Glutamate, metabotropic

Overview: Metabotropic glutamate (mGlu) receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on Metabotropic Glutamate Receptors, Schoepp *et al*., 2000) are activated by the endogenous ligands L-glutamate, L-aspartate, L-serine-*O*-phosphate (LSOP), *N*-acetylaspartylglutamate (NAAG) and L-cysteine sulphonic acid. Examples of agonists selective for mGlu receptors compared with ionotropic glutamate receptors are 1*S*,3*R*-ACPD and L-CCG-I, which show limited selectivity for Group II receptors. 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 $mGlu_1$, $mGlu_4$, $mGlu_5$ and $mGlu_7$ in the micromolar range (Kingston *et al*., 1998). Three groups of native receptors are distinguishable on the bases of similarities of agonist pharmacology, primary sequence and G protein effector coupling: 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). Group I mGlu receptors may be activated by DHPG and 3HPG (Brabet *et al*., 1995) and antagonized by LY393675 (Baker *et al*., 1998). Group II mGlu receptors may be activated by LY389795 (Monn *et al*., 1999), LY379268 (Monn *et al*., 1999), LY354740 (Schoepp *et al*., 1997; Wu *et al*., 1998), DCG-IV and 2*R*,4*R*-APDC (Schoepp *et al*., 1996), and antagonized by EGLU (4.3, Jane *et al*., 1996) and LY307452 (Wermuth *et al*., 1996; Escribano *et al*., 1998). Group III mGlu receptors may be activated by (*RS*)PPG (Gasparini *et al*., 1999a).

In addition to orthosteric ligands that directly interact with the glutamate recognition site, allosteric modulators 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.

Nomenclature	$mGlu_1$	$mGlu_2$	$mGlu_3$	$mGlu_4$
Other names	$mGluR_1$	$mGluR_2$	$mGluR_3$	$mGluR_4$
Ensembl ID	ENSG00000152822	ENSG00000164082	ENSG00000105781	ENSG00000124493
Principal transduction	$G_{q/11}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Selective agonists	–	–	NAAG (Wroblewska *et al*., 1997)	L-AP4, LSOP (Wu *et al*., 1998),
Selective positive allosteric modulators	Ro01-6128, Ro67-4853, Ro67-7476 (Knoflach *et al*., 2001)	LY487379 (Johnson *et al*., 2003), CBiPES (Johnson *et al*., 2005)	–	(–)-PHCCC (Maj *et al*., 2003), SIB1893, MPEP (Mathiesen *et al*., 2003), VU0155041 (Niswender *et al*., 2008)
Selective competitive antagonists	3-MATIDA (Moroni *et al*., 2002), AIDA (Moroni *et al*., 1997), (*S*)-(+)-CBPG (Mannaioni *et al*., 1999), LY367385 (Clark *et al*., 1997), (*S*)-TBPG (Costantino *et al*., 2001)	PCCG-4 (Pellicciari *et al*., 1996)	–	MAP4
Selective negative allosteric modulators	CPCCOEt (Litschig *et al*., 1999), BAY36-7620 (Carroll *et al*., 2001), LY456236 (Li *et al*., 2002), 3,5-DMPPP (Micheli *et al*., 2003), EM-TBPC (Malherbe *et al*., 2003), JNJ16259685 (Lavreysen *et al*., 2004)	–	–	–

Nomenclature	$mGlu_5$	$mGlu_6$	$mGlu_7$	$mGlu_8$
Other names	$mGluR_5$	$mGluR_6$	$mGluR_7$	$mGluR_8$
Ensembl ID	ENSG00000168959	ENSG00000113262	ENSG00000168160	ENSG00000179603
Principal transduction	$G_{q/11}$	$G_{i/o}$	$G_{i/o}$	$G_{i/o}$
Selective agonists	CHPG (Doherty *et al*., 1997), (*S*)-(+)-CBPG (Mannaioni *et al*., 1999)	Homo-AMPA (Bräuner-Osborne *et al*., 1996), 1-benzyl-APDC (Tuckmantel *et al*., 1997)	LSOP (Wu *et al*., 1998), L-AP4	LSOP (Wu *et al*., 1998), L-AP4, (*S*)-3,4-DCPG (Thomas *et al*., 2001)
Selective positive allosteric modulators	DFB (O'Brien *et al*., 2003), CPPHA (O'Brien *et al*., 2004), CDPPB (Kinney *et al*., 2005)	–	AMN082 (Flor *et al*., 2005)	–
Selective competitive antagonists	ACDPP (6.5, Bonnefous *et al*., 2005)	MAP4, THPG (Thoreson *et al*., 1997)	–	MPPG (Wu *et al*., 1998)
Selective negative allosteric modulators	SIB1757 (Varney *et al*., 1999), SIB1893 (Varney *et al*., 1999), MPEP (Gasparini *et al*., 1999b), MTEP (Brodkin *et al*., 2002), fenobam (Porter *et al*., 2005), YM298198 (Kohara *et al*., 2005)	–	MMPIP (Suzuki *et al*., 2007)	–

