

Glutamate Receptors (G Protein Family)

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Overview

The existence of G protein-coupled glutamate receptors (also called "metabotropic" glutamate or mGlu's), belonging to the seven transmembrane spanning superfamily of receptors, was shown definitively with the cloning of the first member in 1991. Since then, eight receptors of this class have been discovered. mGlu's are members of the "Class C" subgroup of G protein-coupled receptors, distinguished by the presence of a large N-terminal domain, which contains the orthosteric agonist binding site. Based on studies with mGlu1, these receptors are proposed to exist as homodimers with the N-terminal domain forming a "clam shell" structure consisting of two lobes linked by a hinge region. Glutamate binds between these lobes to stabilize a closed state that transduces a conformational change in the transmembrane regions of the homodimer to promote G-protein coupling. The existence of C-terminal splice variants for many subtypes and intracellular interacting proteins (e.g. Homer, Pick-1) suggests that mGlu receptor function is subject to complex intracellular regulation. The eight receptors have been classified into three groups based on similarities in their amino acid sequences, G-protein coupling and pharmacology. Group I (mGlu1 and 5) couple to G_q and signal through inositol phospholipid breakdown whereas Group II (mGlu2 and 3) and Group III (mGlu4, 6, 7 and 8) couple to $G_{i/o}$ and inhibit adenylyl cyclase. In addition, members of all three groups can interact directly with voltage-gated calcium or potassium channels through their G proteins. Numerous pharmacological tools for these receptors exist. These include several "Group-selective" agonists, specifically: quisqualate and S-DHPG for Group I; 2R,4R-APDC and LY354740 for Group II; as well as L-AP4 and RS-PPG for Group III. Likewise, several "Group-selective" antagonists have been

identified, specifically: LY393675 for Group I; LY341495 and MGS0039 for Group II; as well as MAP4 and UPB1110 for Group III. Subtype-selective ligands for some of the mGlu receptors have also been described. In Group I, selective antagonists for mGlu1 include the competitive antagonist LY367385; and the non-competitive antagonists CPC-COEt, R214127 and BAY63-7620. CHPG is a selective, but relatively low potency, agonist for mGlu5 receptors and selective non-competitive antagonists include MPEP, MTEP and DeMeOB. In Group II, the naturally occurring dipeptide NAAAG is a selective agonist for mGlu3 receptors. Subtype selective agents within Group III have been less forthcoming, although (S)-homoAMPA is a weak, but selective agonist for mGlu6 receptors, and (S)-3,4-DPCPG is a potent and selective agonist for mGlu8 receptors. A recent exciting development in mGlu pharmacology is the discovery of allosteric modulators of several subtypes. These compounds bind in the 7-transmembrane domains to either positively or negatively modulate receptor activation by glutamate. The subtype selective "non-competitive antagonists" described above act in this way. In addition, positive allosteric modulators (which do not directly activate the receptor, but produce a leftward shift in the agonist dose-response curve) have now been identified, e.g.: Ro 67-7476 and Ro 01-6128 for mGlu1, CPPHA, DFB and CDPBP for mGlu5, LY487379 for mGlu2 and PHCCC for mGlu4. Interestingly, a "neutral" modulator for mGlu5 has also been identified (DCB), that blocks the action of positive and negative allosteric modulators at this subtype without altering the glutamate-site binding or receptor activation. From a therapeutic perspective, allosteric modulators are an attractive approach since they typically exhibit high affinity, excellent subtype selectivity, have better "drug-like"

