# Group-I metabotropic glutamate receptor-induced stimulation of polyphosphoinositide hydrolysis is entirely mediated by mGlu1 receptors in the retina

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Group-I metabotropic glutamate (mGlu) receptors (mGlu1 and mGlu5) are coupled to Gq/11 and their activation leads to polyphosphoinositide (PI) hydrolysis. Stimulation of PI hydrolysis by the mixed mGlu1/5 orthosteric agonist 3,5-dihydroxyphenylglycine (DHPG), is largely mediated by mGlu5 receptors in most brain regions (e.g., hippocampus, cerebral cortex, and corpus striatum), with the exception of the developing cerebellum in which both receptors equally contribute to the stimulation of PI hydrolysis. Both mGlu1 and mGlu5 receptors are found in the retina, where their precise function is largely unknown. Here we measured DHPG-stimulated PI hydrolysis in slices prepared from the bovine retina. Surprisingly, we found that DHPG-stimulated PI hydrolysis was abrogated by the mGlu1 receptor negative allosteric modulator (NAM), 3,4-dihydro-2H-pyrano[2,3]b quinolin-7-yl) (cis-4-methoxycyclohexyl) methanone (JNJ6259685), but was only minimally affected by the mGlu5 receptor NAM, 2-methyl-6-(phenylethynyl)pyridine (MPEP). As expected, however, MPEP was more efficient in reducing DHPG-stimulated PI hydrolysis in the bovine hippocampus. We also measured DHPG-stimulated PI hydrolysis in the mouse retina by incubating one entire retina per single test tube in the PI assay. Individual mouse retinas pre-labeled with [$^3$H]-myo-inositol responded to DHPG with an increased [$^3$H]-inositol phosphate formation. This response was highly sensitive to inhibition by JNJ6259685 but not to MPEP, as we observed in bovine retina. These data show for the first time that excitatory amino acid-stimulated PI hydrolysis in the retina is almost entirely mediated by mGlu1 receptors and suggest that mGlu1 receptors might be a better drug target than mGlu5 receptors in the experimental treatment of degenerative disorders of the retina.