5-HT$_3$ (5-Hydroxytryptamine$_3$)

Overview: The 5-HT$_3$ receptor [nomenclature as agreed by the NC-IUPHAR Subcommittee on 5-hydroxytryptamine (serotonin) receptors (Hoyer *et al*., 1994)] is a transmitter-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, GABA$_A$ and strychnine-sensitive glycine receptors. The receptor exists as a pentamer of 4TM subunits that form an intrinsic cation selective channel. Five human 5-HT$_3$ receptor subunits have been cloned and homo-oligomeric assemblies of 5-HT$_{3A}$ and hetero-oligomeric assemblies of 5-HT$_{3A}$ and 5-HT$_{3B}$ subunits have been characterised in detail. The recently described 5-HT$_{3C}$ (ENSG00000178084), 5-HT$_{3D}$ (ENSG00000186090) and 5-HT$_{3E}$ (ENSG00000186038) subunits (Karnovsky *et al*., 2003; Niesler *et al*., 2003), like the 5-HT$_{3B}$ subunit, do not form functional homomers, but are reported to assemble with the 5-HT$_{3A}$ subunit to influence its functional expression rather than pharmacological profile (Niesler *et al*., 2007). The hetero-oligomeric 5-HT$_{3A}$/5-HT$_{3B}$ receptor has been reported to contain two copies of the 5-HT$_{3A}$ subunit and three copies of the 5-HT$_{3B}$ subunit in the order B-B-A-B-A (Barrera *et al*., 2005). The 5-HT$_{3B}$ subunit imparts distinctive biophysical properties upon hetero-oligomeric 5-HT$_{3A}$/5-HT$_{3B}$ *versus* homo-oligomeric 5-HT$_{3A}$ recombinant receptors (Davies *et al*., 1999; Dubin *et al*., 1999; Hanna *et al*., 2000; Kelley *et al*., 2003; Stewart *et al*., 2003; Peters *et al*., 2005), but generally has little effect upon the apparent affinity of agonists, or the affinity of antagonists (Brady *et al*., 2001; but see Dubin *et al*., 1999). However, 5-HT$_{3A}$ and 5-HT$_{3A}$/5-HT$_{3B}$ receptors differ in their allosteric regulation by some general anaesthetic agents and small alcohols (Solt *et al*., 2005; Rüsch *et al*., 2007). The potential diversity of 5-HT$_3$ receptors is increased by alternatively spliced variants of the 5-HT$_{3A}$ subunit (Hope *et al*., 1993; Bruss *et al*., 2000), and tissue-specific preferences for different transcription start sites in the *HTR3B* gene, which could result in three different 5-HT$_{3B}$ subunit N-termini (Tzvetkov *et al*., 2007). To date, inclusion of the 5-HT$_{3A}$ subunit appears imperative for 5-HT$_3$ receptor function.

Nomenclature	5-HT$_3$
Former names	M
Ensembl ID	5-HT$_{3A}$ ENSG00000166736, 5-HT$_{3B}$ ENSG00000149305
Selective agonists (pEC_{50})	3-Chlorophenyl-biguanide (5.4–5.8), 2-methyl-5-HT (5.5–5.6), 1-phenylbiguanide (4.1)
Selective antagonists (pK_i)	(*S*)-Zacopride (9.0), granisetron (8.6–8.8), tropisetron (8.5–8.8), ondansetron (7.8–8.3)
Channel blockers	Diltiazem, TMB-8, picrotoxin (+5-HT$_{3B}$ potency reduced, Das and Dillon, 2003)
Probes (K_D)	[^{3}H]Ramosetron (0.15 nM), [^{3}H]granisetron (1.2 nM), [^{3}H]-(*S*)-zacopride (2.0 nM), [^{3}H]GR65630 (2.6 nM), [^{3}H]LY278584 (3 nM)
Functional characteristics	$\gamma = 0.4$–0.8 pS (+5-HT$_{3B}$, $\gamma = 16$ pS); inwardly rectifying current (+5-HT$_{3B}$, rectification reduced); n^H 2–3 (+5-HT$_{3B}$ 1–2); relative permeability to divalent cations reduced by co-expression of the 5-HT$_{3B}$ subunit