properties (e.g. blood/brain barrier penetration) than glutamate analogs acting at the transmitter recognition site, and act to either up or down regulate the actions of the glutamate at the targeted subtype in concert with neurotransmitter release. In general, all three groups of G protein-coupled glutamate receptors are widely distributed throughout the CNS and evidence exists for postsynaptic, presynaptic and, in some cases, glial localization. One or more of the Group II and Group III receptors are believed to function as an auto receptor, mediating the self-regulation of glutamate release from its nerve terminals. Presynaptic Group II and III receptors have also been shown to directly decrease the release of other neurotransmitters (for example dopamine and GABA) acting as heteroreceptors. In contrast, a presynaptic Group I receptor may promote glutamate release. Interestingly, a variant of mGlu4 with a truncated N-terminal domain exists on taste buds and is proposed to give rise to umami, the characteristic taste of monosodium glutamate. Activation of (presumably) postsynaptic Group I receptors potentiates NMDA receptor function. mGlu1 and mGlu5 agonists and positive allosteric modulators have been proposed as a novel approach to treat schizophrenia, whereas antagonists at these subtypes have been proposed as potential treatments for pain, drug addiction, anxiety, Parkinson's disease and obesity, and also possess neuroprotective and anti-epileptic properties. Group II receptor agonists and positive allosteric modulators are effective in animal models of epilepsy, anxiety and psychosis, and LY354740 has been reported to be effective in patients with generalized anxiety. Group III agonists and positive allosteric modulators are effective in animal models of epilepsy, are neuroprotective and reverse the motor dysfunction in animal models of Parkinson's disease.

Glutamate Receptors (G Protein Family)

CURRENTLY ACCEPTED NAME ^a	mGlu1	mGlu5	mGlu2	mGlu3	mGlu4	mGlu6	mGlu7	mGlu8
GROUP CLASSIFICATION	Group I	Group I	Group II	Group II	Group III	Group III	Group III	Group III
STRUCTURAL INFORMATION	1194 aa (human)	1212 aa (human)	872 aa (human)	879 aa (human)	912 aa (human)	853 aa (human)	915 aa (human)	908 aa (human)
GLUTAMATE-SITE AGONISTS	S-DHPG (D3689), Quisqualate	S-DHPG (D3689), Quisqualate, CHPG, z-CBQA	2R,4R-APDC, DCG-IV, LY354740, MGS 0039, LY379268	NAAG (A5930), 2R,4R-APDC, DCG-IV, LY354740, LY379268	L-AP-4 (A7929), L-SOP (P0878), RS-PPG	L-AP-4 (A7929), L-SOP (P0878), RS-PPG, S-homo-AMPA	L-AP-4 (A7929)	L-AP-4 (A7929), L-SOP (P0878), RS-PPG, S-3,4-DCPG
GLUTAMATE-SITE ANTAGONISTS	LY367385	Not known	LY341495, ^c EGLU, MGS0039	LY341495, ^c EGLU, MGS0039	MAP4 (M5560), UPB1110	MAP4 (M5560), UPB1110	MAP4 (M5560), UPB1110	MAP4 (M5560), UPB111
POSITIVE ALLOSTERIC MODULATORS ^b	Ro 67-7476, Ro 01-6128	CPPHA, DFB, CDPPB	LY487379	Not known	PHCCC	Not known	Not known	Not known
ALLOSTERIC ANTAGONIST ^b	CPCCOEt (C9611), BAY36-7620, R214127	MPEP (M5435), SIB-1757 (S9186), SIB-1893 (S9311), MTEP, DmeOB (D6317), DCB (neutral ligand) (D1068)	Not known	Not known	Not known	Not known	Not known	Not known
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG)	G _{q/11} (increase IP ₃ /DAG)	G _i (cAMP modulation)	G _i (cAMP modulation)	G _i (cAMP modulation)	G _i (cAMP modulation)	G _i (cAMP modulation)	G _i (cAMP modulation)
RADIOLIGANDS OF CHOICE	[³ H]-Quisqualate [³ H]-R214127	[³ H]-Quisqualate	[³ H]-LY354740 [³ H]-DCG IV [³ H]-LY341495	[³ H]-LY354740 [³ H]-DCG IV [³ H]-LY341495	[³ H]-L-AP4	[³ H]-L-AP4 [³ H]-LY341495 ^d	[³ H]-L-AP4 [³ H]-LY341495 ^d	[³ H]-LY341495 ^d [³ H]-S-3,4-DCPG
TISSUE EXPRESSION	The expression of mGluRs is widespread in the CNS, with the exception of mGluR6 which is found almost exclusively in retina.							
PHYSIOLOGICAL FUNCTION	Group I mGluRs facilitate glutamate neurotransmission; Group II and Group III mGluRs generally inhibit glutamate and GABA-mediated neurotransmission.							
DISEASE RELEVANCE	Group I: schizophrenia, pain, drug addiction, anxiety, Parkinson's disease, obesity, stroke and TBI, epilepsy; Group II: anxiety, epilepsy, psychosis; Group III: Parkinson's disease, stroke, TBI, epilepsy.							

