

Glutamate Receptors (G Protein Family)

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Overview

The existence of G protein-coupled glutamate receptors (also called "metabotropic" glutamate receptors or mGluRs), 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. mGluRs 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 agonist binding site. The glutamate binding site of mGluRs has been shown to be confined to this extracellular region since expression of the extracellular domain of mGlu₁ alone revealed binding affinities for glutamate analogs comparable with those for the full length receptor. This region shares homology with certain bacterial glutamate binding proteins, and recent structural and modeling studies of mGlu₁ have provided new insights into the conformational changes in the N-terminal regions which occur upon agonist binding and how this might translate into G protein coupling. Alternatively spliced variants have also been reported for mGluRs 1, 4, 5, 7 and 8, indicating a further means for receptor regulation.

The eight receptors have been classified into three groups based on similarities in their amino acid sequences, their linkage to second messenger systems and their pharmacology. Group I (mGluRs 1 and 5) signal through inositol phospholipid breakdown whereas Group II (mGluRs 2 and 3) and Group III (mGluRs 4, 6, 7 and 8) inhibit adenylyl cyclase. In addition, members of all three groups can interact directly with voltage-gated calcium or potassium channels through their G proteins. Selective pharmacological tools for these receptors

have emerged in recent years. These include several "Group-selective" agonists, specifically; S-DHPG for Group I; 2R,4R-APDC and LY-354740 for Group II and L-AP4 and RS-PPG for Group III. Likewise, several "Group-selective" antagonists have been identified, specifically, LY-367385 and MPEP for Group I, LY-341495 and ADED for Group II, and MAP4 for Group III.

Subtype-selective ligands have also been described, primarily in Groups I and II. Thus, z-CBQA is a selective agonist for mGlu₅ receptors while LY-367385 is a selective mGlu₁ receptor antagonist; the non-competitive antagonists, MPEP, SIB-1757 and SIB-1893 are selective for mGlu₅ receptors and the naturally occurring dipeptide NAAG acts as 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 the recently described compound (S)-3,4-DCEP is a potent and selective agonist for mGlu₈. With the advent of these potent and more selective tools, the physiological and pathophysiological roles of the different mGluR receptor subtypes are currently under investigation.

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 autoreceptor, mediating the self-regulation of glutamate release from its nerve terminals. 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 may augment neurodegeneration mediated by the ion channel glutamate receptors, whereas Group II and Group III receptor agonists may be neuroprotective. The potent and selective Group II agonist, LY-354740, is active in several models of anxiety and psychosis, and the mGlu₅ antagonist MPEP has been shown to reverse inflammatory pain responses in animal models. Clearly, there is much yet to be learned about the role of mGluRs in the CNS, and a new realm of therapeutic possibilities may open up as a result.

Glutamate Receptors (G Protein Family) ^a

	Group I		Group II		Group III			
CURRENTLY ACCEPTED NAME	mGluR ₁	mGluR ₅	mGluR ₂	mGluR ₃	mGluR ₄	mGluR ₆	mGluR ₇	mGluR ₈
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)
RECEPTOR SELECTIVE AGONISTS	S-DHPG (D 3689) CPCCOEt (C 9611) ^b	S-DHPG (D 3689) z-CBQA	2R,4R-APDC DCG-IV LY-354740 MGS 0028 LY-379268	NAAG (A 5930) 2R,4R-APDC DCG-IV LY-354740 MGS 0028 LY-379268	L-AP-4 (A 7929) L-SOP (P 0878) RS-PPG	L-AP-4 (A 7929) L-SOP (P 0878) RS-PPG S-homo-AMPA	L-AP-4 (A 7929)	L-AP-4 (A 7929) L-SOP (P 0878) RS-PPG S-3,4-DCPG
RECEPTOR SELECTIVE ANTAGONISTS	LY-367385	MPEP (M 5435) ^b SIB-1757 (S 9186) ^b SIB-1893 (S 9311) ^b	LY-341495 ^c EGLU ADED	LY-341495 ^c EGLU ADED	MAP4 (M 5560)	MAP4 (M 5560)	MAP4 (M 5560)	None 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]-Quisqualate	[³ H]-LY-354740 [³ H]-DCG IV [³ H]-LY-341495	[³ H]-LY-354740 [³ H]-DCG IV [³ H]-LY-341495	[³ H]-L-AP4	[³ H]-L-AP4 [³ H]-LY-341495 ^d	[³ H]-L-AP4 [³ H]-LY-341495 ^d	[³ H]-LY-341495 ^d

ABBREVIATIONS

ADED: (2S,4S)-2-Amino-4-(2,2-diphenylethyl)pentane-1,5-dioic acid
L-AP-4: 2-Amino-4-phosphonobutyric acid
(2R,4R)-APDC: (2R,4R)-Aminopyrrolidine-2,4-dicarboxylic acid
z-CBQA: (Z)-1-Amino-3-[2'-(3',5'-dioxo-1',2',4'-oxadiazolidinyl-cyclobutane-1-carboxylic acid
CPCCOEt: 7-Cyclopropan[b]chromen-1a-carboxylic acid ethyl ester
DCG-IV: (2S,1'R,2'R,3'R)-2-(2,3 Dicarboxycyclopropyl)glycine
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
LY-341495: (2S)-2-Amino-2-(1S,2S-2-carboxycyclopropan-1-yl-3-(xanth9-yl)propanoic acid
LY-354740: (+)-2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
LY-367385: (+)-2-Methyl-4-carboxyphenylglycine
LY-379268: (-)-2-Thia-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate
MAP4: (S)-2-Amino-2-methyl-4-phosphonobutyric acid
MGS 0028: (1R,2S,5S,6S)-2-Amino-6-fluoro-4-oxobicyclo[3.1.0]hexane-2,6-dicarboxylic acid
MPEP: 2-Methyl-6-(phenylethynyl)pyridine
NAAG: N-Acetyl-L-aspartyl-L-glutamic acid
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

FOOTNOTES

- a** G Protein family is also referred to as metabotropic.
b Non-competitive.
c Also significant antagonism of Group I and Group III receptors.
d In cell lines expressing recombinant receptor subtypes.