Quantitative Analysis Reveals Multiple Mechanisms of Allosteric Modulation of the mGlu5 Receptor in Rat Astroglia

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Positive allosteric modulators (PAMs) of the type 5 metabotropic glutamate (mGlu5) receptor have demonstrable therapeutic potential in an array of neurological and psychiatric disorders. Here we have used rat cortical astrocytes to investigate how PAMs mediate their activity and reveal marked differences between PAMs with respect to their modulation of orthosteric agonist affinity and efficacy. Affinity cooperativity factors (α) were assessed using [3H]MPEP-PAM competition binding in the absence and presence of orthosteric agonist, whereas efficacy cooperativity factors (β) were calculated from net affinity/efficacy cooperativity parameters (α β) obtained from analyses of the abilities of PAMs to potentiate [3H]inositol phosphate accumulation in astrocytes stimulated with a sub-maximal concentration (EC20) of orthosteric agonist. We report that while DFB (3,3'-difluorobenzaldazine) and CDPPB (3-cyano-N-(1,3-diphenyl-1Hprazol-5-yl)benzamide) primarily exert their allosteric modulatory effects through modifying the apparent orthosteric agonist affinity at the astrocyte mGlu5 receptor, the effects of ADX47273 (S-(4-fluoro-phenyl)-{3-[3-(4-fluoro-phenyl)-{1,2,4]oxadiazol-5-yl}-piperidinl-1-yl}-methanone) are mediated primarily via efficacy-driven modulation.