

Metabotropic glutamate receptors in GtoPdb v.2025.3

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Abstract

Metabotropic glutamate (mGlu) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors [354]**) are a family of G protein-coupled receptors activated by the neurotransmitter glutamate [141]. 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 (mGlu₁ and mGlu₅), Group-II (mGlu₂ and mGlu₃) and Group-III (mGlu₄, mGlu₆, mGlu₇ and mGlu₈) (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. mGlu form constitutive dimers, cross-linked by a disulfide bridge. The structures of the VFTD of mGlu₁, mGlu₂, mGlu₃, mGlu₅ and mGlu₇ have been solved [203, 278, 271, 406]. The structure of the 7 transmembrane (TM) domains of both mGlu1 and mGlu5 have been solved, and confirm a general helical organisation similar to other GPCRs, although the helices appear more compacted [89, 436, 63]. Recent advances in cryo-electron microscopy have provided structures of full-length mGlu receptor homodimers [220, 193], heterodimers [92, 163], and new insights into activation mechanisms [47, 48, 201]. Studies have revealed the possible formation of heterodimers between either group-I receptors, or within and between group-II and -III receptors [90]. First characterised in transfected cells, co-localisation and specific pharmacological properties suggest the existence of such heterodimers in the brain [273, 443, 146, 286, 262, 221]. Beyond heteromerisation with other mGlu receptor subtypes, increasing evidence suggests mGlu receptors form heteromers and larger order complexes with class A GPCRs (reviewed in [141]).

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 antagonised by **(S)-hexylhomobotenic acid** [238]. Group-II mGlu receptors may be activated by **LY389795** [272], **LY379268** [272], **eglumegad** (also referred to as LY354470) [358, 437], **DCG-IV** and **(2R,3R)-APDC** [359], and antagonised by **eGlu** [172]

and LY307452 [428, 106]. Group-III mGlu receptors may be activated by L-AP4 and (R,S)-4-PPG [131]. An example of an antagonist selective for mGlu receptors is LY341495, which blocks mGlu₂ and mGlu₃ at low nanomolar concentrations, mGlu₈ at high nanomolar concentrations, and mGlu₄, mGlu₅, and mGlu₇ in the micromolar range [187]. In addition to orthosteric ligands that directly interact with the glutamate recognition site, allosteric modulators that recognise distinct sites primarily within the TM domain have been described. Negative allosteric modulators are listed separately. Positive allosteric modulators potentiate orthosteric agonist responses solely, or may also possess intrinsic agonist activity.

Contents

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Introduction to Metabotropic glutamate receptors

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Receptors

mGlu₁ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=289>

mGlu₂ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=290>

mGlu₃ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=291>

mGlu₄ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=292>

mGlu₅ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=293>

mGlu₆ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=294>

mGlu₇ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=295>

mGlu₈ receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=296>

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