Glutamate (ionotropic)

Overview: The ionotropic glutamate receptors comprise members of the NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate receptor classes, named originally according to their preferred, synthetic, agonist (Dingledine *et al.*, 1999; Lodge, 2009). Receptor heterogeneity within each class arises from the homo-oligomeric, or hetero-oligomeric, assembly of distinct subunits into cation-selective tetramers. All glutamate receptor subunits have the membrane topology of an extracellular N-terminus, three transmembrane domains (formed by M1, M3 and M4), a channel lining re-entrant 'p-loop' (M2) located between M1 and M3 that enters and exits the membrane at its cytoplasmic surface, and an intracellular C-terminus (see Mayer, 2006). It is beyond the scope of this supplement to discuss the pharmacology of individual ionotropic glutamate receptor isoforms in detail; such information can be gleaned from Dingledine *et al.* (1999), Jane *et al.* (2000), Huettner (2003), Cull-Candy and Leszkiewicz (2004), Kew and Kemp (2005), Erreger *et al.* (2007), Paoletti and Neyton (2007), Chen *et al.* (2008) and Jane *et al.* (2009). Agents that discriminate between subunit isoforms are, where appropriate, noted in the tables, and additional compounds that distinguish between receptor isoforms are indicated in the text below.

The classification of glutamate receptor subunits has been recently been re-addressed by NC-IUPHAR (Collingridge *et al.*, 2009). The scheme developed recommends a revised nomenclature for ionotropic glutamate receptor subunits that is adopted here. Alternative appellations that have been used previously (see Lodge, 2009) are indicated in parenthesis to aid transition to the revised nomenclature, but their continued use is not recommended.

NMDA receptors: NMDA receptors assemble as heteromers that may be drawn from GluN1 (GLU_{N1}, NMDA-R1, NR1, GluRξ1), GluN2A (GLU_{N2A}, NMDA-R2A, NR2A, GluRε1), GluN2B (GLU_{N2B}, NMDA-R2B, NR2B, GluRε2), GluN2C (GLU_{N2C}, NMDA-R2C, NR2C, GluRε3), GluN2D (GLU_{N2D}, NMDA-R2D, NR2D, GluRε4), GluN3A (GLU_{N3A}, NMDA-R3A) and GluN3B (GLU_{N3B}, NMDA-R3B) subunits. Alternative splicing can generate eight isoforms of GluN1 with differing pharmacological properties. Various splice variants of GluN2B, 2C, 2D and GluN3A have also been reported. Activation of NMDA receptors containing GluN1 and GluN2 subunits requires the binding of two agonists, glutamate to the S1 and S2 regions of the GluN2 subunit and glycine to S1 and S2 regions of the GluN1 subunit (Erreger *et al.*, 2004; Chen and Wyllie, 2006). The minimal requirement for efficient functional expression of NMDA receptors *in vitro* is a di-heteromeric assembly of GluN1 and at least one GluN2 subunit variant, most likely in a dimer of heterodimers arrangement (Furukawa *et al.*, 2005; Mayer, 2006). However, more complex tri-heteromeric assemblies, incorporating multiple subtypes of GluN2 subunit, or GluN3 subunits, can be generated *in vitro* and occur *in vivo*. The NMDA receptor channel commonly has a high relative permeability to Ca^{2+} and is blocked, in a voltage-dependent manner, by Mg^{2+} such that at resting potentials the response is substantially inhibited.

