

Glutamate Receptors (Ion Channel Family)

Key References

- Brauner-Osborne, H., et al., Ligands for glutamate receptors: Design and therapeutic prospects., *J. Med. Chem.*, **43**, 2609-2645 (2000).
- Christensen, J.K., et al., A mosaic of functional kainate receptors in hippocampal interneurons., *J. Neurosci.*, **24**, 8986-8993 (2004).
- Dingledine, R., et al., The glutamate receptor ion channels., *Pharmacol. Rev.*, **51**, 7-61 (1999).
- Huettnner, J.E., Kainate receptors and synaptic transmission., *Prog. Neurobiol.*, **70**, 387-407 (2003).
- Kemp, J.A. and McKernan, R.M., NMDA receptor pathways as drug targets., *Nat. Neurosci.*, 5 suppl., 1039-1042 (2002).
- Loftis, J.M. and Janowsky, A., The N-methyl-D-aspartate receptor subunit NR2B: localization, functional properties, regulation and clinical implications., *Pharmacol. Ther.*, **97**, 55-85 (2003).
- Lynch, G., AMPA receptor modulators as cognitive enhancers., *Curr. Opin. Pharmacol.*, **4**, 4-11 (2004).
- Malenka, R.C. and Bear, M.F., LTP and LTD: an embarrassment of riches., *Neuron*, **44**, 5-21 (2004).
- Mayer, M.L. and Armstrong, N., Structure and function of glutamate receptor ion channels., *Annu. Rev. Physiol.*, **66**, 161-181 (2004).
- Mobius, H.J., et al., Memantine hydrochloride: pharmacological and clinical profile., *Drugs Today*, **40**, 685-695 (2004).
- Smolders, I., et al., Antagonists of GLU(K5)-containing kainate receptors prevent pilocarpine-induced limbic seizures., *Nat. Neurosci.*, **5**, 796-804 (2002).
- Tover, K.R. and Westbrook, G.L., Mobile NMDA receptors at hippocampal synapses., *Neuron*, **34**, 255-264 (2002).

Overview

The ion channel family of glutamate receptors ("ionotropic" glutamate receptors or iGluR) 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 and a third subunit, NR3 (A,B). 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. Several classes of compounds have now been identified that 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 and synaptic plasticity.

The α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) subtype is a hetero-oligomer formed from combinations of iGluR1-4. Selective agonists and com-

petitive antagonists acting at the glutamate recognition site have been useful for defining the physiological and pathophysiological roles played by the receptor. Allosteric sites on the receptor mediate the effects of the AMPAkinines that potentiate the response to glutamate while GYKI 52466 and related compounds act as non-competitive inhibitors. The ion channel is cation-permeable, but calcium permeability is regulated by an RNA editing mechanism in the iGluR2 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 iGluR5-7 and KA1 and KA2 subunits. Kainate itself and the AMPA analog ATPA have been used as selective agonists and recently, several competitive antagonists with selectivity for kainate receptors, particularly those containing iGluR5 subunits, have been identified.

The physiological and pathophysiological roles of ionotropic glutamate receptors have been extensively studied with both molecular and pharmacological approaches. 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. Both NMDA and AMPA receptors play key roles in certain forms of synaptic plasticity such as long-term potentiation and depression, phenomena that may underlie physiological processes such as learning and memory. Due to their voltage dependence and calcium permeability, NMDA receptors play a key role in the initiation of synaptic plasticity and the expression of these phenomena are due to alterations in the cell

surface expression of AMPA receptors. The role of kainate receptors is less clear, but in the hippocampus and spinal cord, there is evidence for a presynaptic location and an influence on transmitter release. The evidence that NMDA receptors are involved in neurodegenerative processes led to numerous unsuccessful clinical trials in stroke and head trauma with drugs that antagonize the receptor through binding to the glutamate, glycine and allosteric sites. AMPA receptor antagonists also have neuroprotective and anticonvulsant properties in animal studies. Memantine, which is a low affinity NMDA receptor channel blocker has shown cognitive improvements in Alzheimer's patients. NMDA receptor antagonists have also shown beneficial effects to alleviate the motor dysfunction in Parkinson's disease and relieve pain in animal models. The beneficial effects of AMPAkinines in animal models of cognitive impairment and psychosis have prompted clinical studies in these areas. Kainate receptor antagonists have shown positive effects in animal and human models of pain and migraine.