Radioligand binding using a variety of radioligands has been conducted on recombinant receptors (e.g. [^{3}H]-R214127 (Lavreysen *et al*., 2003) and [^{3}H]-YM298198 (Kohara *et al*., 2005) at $mGlu_1$ receptors and [^{3}H]-methoxy-MPEP (Gasparini *et al*., 2002) and [^{3}H]-methoxymethyl-MTEP (Anderson *et al*., 2002) at $mGlu_5$ receptors. Although a number of radioligands have been used to examine binding using native tissues, correlation with individual subtypes is limited. Many pharmacological agents have not been fully tested across all known subtypes of mGlu receptors. Potential differences linked to the species (e.g. human vs. rat or mouse) of the receptors and the receptor splice variants are generally not known. The influence of receptor expression level on pharmacology and selectivity has not been controlled for in most studies, particularly those involving functional assays of receptor coupling.

(*S*)-(+)-CBPG is an antagonist at $mGlu_1$, but is an agonist (albeit of reduced efficacy) at $mGlu_5$ receptors. DCG-IV also exhibits agonist activity at NMDA glutamate receptors (Uyama *et al*., 1997). A potential novel mGlu receptor coupled to phosphoinositide turnover has been observed in rat brain; it is activated by 4-methylhomoibotenic acid (ineffective as an agonist at recombinant Group I mGlu receptors), but resistant to LY341495 (Chung *et al*., 1997). There are also reports of a novel mGlu receptor coupled to phospholipase D in rat brain, which does not readily fit into the current classification (Pellegrini-Giampietro *et al*., 1996; Klein *et al*., 1997).

