

Glutamate Receptors (Ion Channel Family)

Key References

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Overview

The ion channel family of glutamate receptors (also called "ionotropic" glutamate receptors) comprises three major subtypes based on pharmacology and protein structure.

The N-methyl-D-aspartate (NMDA) subtype is a hetero-oligomer consisting of an NR1 subunit combined with one or more NR2 (A-D) subunits. A third subunit, NR3A, may be a component during development. The receptor has two amino acid recognition sites, one for glutamate and one for glycine, both of which must be occupied to promote channel opening. Antagonists have been discovered which selectively compete for either the glutamate or glycine site, and these act as functional receptor antagonists. The channel is permeable to cations, including calcium, and is blocked by magnesium at membrane potentials close to resting, endowing a voltage dependence to this ligand-gated ion channel which is important for its physiological role as a "conditional" receptor. A variety of drugs have been identified which block the channel selectively. Other sites exist on the receptor through which polyamines, zinc, protons and oxidizing/reducing agents influence receptor function. An interesting recent development is the recognition that polyamines and certain drugs (ifenprodil, Ro 25-6981, CP 101,606) interact selectively with NMDA receptors containing NR2B, providing "subunit-selective" antagonists. The NMDA receptor is now recognized as part of a large complex of cell surface proteins, receptors and intracellular mediators at the post-synaptic density which interact to regulate excitatory neurotransmission.

The α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) subtype is a hetero-oligomer formed from combinations of GluR1-4. Selective agonists and competitive antagonists acting at the glutamate recognition site have been useful for defining the physiological and pathophysiological roles played by the receptor. Additional sites on the receptor mediate the effects of cyclothiazide to inhibit receptor desensitization and GYKI 52466 and related compounds to act as non-competitive inhibitors. The ion channel is cation-permeable, but calcium permeability is regulated by an RNA editing mechanism in the GluR2 subunit. Joro spider toxin blocks the channel of AMPA receptors that do not contain the GluR2 subunit.

The kainate subtype consists of hetero-oligomers, comprising the GluR5-7 and KA1 and KA2 subunits. Agonists and antagonists selective for kainate receptors have been relatively slow to emerge. Consequently, the function of native kainate receptors has mainly been deduced from examining effects remaining after blocking NMDA and AMPA receptors (e.g. using the agonist kainate in combination with GYKI 52466, which selectively blocks the AMPA receptor-mediated effects of kainate). Some new selective tools have appeared, in the shape of the AMPA analog ATPA, which is a selective agonist for GluR5 receptors, and the competitive antagonist LY-294486, which antagonizes kainate receptors containing GluR5, but not GluR6 or GluR7, yet retains affinity, albeit weaker, for AMPA receptors.

The physiological and pathophysiological roles of ionotropic glutamate receptors have been extensively studied with these

pharmacological tools. NMDA receptors are post-synaptic and play important roles in plasticity in the developing and mature CNS and post-synaptic AMPA receptors mediate chemical transmission at the majority of fast excitatory synapses in the CNS. The role of kainate receptors is less clear, but at least in the hippocampus, there is evidence for a presynaptic location. Antagonists of NMDA, AMPA and kainate receptors have been proposed to be of therapeutic benefit in a number of CNS disorders, including stroke, head injury, epilepsy, pain and Alzheimer's disease, and several compounds have progressed to clinical trials for these indications.

Glutamate Receptors (Ion Channel Family) ^a

CURRENTLY ACCEPTED NAME	Glutamate site	NMDA Glycine site	Other	AMPA	Kainate
ALTERNATE NAME	—	—	—	Quisqualate	—
STRUCTURAL INFORMATION	NR1 (920 aa human) NR2A (1464 aa human) NR2B (1484 aa human) NR2C (1233 aa human) NR2D (1329 aa rat) NR3A (1115 aa rat)	—	—	GluR1 (889 aa human) GluR2 (883 aa human) GluR3 (894 aa human) GluR4 (881 aa rat)	GluR5 (978 aa human) GluR6 (877 aa rat) GluR7 (919 aa human) KA1 (956 aa human) KA2 (962 aa human)
SUBTYPE SELECTIVE AGONISTS	N-Methyl-D-aspartic acid (M 3262) Quinolinic acid (P 6,320-4)	Glycine (G 7126) D-Serine (S 4250) R(+)-HA-966 (partial) (H-130)	—	AMPA (A 0326) S(-)-5-Fluorowillardiine (F 2417) CX-614 ^d Cyclothiazide (C 9847) ^d	Kainic acid (K 0250) Domoic acid (D 6152) 4-Methylglutamate (G-137) ATPA (GluR5) (A-263)
SUBTYPE SELECTIVE ANTAGONISTS	D(-)-AP-5 (A-169) D(-)-AP-7 (A-167) CGS19755 (C-105) CGP37849 CPP, (±), D- (C-104 , C-189) D-CPPene EAA-090	7-Chlorokynurenic acid (C 0306) 5,7-Dichlorokynurenic acid (D-138) MNQX L-689,560 L-701,324 (L 0258) GV 150526	Ro 25-6981 (NR2B) (R 7150) Ro 8-4304 (NR2B) (R 8900) CP 101,606 (NR2B) Ifenprodil (NR2B) (I 2892)	NBQX (N-183) GYKI 52466 (G-119) ^c GYKI 53655 ^c CNQX (C-239) DNQX (D 0540) YM90K LY-294486 Ro 48-8587 SPD-502	CNQX (C-239) DNQX (D 0540) NS 102 (N-179) ^b LY-294486 (GluR5)
CHANNEL BLOCKERS	MK-801 (Dizocilpine) (M-107) Phencyclidine (PCP) (P 3029) CNS-1102 (Cerestat) Ketamine (K 2753)	—	—	Joro Spider Toxin (J-100)	—
CHANNEL PERMEABILITY	Intrinsic ion channel (Na ⁺ /K ⁺ /Ca ²⁺)	—	—	Intrinsic ion channel (Na ⁺ /K ⁺ /Ca ²⁺)	Intrinsic ion channel (Na ⁺ /K ⁺ /Ca ²⁺)
RADIOLIGANDS OF CHOICE	[³ H]-CPP [³ H]-L-Glutamate	[³ H]-5,7-Dichlorokynurenic acid [³ H]-L-689,560	[³ H]-MK-801 (channel) [³ H]-Ro 25-6981 (NR2B)	[³ H]-AMPA [³ H]-Ro 48-8587	[³ H]-Kainic acid [³ H]-NBQX

