Type-2 metabotropic glutamate receptors in the treatment of neurodegeneration associated with cerebral ischemia

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Stroke is the second leading cause of death and a major cause of acquired disability in developed countries. Up to date, there are no treatments with the exception of thrombolytic agents, which are effective only in a small percentage of patients and in a very restricted time-window after the onset of brain ischemia. The identification of novel strategies in the treatment of stroke is an urgent clinical need. In the ischemic core, where blood flow is most severely restricted, cells die in minutes. However, in the tissue surrounding the core, known as ischemic penumbra, energy is partially preserved and cells die more slowly in a timeframe that critically depends on their intrinsic vulnerability to ischemic damage. Vulnerable neurons of the ischemic penumbra are salvageable if neuroprotective drugs are administered in the appropriate time window. A large body of evidence demonstrates that excitotoxicity mediated by NMDA receptors contributes to delayed neuronal death in the ischemic penumbra (Iadecola and Anrather, 2011). Several pharmacological classes of NMDA receptor antagonists have been developed as neuroprotective agents in stroke, but they consistently failed in clinical studies. Metabotropic glutamate (mGlu) receptors are considered as potential targets for neuroprotective interventions because they do not 'mediate', but rather 'modulate' excitatory synaptic transmission (Bruno et al., 2001). In our study, we examined the expression profile of different mGlu receptor subtypes in vulnerable and resistant hippocampal neurons in the 4-vessel occlusion (4-VO) model of transient global ischemia in rats (Pulsinelli and Brierley, 1979). Rats subjected to 4-VO show selective degeneration of hippocampal CA1 pyramidal neurons, whereas neurons of the CA3 region are relatively spared. Hence, using this model is possible to study the molecular determinants underlying the selective vulnerability of CA1 pyramidal neurons by comparing molecular changes occurring in the CA1 and CA3 regions. In addition, the 4-VO model allows a precise examination of molecular events preceding neuronal death. We measured the transcripts of mGlu1, mGlu2, mGlu3, and mGlu5 receptors by quantitative PCR in microdissected hippocampal CA1 and CA3 regions at different times that precede neuronal death following ischemia/reperfusion. We found a substantial reduction of mGlu2 receptor mRNA levels in the 'vulnerable' CA1 region after reperfusion, with no changes in the 'protected' CA3 region. No changes in the transcripts of mGlu1, mGlu3, and mGlu5 receptors were found after global ischemia in the CA1 and CA3 regions. The reduction of mGlu2 receptor mRNA levels found in the CA1 neurons after ischemia was associated with a decrease in the histone H3 acetylation levels at the mGlu2 gene promoter, and with a CA1 selective up-regulation of type-2 histone deacetylase (HDAC-2), which is known to epigenetically regulate the expression of mGlu2 receptors (Kurita et al., 2012). This suggests an hypothetical epigenetic cascade in which global ischemia up-regulates HDAC2 in vulnerable neurons, thereby suppressing the expression of mGlu2 receptors. We then performed pharmacological studies to test the potential therapeutic effects of drugs that selectively target mGlu2 receptors. Data obtained by systemic administration of mGlu2 receptors positive and negative allosteric modulators suggest that mGlu2 receptors may exert a neurotoxic function in neurons, and their expression positively correlates with the selective vulnerability of CA1 neurons to the ischemic insult.

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