Nomenclature	NMDA
Ensembl Gene family ID	ENSF00000000436
Selective agonists (glutamate site)	NMDA (GluN2D > GluN2C > GluN2B > GluN2A), L-aspartate (GluN2D = GluN2B > GluN2C = GluN2A), D-aspartate (GluN2D > GluN2C = GluN2B > GluN2A), (*RS*)-(tetrazol-5-yl)glycine (GluN2D > GluN2C = GluN2B > GluN2A), homoquinolinic acid (GluN2B ≥ GluN2A ≥ GluN2D > GluN2C; partial agonist at GluN2A and GluN2C)
Selective antagonists (glutamate site)	D-AP5, CGS19755, CGP37849, LY233053, D-CCPene (GluN2A = GluN2B > GluN2C = GluN2D), PPDA (GluN2C = GluN2D > GluN2B = GluN2A, Feng *et al.*, 2004), NVP-AAM077 [GluN2A > GluN2B (human), Auberson *et al.*, 2002; but weakly selective for rat GluN2A vs. GluN2B, Feng *et al.*, 2004; Frizelle *et al.*, 2006; Neyton and Paoletti, 2006], conantokin-G (GluN2B > GluN2D = GluN2C = GluN2A)
Selective agonists (glycine site)	Glycine (GluN2D > GluN2C > GluN2B > GluN2A), D-serine (GluN2D > GluN2C > GluN2B > GluN2A), (+)-HA966 (partial agonist)
Selective antagonists (glycine site)	5,7-Dichlorokynurenate, L689560, L701324, GV196771A
Channel blockers	Mg^{2+} (GluN2A = GluN2B > GluN2C = GluN2D), (+)-MK801, ketamine, phencyclidine, memantine (GluN2C ≥ GluN2D ≥ GluN2B > GluN2A), amantidine, N^1-dansyl-spermine (GluN2A = GluN2B >> GluN2C = GluN2D),
Probes	
Glutamate site	$[^3H]$CPP, $[^3H]$CGS19755, $[^3H]$CGP39653
Glycine site	$[^3H]$Glycine, $[^3H]$L689560, $[^3H]$MDL105519
Cation channel	$[^3H]$-MK801 (dizocilpine)

Potency orders unreferenced in the table are from Kuner and Schoepfer (1996), Dravid *et al.* (2007), Erreger *et al.* (2007), Paoletti and Neyton (2007) and Chen *et al.* (2008). In addition to the glutamate and glycine binding sites documented in the table, physiologically important inhibitory modulatory sites exist for Mg^{2+}, Zn^{2+} and protons (Dingledine *et al.*, 1999; Cull-Candy and Leszkiewicz, 2004). Voltage-independent inhibition by Zn^{2+} binding within N-terminal domain (NTD) is highly subunit-selective (GluN2A >> GluN2B > GluN2C ≥ GluN2D; Paoletti and Neyton, 2007). The receptor is also allosterically modulated, in both positive and negative directions, by endogenous neuroactive steroids in a subunit dependent manner (Malayev *et al.*, 2002; Horak *et al.*, 2006). Tonic proton blockade of NMDA receptor function is alleviated by polyamines and the inclusion of exon 5 within GluN1 subunit splice variants, whereas the non-competitive antagonists ifenprodil and CP101606 (traxoprodil) increase the fraction of receptors blocked by protons at ambient concentration. Inclusion of exon 5 also abolishes potentiation by polyamines and inhibition by Zn^{2+} that occurs through binding in the NTD (Traynelis *et al.*, 1998). Ifenprodil, CP101606, haloperidol, felbamate and Ro84304 discriminate between recombinant NMDA receptors assembled from GluN1 and either GluN2A, or GluN2B, subunits by acting as selective, non-competitive, antagonists of hetero-oligomers incorporating GluN2B. LY233536 is a competitive antagonist that also displays selectivity for GluN2B over GluN2A subunit-containing receptors. Similarly, CGP61594 is a photoaffinity label that interacts selectively with receptors incorporating GluN2B versus GluN2A, GluN2D and, to a lesser extent, GluN2C subunits. In addition to influencing the pharmacological profile of the NMDA receptor, the identity of the GluN2 subunit co-assembled with GluN1 is an important determinant of biophysical properties that include sensitivity to block by Mg^{2+}, single-channel conductance and maximal open probablity and channel deactivation time (Cull-Candy and Leszkiewicz, 2004; Erreger *et al.*, 2004; Gielen *et al.*, 2009). Incorporation of the GluN3A subunit into tri-heteromers containing GluN1 and GluN2 subunits is associated with decreased single-channel conductance, reduced permeability to Ca^{2+} and

decreased susceptibility to block by Mg^{2+} (Cavara and Hollmann, 2008). Reduced permeability to Ca^{2+} has also been observed following the inclusion of GluN3B in tri-heteromers. The expression of GluN3A, or GluN3B, with GluN1 alone forms, in *Xenopus laevis* oocytes, a cation channel with unique properties that include activation by glycine (but not NMDA), lack of permeation by Ca^{2+} and resistance to blockade by Mg^{2+} and NMDA receptor antagonists (Chatterton *et al.*, 2002). The function of heteromers composed of GluN1 and GluN3A is enhanced by Zn^{2+}, or glycine site antagonists, binding to the GluN1 subunit (Madry *et al.*, 2008). Zn^{2+} also directly activates such complexes. The co-expression of GluN1, GluN3A and GluN3B appears to be required to form glycine-activated receptors in mammalian cell hosts (Smothers and Woodward, 2007).

