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The metabotropic glutamate receptors group II (mGluR2/3) agonists post-conditioning reduces brain damage in the model of birth asphyxia in seven day old rats

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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 neuro-protection but the exact mechanism of this effect is not clear. 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. We used an animal model of hipoxia-ischemia (H-I) on seven day old rat pups. Animals underwent unilateral common carotid artery ligation combined with 75 min hypoxia at 7.4% oxygen. Control pups were sham-operated (anaesthetized and left C.C.A. dissected, but not ligated). Animals were injected intraperitoneally with mGluR2 (LY 379268) and mGluR3 (NAAG) agonists 1 h or 6 h after H-I (5 mg/kg of body weight). We examined the weight deficit of the ischemic brain hemisphere and the expression of SMAC/DIABLO, cytochrome C and Apaf-1. The activation of caspase 3 and 9 was also measured. Our results show that application of each agonist decreased brain tissue weight loss in ischemic hemisphere independently on the time of application (from 40% in H-I to 15-20% in treated). Both agonists of mGluR2/3 applied 1 h or 6 h after H-I decreased expression of SMAC/DIABLO, cytochrome C and Apaf-1 proteins compared to untreated H-I. mGluR2/3 agonists application decreased expression of caspase 3 and caspase 9 in the ischemic hemisphere compared to H-I. Hypoxic-ischemic injury to the central nervous system can have devastating lifelong effects on the developing fetus and the neonate. This study is the demonstration of the neuro-protective effect of mGluR 2/3 agonist on neonatal hypoxic-ischemic brain injury. These data suggest the possibility that post-conditioning reduces irreversible ischemic injury in part by decreasing apoptosis.

Biography

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