Abbreviations: **[^{11}C]-JNJ-16567083**, (3-ethyl-2-[^{11}C]methyl-6-quinolinyl)(*cis*-4-methoxycyclohexyl) methanone; **(*RS*)PPG**, (*R*,*S*)-4-phosphonophenylglycine; **(*S*)-(+)-CBPG**, (*s*)-(1)-2-(39-carboxybicycle[1.1.1]pentyl)glycine; **(*S*)-3,4-DCPG**, (*S*)-3,4-dicarboxylphenylglycine; **1*S*,3*R*-ACPD**, 1-aminocyclopentane-1*S*,3*R*-dicarboxylate; **2*R*,4*R*-APDC**, aminopyrrolidine-2*R*,4*R*-dicarboxylate; also known as LY314593; **3-MATIDA**, α-amino-5-carboxy-3-methyl-2-thiopheneacetic acid; **3HPG**, 3-hydroxyphenylglycine; **4CPG**, 4-carboxyphenylglycine; **AIDA**, 1-aminoindan-1,5(*RS*)-dicarboxylic acid; also known as UPF523; **AMN082**, *N*,*N*′-bis(diphenylmethyl)-1,2-ethanediamine dihydrochloride; **BAY 36-7620**, (3a*S*,6a*S*)-6a-naphtalan-2-ylmethyl-5-methyliden-hexahyrol-cyclopenta[c]furan-1-one; **CBiPES**, *N*-[4′-cyano-biphenyl-3-yl]-*N*-(3-pyridinylmethyl)-ethanesulphonamide hydrochloride; **CDPPB**, 3-cyano-*N*-(1,3-diphenyl-1*H*-[pyrazol-5-yl)benzamide; **CHPG**, 2-chloro-5-hydroxyphenylglycine; **CPCCOEt**, cyclopropan[*b*]chromen-1*a*-carboxylate; **CPPHA**, *N*-{4-chloro-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl) methyl]phenyl}-2-hydroxybenzamide; **DCG-IV**, (2*S*,1′*R*,2′*R*,3′*R*)-2-(2,3-dicarboxycyclopropyl)glycine; **DFB**, 3,3′-difluorobenzaldazine; **DHPG**, *S*-3,5-dihydroxyphenylglycine; **DMPPP**, 3,5-dimethyl pyrrole-2,4-dicarboxylic acid 2-propyl ester 4-(1,2,2-tri-methyl-propyl) ester; **EGLU**, (*s*)-α-ethylglutamate; **fenobam**, *N*-(3-chlorophenyl)-*N*′-(4,5-dihydrol-1-methyl-4-oxo-1-*H*-imidazole-2-yl)-urea; **JNJ16259685**, (3,4-dihydro-2*H*-pyrano[2,3]b-quinolinyl-7-yl)(*cis*-4-methoxycyclohexyl)methanone; **L-AP4**, *S*-2-amino-4-phosphonobutyrate; **L-CCG-I**, (2*S*,3*S*,4*S*) α-(carboxycyclopropyl)glycine; **LY307452**, 2*S*,4*S*-2-amino-4-(4,4-diphenylbut-1-yl)pentan-1,5-dioc acid; **LY341495**, 2*S*-2-amino-2-(1*S*,2*S*-2-carboxycyclopropan-1-yl)-3-(xanth-9-yl)propanoic acid; **LY354740**, (+)-2-aminobicyclic[3.1.0]hexane-2,6-dicarboxylate; **LY367385**, (+)-2-methyl-4-carboxyphenylglycine; **LY379268**, (−)-2-oxa-4-aminobicylco[3.1.0]hexane-4,6-dicarboxylic acid; **LY389795**, (−)-2-thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylic acid; **LY393675**, α-substituted-cyclobutylglycine; **LY456066**, (2-[4-(indan-2-ylamino)-5,6,7,8-tetrahydro-quinazolin-2-ylsulfanyl]-ethanol,hydrochloride; **LY456236**, [(4-methoxy-phenyl)-(6-methoxy-quinazolin-4-yl)-amine hydrochloride; **LY487379**, 2,2,2-trifluoro-*N*-[4-(2-methoxyphenoxy)phenyl]-*N*-(3-pyridinylmethyl)-ethanesulphonamide; **MAP4**, (*S*)-2-methyl-2-amino-4-phosphonobutanoate; **methoxy-MPEP**, 2-methyl-6-((3-methoxyphenyl)ethynyl)-pyridine; **methoxy-PEPy**, 3-methoxy-5-(pyridin-2-yl-ethynyl)-pyridine; **methoxymethyl-MTEP**, 3-(methoxymethyl)-5-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; **MMPIP**, 6-(4-methoxyphenyl)-5-methyl-3-(4-pyridinyl)-isoxazolo[4,5-c]pyridin-4(5*H*)-one hydrochloride; **MPEP**, 2-methyl-6-(phenylethynyl)-pyridine; **MPPG**, (*RS*)-α-methyl-4-phosphonophenylglycine; **MTEP**, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine; **NAAG**, *N*-acetylaspartylglutamate, also known as spaglumic acid; **PCCG-4**, (2*S*,1′S,2′S,3′*R*)-2-(2′-carboxy-3′-phenylcyclopropyl)glycine; **PHCCC**, *N*-phenyl-7-(hydroxylimino)cyclopropa[b]chromen-1a-carboxamide; **R214127**, 1-(3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-2-phenyl-1-ethanone; **Ro01-6128**, diphenylacetyl-carbamic acid ethyl ester; **Ro67-4853**, (9*H*-xanthene-9-carbonyl)-carbamic acid butyl ester; **Ro67-7476**, (*S*)-2-(4-fluoro-phenyl)-1-(toluene-4-sulphonyl)-pyrrolidine; ***S*-TBPG**, 2-(3′-(1*H*-tetrazol-5-yl)bicyclo[1.1.1]pent-1-yl)glycine; **SIB1757**, 6-methyl-2-(phenylazo)-3-pyrindol; **SIB1893**, ([phenylazo]-3-pyrindole)-2-methyl-6-(2-phenylethenyl)pyridine; **THPG**, (*RS*)-3,4,5-trihydroxyphenylglycine; **VU0155041**, *cis*-2-[[(3,5-dichlorophenyl)amino]carbonyl]cyclohexanec arboxylic acid; **YM298198**, (6-{[(2-methoxyethyl)amino]methyl}-*N*-methyl-*N*-neopentylthiaolo[3,2-a]benzoimidazole-2-carboxamide

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