AMPA and kainate receptors: AMPA receptors assemble as homomers, or heteromers, that may be drawn from GluA1 (GLU_{A1}, GluR1, GluRA, GluR-A, GluR-K1), GluA2 (GLU_{A2}, GluR2, GluRB, GluR-B, GluR-K2), GluA3 (GLU_{A3}, GluR3, GluRC, GluR-C, GluR-K3) or GluA4 (GLU_{A4}, GluR4, GluRD, GluR-D) subunits. Transmembrane AMPA receptor regulatory proteins (TARPs) of class I (i.e. γ2, γ3, γ4 and γ8) act, with variable stoichiometry, as auxiliary subunits to AMPA receptors and influence their trafficking, single-channel conductance and gating (reviewed by Ziff, 2007; Esteban, 2008; Milstein and Nicoll, 2008). The nomenclature of kainate receptor subunits has been revised to provide a logical numerical sequence that harmonizes with their gene names (Collingridge *et al.*, 2009). Functional kainate receptors can be expressed as homomers of GluK1 (GLU_{K5}, GluR5, GluR-5, EAA3), GluK2 (GLU_{K6}, GluR6, GluR-6, EAA4) or GluK3 (GLU_{K7}, GluR7, GluR-7, EAA5) subunits. GluK1–3 subunits are also capable of assembling into heterotetramers (see Lerma, 2003; Pinheiro and Mulle, 2006). Two additional kainate receptor subunits, GluK4 (GLU_{K1} ,KA1, KA-1, EAA1) and GluK5 (GLU_{K2}, KA2, KA-2, EAA2), when expressed individually, form high-affinity binding sites for kainate, but lack function, probably due to retention within the endoplasmic reticulum (reviewed by Huettner, 2003 and Jane *et al.*, 2009). GluK4 and GluK5 can form heteromers when co-expressed with GluK1–3 subunits (Lerma, 2003). Kainate receptors may also exhibit 'metabotropic' functions (Rodriguez-Morino and Sihra, 2007). RNA encoding the GluA2 subunit undergoes extensive RNA editing in which the codon encoding a p-loop glutamine residue (Q) is converted to one encoding arginine (R). This Q/R site strongly influences the biophysical properties of the receptor. The class II TARP γ5 interacts selectively with AMPA receptors containing edited GluA2 subunits to uniquely modify their biophysical properties (Kato *et al.*, 2008). Recombinant AMPA receptors lacking RNA edited GluA2 subunits are: (i) permeable to Ca^{2+}; (ii) blocked by intracellular polyamines at depolarized potentials causing inward rectification (the latter being reduced by TARPs); (iii) blocked by extracellular argiotoxin and Joro spider toxins; and (iv) demonstrate higher channel conductances than receptors containing the edited form of GluA2 (Seeburg and Hartner, 2003; Isaac *et al.*, 2007). GluK1 and GluK2, but not other kainate receptor subunits, are similarly edited and broadly similar functional characteristics apply to kainate receptors lacking either an RNA edited GluK1, or GluK2, subunit (Lerma, 2003). Native AMPA and kainate receptors displaying differential channel conductances, Ca^{2+} permeabilites and sensitivity to block by intracellular polyamines have been identified (Cull-Candy *et al.*, 2006; Isaac *et al.*, 2007, Liu and Zukin, 2007). GluA1–4 can exist as two variants generated by alternative splicing (termed 'flip' and 'flop') that differ in their desensitization kinetics and their desensitization in the presence of cyclothiazide that stabilizes the non-desensitized state. TARPs also stabilize the non-desensitized conformation of AMPA receptors and facilitate the action of cyclothiazide (Milstein and Nicoll, 2008). Splice variants of GluK1–3 also exist, but their functional significance is unknown (Lerma, 2003).