Quantitative data in the table refer to homo-oligomeric assemblies of the human 5-HT$_{3A}$ subunit, or the receptor native to human tissues. Significant changes introduced by co-expression of the 5-HT$_{3B}$ subunit are indicated in parenthesis. Human (Belelli *et al*., 1995; Miyake *et al*., 1995), rat (Isenberg *et al*., 1993), mouse (Maricq *et al*., 1991), guinea-pig (Lankiewicz *et al*., 1998) ferret (Mochizuki *et al*., 2000) and canine (Jensen *et al*., 2006) orthologues of the 5-HT$_{3A}$ receptor subunit have been cloned that exhibit intraspecies variations in receptor pharmacology. Notably, most ligands display significantly reduced affinities at the guinea-pig 5-HT$_3$ receptor in comparison with other species. In addition to the agents listed in the table, native and recombinant 5-HT$_3$ receptors are subject to allosteric modulation by extracellular divalent cations, alcohols, several general anaesthetics and 5-hydroxy- and halide-substituted indoles (see reviews by Parker *et al*., 1996; Lovinger, 1999; Thompson and Lummis, 2006, 2007).

Abbreviations: GR65630, 3-(5-methyl-1*H*-imidazol-4-yl)-1-(1-methyl-1*H*-indol-3-yl)-1-propanone; **LY278584**, 1-methyl-*N*-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1*H*-indazole- 3-carboxamide; **TMB-8**, 8-(diethylamine)octyl-3,4,5-trimethoxybenzoate

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Acetylcholine (nicotinic)

Nicotinic acetylcholine receptors are members of the Cys-loop family of transmitter-gated ion channels that includes the $GABA_A$, strychnine-sensitive glycine and 5-HT_3 receptors. All nicotinic receptors are formed as pentamers of subunits. Genes (Ensembl family ID ENSF00000000049) encoding a total of 17 subunits (α1–10, β1–4, δ, ε and γ) have been identified (see Kalamida *et al.*, 2007). All subunits are of mammalian origin with the exception of α8 (avian). Each subunit possesses 4 TM domains. All α subunits possess two tandem cysteine residues near to the site involved in acetylcholine binding, and subunits not named α lack those tandem cysteines. The acetylcholine binding site is formed by at least three peptide domains on the α subunit (principal component), and three on the adjacent subunit (complementary component). The determination of a high resolution (2.7 Å) crystal structure of the acetylcholine binding protein from *Lymnaea stagnalis*, a structural homologue of the extracellular binding domain of a nicotinic receptor pentamer, and the crystal structure of the extracellular domain of the α1 subunit bound to α-bungarotoxin at 1.94 Å resolution (Dellisanti *et al.*, 2007), has revealed the binding site in detail (reviewed by Karlin, 2002, Smit *et al.*, 2003; Sine and Engel, 2006; Kalamida *et al.*, 2007). Nicotinic receptors at the somatic neuromuscular junction of adult animals have the stoichiometry $(\alpha1)_2\beta1\varepsilon\delta$, whereas an extrajunctional $(\alpha1)_2\beta1\gamma\delta$ receptor predominates in embryonic and denervated skeletal muscle. Other nicotinic receptors are assembled as combinations of α(2–6) and β(2–4) subunits. For α2, α3, α4 and β2 and β4 subunits, pairwise combinations of α and β (e.g. α3β4, α2β4) are sufficient to form a functional receptor *in vitro*, but more complex isoforms may exist *in vivo* (reviewed by Gotti *et al.*, 2006, 2007). α5 and β3 subunits lack function when expressed alone, or pairwise, but participate in the formation of functional hetero-oligomeric receptors (e.g. α4α5αβ2, α6β2β3) when co-expressed with at least two other subunits. The α6 subunit can form a functional receptor when co-expressed with β4 *in vitro*, but more efficient expression ensues from incorporation of a third partner, such as β3. The α7, α8, and α9 subunits form functional homo-oligomers, but can also combine with a second α subunit to constitute a hetero-oligomeric assembly (e.g. avian α7α8). For functional expression of the α10 subunit, co-assembly with α9 is necessary. The latter, along with the α10 subunit, appears to be largely confined to cochlear and vestibular hair cells.

The nicotinic receptor subcommittee of NC-IUPHAR has recommended a nomenclature and classification scheme for nicotinic acetylcholine (nACh) receptors based on the subunit composition of known, naturally- and/or heterologously-expressed nACh receptor subtypes (Lukas *et al.*, 1999). Headings for this table reflect abbreviations designating nACh receptor subtypes based on the predominant α subunit contained in that receptor subtype. An asterisk following the indicated α subunit denotes that other subunits are known to, or may, assemble with the indicated α subunit to form the designated nACh receptor subtype(s). Where subunit stoichiometries within a specific nACh receptor subtype are known, numbers of a particular subunit larger than 1 are indicated by a subscript following the subunit (enclosed in parentheses).

