A functional cross-talk between group-I and group-II metabotropic glutamate receptors occurs in heterologous expression systems and brain tissue

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Group-I metabotropic glutamate (mGlu) receptors, mGlu1 and mGlu5 receptors, are coupled to polyphosphoinositide (PI) hydrolysis via a Gq/11 protein, whereas group-II mGlu receptors, mGlu2 and mGlu3, are negatively coupled to adenylyl cyclase activity via a Gi/o protein. This general belief has conditioned functional studies carried out in *in vitro* preparations such as cultured neurons and in *ex vivo* brain tissues. However, an intriguing observation is that the prototypical mGlu1/5 receptor agonist, 3,5-dihydroxyphenylglycine (DHPG), is less efficacious than (1S,3R,4S)-1-aminocyclo-pentane-1,3,4-tricarboxylic acid (1S,3R-ACPD) in stimulating PI hydrolysis in brain slices. This difference does not reflect a greater intrinsic efficacy of 1S,3R-ACPD at mGlu1 and mGlu5 receptors, but rather the ability of the compound to recruit either mGlu2 or mGlu3 receptors. When DHPG is combined with selective mGlu2/3 receptor agonists, which are inactive on their own, it stimulates PI hydrolysis to the same extent as 1S,3R-ACPD in hippocampal slices (Genazzani et al., 1994; Schoepp et al., 1996). This suggests that a functional cross-talk between group-I and group-II mGlu receptors exists, but the molecular nature of this cross-talk is unknown. Here we used HEK-293 cells co-expressing mGlu1 receptors with either mGlu2 or mGlu3 receptors. In these cultures, DHPG-stimulated PI hydrolysis was amplified by the mGlu2/3 receptor agonist, (-)-2-oxa-4-aminocyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY379268). A similar potentiation was observed when the mGlu5 receptor was co-expressed with either mGlu2 or mGlu3 receptors. Accordingly, in cortical slices prepared from adult mice, LY379268 was able to potentiate DHPG-stimulated PI hydrolysis. However, potentiation was lost in slices prepared from mGlu3 receptor knockout mice and was unaffected in slices prepared from mGlu2 receptor knockout mice. This suggested that native mGlu3, but not mGlu2, receptors are functionally linked to mGlu1/5 receptors and play a permissive role on mGlu1/5 receptor-mediated PI hydrolysis. This hypothesis was supported by data obtained in cortical slices prepared from mice at postnatal day 14 (PND14). mGlu5 and mGlu3 receptors are known to be highly expressed in the early postnatal life, and all group-I mGlu receptor agonists are known to cause large stimulations of PI hydrolysis at this age. Interestingly, DHPG-stimulated PI hydrolysis was largely reduced in cortical slices prepared from PND14 mGlu3 receptor knockout mice as compared to age-matched wild-type or mGlu2 receptor knockout mice. These data suggest that endogenous activation of mGlu3 receptors largely contributes to mGlu1/5 receptor-mediated PI hydrolysis during early brain development.

Genazzani et al (1994) *Brain Res* 659:10-16.
Schoepp et al (1996) *Neuropharmacology* 35:1661-1672.