Glutamate Receptors (Ion Channel Family)

CURRENTLY ACCEPTED NAME ^a	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) NR3B (1003 aa mouse)	Not known	Not known	iGluR1 (889 aa human) iGluR2 (883 aa human) iGluR3 (894 aa human) iGluR4 (881 aa rat)	iGluR5 (978 aa human) iGluR6 (877 aa rat) iGluR7 (919 aa human) KA1 (956 aa human) KA2 (962 aa human)
SUBTYPE SELECTIVE AGONISTS	N-Methyl-D-aspartic acid (M3262), Quinolinic acid (P63204)	Glycine (G7126), D-Serine (S4250), R(+)-HA-966 (partial) (H130)	Cyclothiazide (C9847), ^d LY503430 ^d	AMPA (A0326), S(-)-5-Fluorowillardiine (F2417), CX-614, ^d ATPA (iGluR5) (A263)	Kainic acid (K0250), Domoic acid (D6152), 4-Methylglutamate (G137)
SUBTYPE SELECTIVE ANTAGONISTS	D(-)-AP-5 (A169), D(-)-AP-7 (A167), CGS19755 (C105), CGP37849, LY382884 (GluR5), CPP, (±)-, D- (C104 , C189), D-CPPene, EAA-090	7-Chlorokynurenic acid (C0306), 5,7-Dichlorokynurenic acid (D138), MNQX, L-689,560, L-701,324 (L0258), GV 150526	Ro 25-6981 (NR2B) (R7150), Ro 8-4304 (NR2B) (R8900), CP 101,606 (NR2B), Ifenprodil (NR2B) (I2892), SPD-502	NBQX (N183), GYKI 52466 (G119), ^c GYKI 53655, ^c CNQX (C239), DNQX (D0540), YM90K, LY294486, Ro 48-8587	CNQX (C239), DNQX (D0540), NS 102 (N179), ^b LY293558 (iGluR5), NS3763 (iGluR5)
CHANNEL BLOCKERS	MK-801 (Dizocilpine) (M107), Phencyclidine (PCP) (P3029), CNS-1102 (Cerestat) (C4238), Ketamine (K2753), Memantine	Not known	Not known	Joro Spider Toxin (J100)	Not known
CHANNEL PERMEABILITY	Intrinsic ion channel (Na ⁺ /K ⁺ /Ca ²⁺)	Not known	Not known	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-Dichlorokynurenate, [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
TISSUE EXPRESSION	NMDA and AMPA receptors are widespread in the CNS; kainate receptors are more discretely localized in areas of cortex, hippocampus, thalamus and spinal cord				
PHYSIOLOGICAL FUNCTION	Each class of receptors is involved in fast synaptic transmission, and neuronal plasticity in the developing and adult CNS. Kainate receptors have presynaptic role				
DISEASE REVELANCE	NMDA: stroke, Alzheimer's disease, Parkinson's disease, schizophrenia, pain, epilepsy; AMPA: epilepsy, stroke, Alzheimer's disease, schizophrenia; Kainate receptors: pain, epilepsy				

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

CNS 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

LY293558: (3S,4aR,6R,8aR)-6-[2-[[1H-tetrazol-5-yl]ethyl]decahydroisoquinoline-3-carboxylic acid

LY382884: 3S,4aR,6S,8aR-6-[(4-Carboxyphenyl)methyl]-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid

LY503430: (R)-4'-[1-Fluoro-1-methyl-2-(propane-2-sulfonylamino)ethyl]-biphenyl-4-carboxylic acid methylamide

MNQX: 5,7-Dinitro-1,4-dihydro-2,3-quinoxalinedione

NBQX: 2,3-Dihydro-6-nitro-7-sulphamoyl-benzof[quinoxaline

NMDA: N-Methyl-D-aspartic acid

NS 102: 5-Nitro-6,7,8,9-tetrahydrobenzo[g]indole-2,3-dione-3-oxime

NS3763: 5-Carboxyl-2,4-dibenzamido-benzoic acid

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-hydroxy-propoxy]-benzamide

Ro 48-8587: 9-(1H-Imidazol-1-yl)-8-nitro-[1,2,4]triazolo[1,5-c]quinazolin-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.

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