Nomenclature	α1*	α2*	α3*
Previous names	Muscle-type, muscle	—	Autonomic, ganglionic
Selective agonists	—	—	—
Potency order of commonly used agonists	$(\alpha1)_2\beta1\gamma\delta$ (embryonic): sub > epi > DMPP > ACh > carb ~ sux > nico ~ cyt ≫ cho $(\alpha1)_2\beta1\varepsilon\delta$ (adult): sux > cyt = DMPP > nic	α2β2: epi > ana-a > DMPP > nic = cyt > ACh α2β4: epi > DMPP = nic = cyt† > ACh	α3β2: epi > DMPP = cyt > nic > ACh α3β4: epi > ana-a > DMPP > cyt† = nic > ACh
Selective antagonists	α-bungarotoxin, α-conotoxin GI, α-conotoxin MI, pancuronium	—	α3β2: α-conotoxin MII (also blocks α6β2*), α-conotoxin-GIC α3β4: α-conotoxin AuIB
Commonly used antagonists	$(\alpha1)_2\beta1\gamma\delta$: Bgt > pan > (+)-Tc [high affinity α1/δ binding site, low affinity α/γ site] $\alpha(1)_2\beta1\varepsilon\delta$: Bgt > pan > (+)-Tc	α2β2: DHβE (K_B = 0.9 μM), (+)-Tc (K_B = 1.4 μM) α2β4: DHβE (K_B = 3.6 μM), (+)-Tc (K_B = 4.2 μM)	α3β2: DHβE (K_B = 1.6 μM), (+)-Tc (K_B = 2.4 μM) α3β4: DHβE (K_B = 19 μM), (+)-Tc (K_B = 2.2 μM)
Channel blockers	Gallamine	—	Mecamylamine, hexamethonium
Probes (K_d)	[^{3}H]/[^{125}I]-α-bungarotoxin	[^{3}H]/[^{125}I]-epibatidine (hα2β4, 42 pM; rα2β2, 10 pM; rα2β4, 87 pM), [^{3}H]-cytisine	[^{3}H]/[^{125}I]-epibatidine (hα3β2, 7 pM; hα3β4, 230 pM; rα3β2, 14 pM, rα3β4, 300 pM), [^{3}H]-cytisine
Functional characteristics	$\alpha(1)_2\beta\gamma\delta$: P_{Ca}/P_{Na} = 0.16–0.2, P_f = 2.1–2.9%; $\alpha(1)_2\beta\varepsilon\delta$: P_{Ca}/P_{Na} = 0.65–1.38, P_f = 4.1–7.2%	α2β2: P_{Ca}/P_{Na} ~ 1.5	α3β2: P_{Ca}/P_{Na} = 1.5; α3β4: P_{Ca}/P_{Na} = 0.78−1.1, P_f = 2.7–4.6%

Nomenclature	α4*	α6*	α7*
Previous names	Neuronal, α-bungarotoxin-insensitive	—	Neuronal, α-bungarotoxin-sensitive
Selective agonists	α4β2: TC-2559 (Chen *et al*., 2003), TC-2403 (RJR-2403, Papke *et al*., 2000)	—	AR-R17779 (Mullen *et al*., 2000), PSAB-OFP (also activates 5-HT_3 receptors) (Broad *et al*., 2002), PNU-282987 (Bodnar *et al*., 2005)
Potency order of commonly used agonists	α4β2: epi ≫ nic > cyt > ACh > DMPP = sub > carb ≫ cho > sux α4β4: epi > cyt > nic > DMPP ≫ ACh	rα6hβ4: ACh > cyt > nic > DMPP cα6hβ4: epi > cyt ≥ nic = > ACh†	$(α7)_5$: ana-a > epi > DMAC > OH-GTS-21 = DMPP† > cyt† > nic† = GTS-21 = > ACh > cho
Selective antagonists	—	α6/α3β2β3 chimera: α-conotoxin PIA α6β2*: α-conotoxin MII (also blocks α3β2)	$(α7)_5$: α-bungarotoxin, methyllycaconitine, α-conotoxin ImI, α-conotoxin ArIB
Commonly used antagonists	α4β2: DHβE (K_B = 0.1 μM), (+)-Tc (K_B = 3.2 μM) α4β4: DHβE (K_B = 0.01 μM), (+)-Tc (K_B = 0.2 μM)	cα6hβ4: mec, (+)-Tc, hex rα6hβ4: (+)-Tc	$(α7)_5$: Bgt > MLA > (+)-Tc† > atr > DHβE
Channel blockers	—	Mecamylamine, hexamethonium	—
Probes (K_d)	[^{3}H]/[^{125}I]-epibatidine (hα4β2, 10–33 pM; hα4β4, 187 pM; rα4β2, 30 pM, rα4β4, 85 pM), [^{3}H]-cytisine, [^{3}H]-nicotine	[^{3}H]-epibatidine (native chick cα6β4*, 35 pM)	[^{3}H]/[^{125}I]-α-bungarotoxin ($(hα7)_5$, 700–800 pM), [^{3}H]-methyllycaconitine (native rα7*, 1.9 nM), [^{3}H] A585539 (native hα7*, 0.07nM; Anderson *et al*., 2008)
Functional characteristics	α4β2: P_{Ca}/P_{Na} = 1.65, P_f = 2.6–2.9%; α4β4: P_f = 1.5–3.0 %	—	P_{Ca}/P_{Na} = 6.6–20, P_f = 8.8–11.4%

