Metabotropic glutamate receptors, subtype 1, epigenetically regulate the expression of mGlu5 receptors in the cerebellum

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We have recently shown that metabotropic glutamate (mGlu) receptors subtype 1 are down-regulated in Purkinje cells of a mouse model of type-1 spinocerebellar ataxia (SCA1). Interestingly, the loss of mGlu1 receptors was associated with the appearance of mGlu5 receptors in this cell population. Systemic treatment of SCA1 mice with the mGlu1 receptor enhancer, RO0711401, prevented the expression of mGlu5 receptors (Notartomaso et al., 2013). Here we extended the study and have confirmed that mGlu5 receptors are highly expressed in Purkinje cells in the first two weeks of postnatal life and their expression declines afterwards, whereas expression of mGlu1 receptors increases, as shown by immunohistochemistry, immunoblotting, and measurements of mRNA levels by quantitative PCR. Cerebellar maturation from PND9 to PND18 was associated with an increased methylation of the Grm5 gene promoter and a reduced methylation of the Grm1 gene promoter. We measured polyphosphoinositide (PI) hydrolysis in cerebellar slices using the mixed mGlu1/5 orthosteric agonist 3,5-dihydroxyphenylglycine (DHPG). In order to identify the mGlu1 and/or the mGlu5 component of the stimulation, we used two selective negative allosteric modulators, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP) for mGlu5 and (3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-(*cis*-4-methoxycyclohexyl)-methanone (JNJ6259658) for mGlu1 receptors. We found a strong DHPG-stimulated PI hydrolysis at PND9, when both mGlu1 and mGlu5 receptors contributed to the action of the agonist. At PND16, the residual stimulation by DHPG was exclusively mediated by mGlu1 receptors. However, in mice pre-treated systemically with JNJ6259685 for 7 days, mGlu5 receptors were still functional at PND16. In adult mice, systemic treatment with JNJ6259685 restored the expression of mGlu5 receptors in Purkinje cells, and caused a substantial reduction in *Grm5* methylation. These findings suggest that expression of mGlu5 receptors in Purkinje cells is down-regulated by an epigenetic mechanism that is triggered by the activation of mGlu1 receptors. This mechanism may be relevant to processes of developmental neuronal plasticity that rely on the activation of mGlu1 receptors, such as the elimination of supernumerary climbing fibers.

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