

Metabotropic glutamate receptors in GtoPdb v.2021.3

Francine Acher¹, Giuseppe Battaglia², Hans Bräuner-Osborne³, P. Jeffrey Conn⁴, Robert Duvoisin⁵, Francesco Ferraguti⁶, Peter J. Flor⁷, Cyril Goudet⁸, Karen J. Gregory⁹, David Hampson¹⁰, Michael P. Johnson¹¹, Yoshihiro Kubo¹², James Monn¹³, Shigetada Nakanishi¹⁴, Ferdinando Nicoletti¹⁵, Colleen Niswender⁴, Jean-Philippe Pin⁸, Philippe Rondard⁸, Darryle D. Schoepp¹¹, Ryuichi Shigemoto¹⁶ and Michihiro Tateyama¹²

1. Université René Descarte, France
2. IRCCS NEUROMED, Italy
3. University of Copenhagen, Denmark
4. Vanderbilt University, USA
5. Oregon Health & Science University, USA
6. Innsbruck University, Austria
7. Novartis Institutes for Biomedical Research, Switzerland
8. Université de Montpellier, France
9. Monash University, Australia
10. University of Toronto, Canada
11. Lilly Research Laboratories, USA
12. National Institute for Physiological Sciences, Japan
13. Eli Lilly and Company, USA
14. Kyoto University Faculty of Medicine, Japan
15. University of Rome 'La Sapienza', Italy
16. Institute of Science and Technology, Austria

Abstract

Metabotropic glutamate (mGlu) receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors [347]**) are a family of G protein-coupled receptors activated by the neurotransmitter glutamate [138]. 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 [198, 271, 264, 399]. 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 [87, 429, 61]. Recent advances in cryo-electron microscopy have provided structures of full-length mGlu receptor dimers [189]. Studies have revealed the possible formation of heterodimers between either group-I receptors, or within and between group-II and -III receptors [88]. First well characterized in transfected cells, co-localization and specific pharmacological properties also suggest the existence of such heterodimers in the brain [266],[436, 143, 279]. Beyond heteromerization with other mGlu receptor subtypes, increasing evidence suggests mGlu receptors form heteromers and larger order complexes with class A GPCRs (reviewed in [138]).

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** [30] and antagonized by **(S)-hexylhomoibotenic acid** [232]. Group-II mGlu receptors may be activated by **LY389795** [265], **LY379268** [265], **eglumegad** [350, 430], **DCG-IV** and **(2R,3R)-APDC** [351], and antagonised by **eGlu** [168] and **LY307452** [421, 103]. Group-III mGlu receptors may be activated by **L-AP4** and **(R,S)-4-PPG** [128]. 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 [183]. 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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Introduction to Metabotropic glutamate receptors

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Receptors

mGlu₁ receptor

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

mGlu₂ receptor

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mGlu₃ receptor

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mGlu₇ receptor

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mGlu₈ receptor

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