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Neuroprotective effects of metabotropic glutamate receptors group II (mGluR2/3) agonists in an animal model of birth asphyxia

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Introduction: Hypoxic-ischemic encephalopathy (HIE) results in permanent damage of central nervous system that may result in neonatal death or developmental disorders. 20%–30% of infants with HIE die in the neonatal period and 33%–50% of survivors demonstrate permanent neurodevelopmental abnormalities (such as cerebral palsy) and mental retardation. It was shown recently that group II metabotropic glutamate receptors (mGluR2/3) activation before or after ischemic insult results in neuroprotection but the exact mechanism of this effect is not clear.

Aim: The aim of present study was to investigate whether mGluR2/3 activation after experimental hypoxia-ischemia reduces brain damage and if the reduction of the expression of pro-apoptotic factors is one of the mechanisms involved.

Methods: We used an animal model of hypoxia-ischemia (H-I) on 7-day old rat pups. Animals were anesthetized and the left common carotid artery was isolated, double-ligated and then cut between the ligatures. After completion of the surgical procedure the pups were subjected to hypoxia (7.4% oxygen in nitrogen for 75 min at 35 C). Control pups were sham-operated (anaesthetized and left c.c.a. dissected, but not ligated). Animals were injected intra-peritoneal with specific mGluR2 (LY 379268) and mGluR3 (NAAG) agonists 24 h or 1 h before H-I (5 mg/kg of body weight). The weight deficit of the ischemic brain hemisphere was measured and the expression of Bax, Bcl-2 and HTR/OMI was examined. The damage in the hippocampal CA1 region was examined by Cresyl violet (CV) staining. Also the differences in the expression of neurotrophic factors (BDNF, GDNF, TGF –beta) were measured (ELISA).

Results & Discussions: Our results show that application of mGluR2/3 agonists before H-I results in neuroprotection. Application of both agonists resulted in decrease in brain tissue weight loss in ischemic hemisphere independently on the time of application (from 40% in H-I to 15-20% in treated). Histological examination of the brain tissue showed that both mGluR2/3 agonists applied 24 h or 1 h before H-I decrease the damage of neuronal cells and the disorganization of CA1 region of hippocampus. In our study we also observed the relative changes in the expression of Bax, Bcl-2 and HTR/OMI proteins in ipsilateral and contra-lateral hemisphere. Both agonist mGluR2/3 applied 24 h or 1 h before H-I decreased expression of Bax and HTR/OMI and increased expression of Bcl-2 in the ischemic brain hemisphere compared to untreated H-I. Both mGluR2/3 agonists (LY379268 and NAAG applied 24 h or 1 h before HI) decreased TGF beta expression and increased BDNF and GDNF expression in the ischemic brain hemisphere compared to H-I.

Conclusions: Our results show that activation of mGluR2 or mGluR3 in a short time before H-I insult reduce brain damage in 7-days old rats and decrease apoptotic processes initiated by HI in developing brain. These results suggest that activation of group II mGluR before H-I triggers mechanisms that result in neuroprotection.

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