Differential role of metabotropic glutamate 4 (mGlu4) receptor expressed in glial cells

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Demyelinating diseases such as multiple sclerosis (MS) and the pre-clinical model, experimental autoimmune encephalomyelitis (EAE), are characterized by damage of oligodendrocytes (OL) that are very sensitive to oxidative stress and excitotoxicity. OLs express metabotropic glutamate receptors (mGluR) that are widely distributed in the CNS and are differently involved in neurodegeneration/neuroinflammation. The expression of mGlu1, mGlu5 and mGlu2/3 receptors is in fact enhanced in acute and chronic active MS lesions whereas overexpression of mGlu8 involves mainly astrocytes and microglia. mGlu4 receptor also is overexpressed in reactive astrocytes localized at the rim of chronic active lesions in MS brain. We have specifically be intrigued by mGlu4 receptor because L-2-amino-4-phosphonobutanoate (L-AP4), an orthosteric agonist specific for group III mGluRs, including mGluR4, attenuates clinical signs of EAE and mice lacking mGluR4 are more susceptible to EAE. These effects have been ascribed to a peripheral protective action mediated by mGluR4, limiting the immune response during neuroinflammation (Fallarino et al., 2010), but the direct effect of mGlu4 receptor activation on glial cells have not been investigated. mGlu4 receptors are expressed in OLs and a 48-h treatment with L-AP4 causes earlier OL differentiation, as shown by their morphology and immunostaining with myelin basic protein (MBP). OLs that are not fully differentiated and stain positively for PDGF receptor, are sensitive to kainate toxicity (1 mM for 24 h) and pre-treatment with L-AP4 (50 μM, added 30 min before kainate) partially prevents their death. However, this effect is visible only when a low percentage of contaminating astrocytes is present and OLs are not mature enough to express MBP. Indeed, at that stage of maturation OLs do not express anymore mGlu4 receptor. mGlu4 receptors are also present on astrocytes and microglia, as revealed by co-immunostaining techniques with specific cell markers. Conditioned medium (CM) from astrocytes, either under basal conditions or activated by exposure to lipopolysaccharide (1 μg/ml for 48 h), and pre-treated with L-AP4, reduces kainate-induced OL toxicity, an effect prevented by the selective mGlu4 receptor antagonist CPPG. In contrast, CM from L-AP4-treated microglia fails to modify OL response to kainate toxicity. Diffuse expression of mGlu4 receptor in microglia and its marked increase in LPS-activated microglia is however justified by the ability of L-AP4 to reduce the expression of MHC class II molecule that is stimulated by exposure to LPS (0.1 μg/ml for 48 h) in the BV2 microglial cell line. The present results demonstrate that activation of mGlu4 receptor results in a protective effect on OL survival and that astrocytes and microglia differently participate to the protective effect mediated by this receptor.