Nomenclature	AMPA	Kainate
Ensembl gene family ID	ENSF00000000118	ENSF00000000118
Selective agonists	AMPA, (*S*)-5-fluorowillardiine	ATPA, (*S*)-4-AHCP, 8-deoxy-neodysiherbaine, (*S*)-5-iodowillardiine, LY339434 (all selective for receptors containing a GluK1 subunit), (2*S*,4*R*)-4-methylglutamate (SYM2081), dysiherbaine, domoic acid (inactive at GluK3), kainate (low potency at GluK3)
Selective antagonists	NBQX, ATPO, LY293558, GYKI53655/LY300168 (active isomer GYKI53784/LY303070) (non-competitive)	UBP302, UBP310, ACET, LY382884, LY466195 (all selective for receptors containing a GluK1 subunit), NS3763 (non-competitive, GluK1-selective), MSVIII-19 (GluK1-selective), 2,4-epi-neodysiherbaine (GluK1- and GluK2-selective)
Positive modulators	Pyrrolidones (piracetam, aniracetam), benzothiadiazides (cyclothiazide, S18986), benzylpiperidines [CX-516 (BDP-12), CX-546], biarylpropylsulfonamides (LY392098, LY404187 and LY503430)	Concanavalin A (GluK1 and GluK2, not GluK3)
Channel blockers	Intracellular polyamines, extracellular argiotoxin, extracellular Joro toxin, (selective for channels lacking GluA2)	Intracellular polyamines (subtype-selective)
Probes	[^{3}H]AMPA, [^{3}H]CNQX	[^{3}H]Kainate, [^{3}H](2*S*,4*R*)-4-methylglutamate

All AMPA receptors are additionally activated by kainate (and domoate) with relatively low potency (EC_{50} ~ 100 μM). Inclusion of TARPs within the receptor complex increases the potency and maximal effect of kainate (Milstein and Nicoll, 2008). AMPA is weak partial agonist at GluK1 and at heteromeric assemblies of GluK1/GluK2, GluK1/GluK5 and GluK2/GluK5 (Jane *et al.*, 2009). Quinoxalinediones such as CNQX and NBQX show limited selectivity between AMPA and kainate receptors. LY293558 also has kainate (GluK1) receptor activity as has GYKI53655 (GluK3 and GluK2/GluK3) (Jane *et al.*, 2009). ATPO is a potent competitive antagonist of AMPA receptors, has a weaker antagonist action at kainate receptors comprising GluK1 subunits, but is devoid of activity at kainate receptors formed from GluK2 or GluK2/GluK5 subunits. The pharmacological activity of ATPO resides with the (*S*)-enantiomer. ACET and UBP310 may block GluK3, in addition to GluK1 (Perrais *et al.*, 2009). (2*S*,4*R*)-4-methylglutamate (SYM2081) is equipotent in activating (and desensitizing) GluK1 and GluK2 receptor isoforms and, via the induction of desensitization at low concentrations, has been used as a functional antagonist of kainate receptors. Both (2*S*,4*R*)-4-methylglutamate and LY339434 have agonist activity at NMDA receptors. (2*S*,4*R*)-4-methylglutamate is also an inhibitor of the glutamate transporters EAAT1 and EAAT2.

Delta subunits: GluD1 (GluRδ1) and GluD2 (GluRδ2) comprise, on the basis of sequence homology, an 'orphan' class of ionotropic glutamate receptor subunit. They form do not form a functional receptor when expressed solely, or in combination with other ionotropic glutamate

receptor subunits, in transfected cells (Yuzaki, 2003). However, GluD2 subunits bind D-serine and glycine and GluD2 subunits carrying the mutation A654T form a spontaneously open channel that is closed by D-serine (Naur *et al*., 2007).

