonists in experimental hypoxia-ischemia therapy, this compounds can be considered as part of new therapeutic strategies for treatment in birth asphyxia.