Orphan receptor GPR158 serves as a metabotropic glycine receptor: mGlyR

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Glycine is a major neurotransmitter involved in several fundamental neuronal processes. The identity of the metabotropic receptor mediating slow neuromodulatory effects of glycine is unknown. We identified an orphan G protein–coupled receptor, GPR158, as a metabotropic glycine receptor (mGlyR) and validated its pharmacology using Promega Bright NanoLuc® BRET technology. We used a live-cell assay to monitor GAP activity by following kinetics of G protein deactivation. In this assay, activation of G proteins by GPCR stimulation generates the BRET signal upon interaction of liberated Venus-Gbg subunits with the masGRK3CT-NanoLuc® reporter illuminated with Nano-Glo®. This signal is quenched when Ga deactivation is triggered by GPCR antagonism and recombines with Venus-Gbg to form inactive heterotrimer. Glycine and a related modulator, taurine, directly bind to a Cache domain of GPR158, and this event inhibits the activity of the intracellular signaling complex regulator of G protein signaling 7/G protein b5 (RGS7-Gb5), which is associated with the receptor. Glycine signals through mGlyR to inhibit production of the second messenger adenosine 3′,5′-monophosphate. We further show that glycine, but not taurine, acts through mGlyR to regulate neuronal excitability in cortical neurons. These results identify a major neuromodulatory system involved in mediating metabotropic effects of glycine, with implications for understanding cognition and affective states.
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