Abbreviations: (*S*)-4-AHCP, (*S*)-2-amino-3-(3-hydroxy-7,8-dihydro-6*H*-cyclohepta[*d*]isoxazol-4-yl)propionic acid; **ACET**, (*S*)-1-(2-amino-2-carboxyethyl)-3-(2-carboxy-5-phenylthiophene-3-yl-methyl)-5-methylpyrimidine-2,4-dione; **AMPA**, (*RS*)-α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; **APTA**, (*RS*)-2-amino-3-(3-hydroxy-5-*tert*-butylisoxazol-4-yl)propionic acid; **ATPO**, (*RS*)-2-amino-3-(3-[5-*tert*-butyl-3-(phosphonomethoxy)-4-isoxazolyl]propionic acid; **CGP37849**, (*RS*)-(*E*)-2-amino-4-methyl-5-phosphono-3-pentenoic acid; **CGP39653**, (*RS*)-(*E*)-2-amino-4-propyl-5-phosphono-3-pentenoic acid; **CGS19755**, (±)-*cis*-4-phosphonomethylpiperidine-2-carboxylic acid; **CNQX**, 6-cyano-7-nitroquinoxaline-2,3-dione; **CP101606**, (1*S*,2*S*)-1-4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol; **CPP**, (*R*)-3-(2-carboxypiperazine-4-yl)propyl-1-phosphonic acid; **CX-516**; 1-(quinoxalin-6-yl-carbonyl)piperidine; **CX-546**, 1-(1,4-benzodioxan-6-ylcarbonyl)piperidine; **D-AP5**, (*R*)-2-amino-5-phosphonopentanoate; **D-CCPene**, (*R*)-(*E*)-3-(2-carboxypiperazine-4-yl)propenyl-1-phosphonic acid; **GV196771A**, *E*-4,6-dichloro-3-(2-oxo-1-phenylpyrrolidin-3-ylidenemethyl)-1*H*-indole-2-carboxylic acid; **GYKI53655**, (±)-1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-3,4-dihydro-7,8-(methylenedioxy)-5*H*-2,3-benzodiazepine, also known as LY300168; **GYKI53784**, (-)-1-(4-aminophenyl)-3-methylcarbamoyl-4-methyl-3,4-dihydro-7,8-(methylenedioxy)-5*H*-2,3-benzodiazepine, also known as LY303070; **HA966**, 3-amino-1-hydroxypyrrolidin-2-one; **L689560**, *trans*-2-carboxy-5,7-dichloro-4-phenylaminocarbonylamino-1,2,3,4-tetrahydroquinoline; **L701324**, 7-chloro-4-hydroxy-3-(3-phenoxy)phenyl-2(*H*)quinolone; **LY233053**, (±)-*cis*-4-[(2*H*-tetrazol-5-yl)methyl]piperidine-2-carboxylic acid; **LY233536**, (±)-6-(1*H*-tetrazol-5-ylmethyl)decahydraisoquinoline-3-carboxylic acid; **LY293558**, (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1*H*)-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid; **LY339434**, (2*S*,4*R*,6*E*)-2-amino-4-carboxy-7-(2-naphthyl)hept-6-enoic acid; **LY382884**, (3*S*,4a*R*,6*S*,8a*R*)-6-((4-carboxyphenyl)methyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid; **LY392098**, propane-2-sulfonic acid [2-(4-thiophen-3-yl-phenyl)propyl]amide; **LY404187**, propane-2-sulfonic acid [2-(4′-cyanobiphenyl-4-yl)propyl]amide; **LY466195**, (3*S*,4*aR*,6*S*,8*aR*)-6-[[(2*S*)-2-carboxy-4,4-difluoro-1-pyrrolidinyl]-methyl]decahydro-3-isoquinolinecarboxylic acid; **LY503430**, (*R*)-4′-[1-fluoro-1-methyl-2-(propane-2-sulfonylamino)ethyl]biphenyl-4-carboxylic acid methylamide; **MDL105519**, (*E*)-3-(2-phenyl-2-carboxyethenyl)-4,6-dichloro-1*H*-indole-2-carboxylic acid; **MSVIII-19**, (2*R*,3a*R*,7a*R*)-2-[(2*S*)-2-amino-2-carboxyethyl]-hexahydro-furo-[3,2-*b*]pyran-2-carboxylic acid; **NBQX**, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(*f*)quinoxaline; **NS3763**, 5-carboxy-2,4-di-benzamidobenzoic acid; **NVP-AAM077**, (*R*)-[(*S*)-1-(4-bromophenyl)ethylamino]-(2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-5-yl)methyl]phosphonic acid; **PPDA**, (2*S**,3*R**)-1-(phenanthrene-2-carbonyl)piperazine-2,3-dicarboxylic acid; **Ro8-4304**, 4-3-[4-(4-fluorophenyl)-3,6-dihydro-2*H*-pyridin-1-yl]-2-hydroxypropoxybenzamide; **S10986**, (*S*)-2,3-dihydro-[3,4]cyclopentano-1,2,4-benzothiadiazine-1,1-dioxide; **UBP302**, (*S*)-1-(2-amino-2-carboxyethyl)-3-(2-carboxybenzyl)pyrimidine-2,4-dione; **UBP310**, (*S*)-1-(2-amino-2-carboxyethyl)-3-(2-carboxythiophene-3-yl-methyl)-5-methylpyrimidine-2,4-dione

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