ABBREVIATIONS

AMPA: α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid
AP-5: 2-Amino-5-phosphonopentanoic acid
AP-7: 2-Amino-7-phosphonoheptanoic acid
ATPA: (RS)-2-Amino-3-(3-hydroxy-5-tert-butylisoxazol-4-yl)propanoic acid
D-CCPene: D-3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonene
CGP37849: D,L-(E)-2-Amino-4-methylphosphono-3-pentanoic acid
CGS19755: 4-Phosphonomethyl-2-piperidinecarboxylic acid (Selfotel)
CNQX: 6-Cyano-7-nitroquinoxaline-2,3-dione
NS 1102: N-(1-Naphthyl)-N'-(3-ethylphenyl)-N'-methyl-guanine HCl
CP 101,606: (1S,2S)-1-(4-Hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol
CPP: 3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid
CX-614: 2H,3H,6aH-Pyrolidino[2",1"-3',2"]1,3-oxazino[6',5',-5,4]benzo[e]1,4-dioxan-10-one

DNQX: 6,7-Dinitroquinoxaline-2,3-dione
EAA-090: [2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]phosphonic acid
GV 150526: 3-[2-(Phenylamino)carbonyl]ethenyl-4,6-dichloroindole-2-carboxylic acid
GYKI 52466: 1-(4-Aminophenyl)-4-methyl-7,8-methylenedioxy-5H-2,3-benzodiazepine
GYKI 53655: 1-(4-Aminophenyl)-3-methylcarbonyl-4-methyl-7,8-methylenedioxy-3,4-dihydro-5H-2,3-benzodiazepine
HA-966: 1-Hydroxy-3-aminopyrrolid-2-one
L-689,560: (±)-4-(trans)-2-Carboxy-5,7-dichloro-4-phenylaminocarbonylamino-1,2,3,4-tetrahydroquinoline
L-701,324: 7-Chloro-4-hydroxy-3-(3-phenoxy)phenyl-2(H)-quinolinone
LY-294486: (3SR,4aRS,6SR,8aRS)-6-(((1H-Tetrazol-5-yl)methyl)oxy)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid

MNQX: 5,7-Dinitro-1,4-dihydro-2,3-quinoxalinedione
NBQX: 2,3-Dihydro-6-nitro-7-sulphamoyl-benzo(f)quinoxaline
NMDA: N-Methyl-D-aspartic acid
NS 102: 5-Nitro-6,7,8,9-tetrahydrobenzo[G]indole-2,3-dione-3-oxime
Ro 25-6981: R-(R*,S*)-α-(4-Hydroxyphenyl)-β-methyl-4-(phenylmethyl)-1-piperidine propanol
Ro 8-4304: 4-{3-[4-(4-Fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl]-2-hydroxypropoxy}-benzamide
Ro 48-8587: 9-(1H-Imidazol-1-yl)-8-nitro-[1,2,4]triazolo[1,5-c]quinazoline-2,5(3H,6H)-dione
SPD-502: 8-Methyl-5(4-(N,N-dimethylsulfamoyl)phenyl)6,7,8,9-tetrahydro-1H-pyrrolo[3,2-h]-isoquinoline-2,3-dione-3-O-(4-hydroxybutyrate-2-yl)oxime
YM90K: 6-(1H-Imidazol-1-yl)-7-nitro-2,3(1H,4H)-quinoxalinedione

FOOTNOTES

a Ion channel family is also referred to as ionotropic.
b Selectively inhibits low affinity [³H]-kainate binding.

c Non-competitive antagonist.
d Allosteric potentiator.