IUPHAR/BPS Guide to Pharmacology CITE
https://doi.org/10.2218/gtopdb/F40/2019.4

Metabotropic glutamate receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

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Abstract

Metabotropic glutamate (mGlu) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors [334]**) are a family of G protein-coupled receptors activated by the neurotransmitter glutamate. The mGlu family is composed of eight members (named mGlu1 to mGlu8) which are divided in three groups based on similarities of agonist pharmacology, primary sequence and G protein coupling to effector: Group-I ($mGlu_1$ and $mGlu_5$), Group-II ($mGlu_2$ and $mGlu_3$) and Group-III ($mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$) (see Further reading).

Structurally, mGlu are composed of three juxtaposed domains: a core G protein-activating seven-transmembrane domain (TM), common to all GPCRs, is linked via a rigid cysteine-rich domain (CRD) to the Venus Flytrap domain (VFTD), a large bi-lobed extracellular domain where glutamate binds. The structures of the VFTD of $mGlu_1$, $mGlu_2$, $mGlu_3$, $mGlu_5$ and $mGlu_7$ have been solved [190, 262, 255, 386]. The structure of the 7 transmembrane (TM) domains of both mGlu1 and mGlu5 have been solved, and confirm a general helical organization similar to that of other GPCRs, although the helices appear more compacted [85, 415, 59]. mGlu form constitutive dimers crosslinked by a disulfide bridge. Recent studies revealed the possible formation of

heterodimers between either group-I receptors, or within and between group-II and -III receptors [86]. Although well characterized in transfected cells, co-localization and specific pharmacological properties also suggest the existence of such heterodimers in the brain [422, 257].

The endogenous ligands of mGlu are L-glutamic acid, L-serine-O-phosphate, N-acetylaspartylglutamate (NAAG) and L-cysteine sulphinic acid. Group-I mGlu receptors may be activated by 3,5-DHPG and (*S*)-3HPG [29] and antagonized by (S)-hexylhomoibotenic acid [223]. Group-II mGlu receptors may be activated by LY389795 [256], LY379268 [256], eglumegad [337, 416], DCG-IV and (2*R*,3*R*)-APDC [338], and antagonised by eGlu [161] and LY307452 [408, 100]. Group-III mGlu receptors may be activated by L-AP4 and (*R,S*)-4-PPG [125]. An example of an antagonist selective for mGlu receptors is LY341495, which blocks $mGlu_2$ and $mGlu_3$ at low nanomolar concentrations, $mGlu_8$ at high nanomolar concentrations, and $mGlu_4$, $mGlu_5$, and $mGlu_7$ in the micromolar range [176]. In addition to orthosteric ligands that directly interact with the glutamate recognition site, allosteric modulators that bind within the TM domain have been described. Negative allosteric modulators are listed separately. The positive allosteric modulators most often act as 'potentiators' of an orthosteric agonist response, without significantly activating the receptor in the absence of agonist.

Contents

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mGlu$_8$ receptor

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