

DIFFERENTIAL ROLE OF mGlu1 and mGlu5 RECEPTORS IN RAT HIPPOCAMPAL SLICE MODELS OF ISCHEMIC TOLERANCE

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Activation of ionotropic glutamate receptors has been proposed as a key factor in the induction of ischemic tolerance in the brain (1) but no study has yet investigated the possible role of group I metabotropic glutamate (mGlu) receptors in this process. In the present study, we used organotypic rat hippocampal slices exposed to 30 min oxygen glucose deprivation (OGD) as a model of post-ischemic cell death that leads to selective injury of the CA1 subregion 24 h later (2). In this model, 10 min exposure to OGD 24 h before the exposure to toxic OGD was not lethal and reduced the subsequent OGD neurotoxicity by approximately 53% (ischemic preconditioning). Similarly, a 30 min exposure to the group I mGlu receptor agonist DHPG (10 μ M) significantly reduced OGD neurotoxicity 24 h later by approximately 49% (pharmacological preconditioning). Ischemic tolerance did not develop when either the selective mGlu1 antagonists LY367385 and 3-MATIDA or the AMPA/KA antagonist CNQX were present in the incubation medium during exposure to the preconditioning OGD stimulus. Neither the NMDA antagonist MK801 nor the mGlu5 receptor antagonist MPEP affected the preconditioning process. On the other hand, pharmacological preconditioning was prevented not only by LY367385 or CNQX, but also by MPEP. In both ischemically and pharmacologically preconditioned slices, the toxic responses to AMPA (3-30 μ M, 60 min) or NMDA (10-100 μ M, 60 min) were significantly reduced. Conversely, the neurotoxicity of 100 μ M DHPG in slices simultaneously exposed to a mild (20 min) OGD was differentially altered in the two preconditioning paradigms. After ischemic preconditioning, DHPG neurotoxicity was reduced in a manner that was sensitive to LY367385 but not to MPEP, whereas after pharmacological preconditioning it was enhanced in a manner that was sensitive to MPEP but not to LY367385. Our results show that mGlu1 and mGlu5 receptors are differentially involved in the induction and expression of ischemic tolerance following two diverse preconditioning stimuli.

1. Gidday G.F. (2006) *Nat. Rev. Neurosci.* 7: 437-448.

2. Pellegrini-Giampietro D.E., Cozzi A., Peruginelli F., Leonardi P., Meli E., Pellicciari R. and Moroni F. (1999) *Eur. J. Neurosci.* 11: 3637-3647.