FOOTNOTES

a G Protein family is also referred to as metabotropic.

b Allosteric ligands bind outside of the glutamate recognition site and either positively modulate glutamate response, act as non-competitive antagonists or neutral ligands blocking allosteric site interaction only.

c Also significant antagonism of Group I and Group III receptors.

d In cell lines expressing recombinant receptor subtypes.

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Abbreviations

L-AP-4: 2-Amino-4-phosphonobutyric acid
(2R,4R)-APDC: (2R,4R)-Aminopyrrolidine-2,4-dicarboxylic acid
BAY36-7620: (3aS,6aS)-6a-Naphtalen-2-ylmethyl-5-methyliden-hexahydro-cyclopental[c]furan-1-on
z-CBQA: (Z)-1-Amino-3-[2'-(3',5'-dioxo-1',2',4'-oxadiazolidinyl)-cyclobutane-1-carboxylic acid
CDPPB: 3-Cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide
CHPG: (R/S)-2-Chloro-5-hydroxyphenylglycine
Compound 4: 1-(2-Hydroxy-3-propyl-4-[4-(2H-tetrazol-5-yl)phenoxy]-butoxy]phenyl)ethanone – see Pinkerton, et al., *J. Med. Chem.*, **47**, 4595 (2004).
Compound 10: 2-[2-[3-(Pyridine-3-yloxy)phenyl]-2H-tetrazole-5-yl]pyridine – see Huang, et al., *Bioorg. Med. Chem. Lett.*, **14**, 5473 (2004)
CPCCOEt: 7-Cyclopropan[b]chromen-1a-carboxylic acid ethyl ester
CPPHA: N-[4-Chloro-2-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]phenyl]-2-hydroxybenzamide
DCG-IV: (2S,1'R,2'R,3'R)-2-(2,3 Dicarboxycyclopropyl)glycine
DCB: 3,3'-Dichlorobenzaldazine
DFB: 3,3'-Difluorobenzaldazine
DMeOB: 3,3'-Dimethoxybenzaldazine
S-DHPG: (R,S)-3,5-Dihydroxyphenylglycine
S-3,4-DCPG: (S)-3,4-Dicarboxyphenylglycine
E-GLU: (S)- α -Ethylglutamic acid
S-Homo-AMPA: (RS)-2-Amino-4-(3-hydroxy-5-methylisoxazol-4-yl)butyric acid
LY341495: (2S)-2-Amino-2-(1S,2S-2-carboxycyclopropan-1-yl-3-(xanth-9-yl)propanoic acid
LY354740: (+)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
LY367385: (+)-2-Methyl-4-carboxyphenylglycine
LY379268: (-)-2-Thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate
LY487379: 2,2,2-Trifluoro-N-[4-(2-methoxyphenoxy)phenyl]-N-(3-pyridinylmethyl)-ethanesulfonamide
MAP4: (S)-2-Amino-2-methyl-4-phosphonobutyric acid
MGS 0039: (1R,2R,3R,5R,6R)-2-Amino-3-(3,4-dichlorobenzoyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
MPEP: 2-Methyl-6-(phenylethynyl)pyridine
MTEP: 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine
NAAG: N-Acetyl-L-aspartyl-L-glutamic acid
PHCCC: N-Phenyl-7-(hydroxylimino)cyclopropa[b]-chromen-1a-carboxamide
Ro 01-6128: Diphenylacetyl-carbamic acid ethyl ester
Ro 67-7476: (S)-2-(4-Fluoro-phenyl)-1-(toluene-4-sulfonyl)-pyrrolidine
R214127: 1-(3,4-Dihydro-2H-pyran[2,3-b]quinolin-7-yl)-2-phenyl-1-ethanone
RS-PPG: (RS)-4-Phosphonophenylglycine
SIB-1757: 6-Methyl-2-(phenylazo)-pyridinol
SIB-1893: (E)-2-Methyl-6-(2-phenylethenyl)pyridine
L-SOP: L-Serine-O-phosphate
UBP1110: (RS)- α -Methyl-3-chloro-4-phosphonophenylglycine

FOOTNOTES