Nomenclature	α8* (avian)	α9*	α10*
Previous names	Neuronal, α-bungarotoxin-sensitive	—	—
Selective agonists	—	—	—
Potency order of commonly used agonists	$(α8)_5$: cyt ~ nic ≥ ACh > DMPP	$(α9)_5$: cho > ACh > sub > car	ACh
Selective antagonists	—	$(α9)_5$: α-bungarotoxin, strychnine, nicotine, muscarine	α10α9: α-bungarotoxin, strychnine, nicotine, muscarine
Commonly used antagonists	$(α8)_5$: Bgt > atr ≥ (+)-Tc ≥ str	$(α9)_5$: Bgt > MLA > str ~ tropisetron > (+)-TC > bic ≥ atr ~ epi > mec > DHβE > cyt > nic > mus	α10α9: Bgt > tropisetron = str > (+)-Tc > bic = atr > nic > mus
Channel blockers	—	—	—
Probes (K_d)	[^{3}H]/[^{125}I]-α-bungarotoxin	[^{3}H]/[^{125}I]-α-bungarotoxin	—
Functional characteristics	—	α9: P_{Ca}/P_{Na} = 9; α9α10: P_{Ca}/P_{Na} = 9, P_f=22%	—

A firm consensus has yet to emerge concerning the pharmacological profiles at different nACh receptor subtypes. There are differences in profiles for a given receptor subtype across species. Moreover, measures of agonist potencies and efficacies, or antagonist affinities, are confounded by differences in experimental design across studies (oocyte or mammalian cell heterologous expression systems or natural expression; test agonist concentrations; competitive/non-competitive modes of antagonism; electrophysiological, ion flux, or calcium ion mobilization measurements; etc.). Therefore, provisional and incomplete information about pharmacological rank order potency profiles (no efficacy data) is provided in the table based largely on data from studies of heterologously expressed, human nACh receptors. The dagger (†) as superscript designates ligands whose rank order placement differs across species and/or experimental design.

Abbreviations: (+)-Tc, (+)-tubocurarine; **A-585539**, (1*S*,4*S*)-2,2-dimethyl-5-(6-phenylpyridazin-3-yl)-5-aza-2-azaniabicyclo [2.2.1] heptane; **ABT-594**, (*R*)-5-(2-azetidinylmethoxy)-2-chloropyridine; **ACh**, acetylcholine; ana-a, anatoxin-a; **AR-R17779**, (−)-Spiro[1-azabicyclo[2.2.2] octane-3,5′-oxazolidin-2′-one; **atr**, atropine; **Bgt**, α-bungarotoxin; **bic**, bicuculline; **car**, carbamylcholine; **cho**, choline; **cyt**, cytisine; **DHβE**, dihydro-β-erythroidine; **DMAC**, 3-(4)-dimethylaminocinnamylidine anabaseine; **DMPP**, 1,1-dimethyl-4-phenylpiperazinium; **epi**, epibatidine; **GTS-21**, 3-(2,4)-dimethoxybenzylidine anabaseine (DMXB); **hex**, hexamethonium; **mec**, mecamylamine; **MLA**, methyllycaconitine; **mus**, muscarine; **nic**, nicotine; **OH-GTS-21**, 3-(4-hydroxy,2-methoxy)benzylidine anabaseine; **pan**, pancuronium; **PNU-282987**, *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide hydrochloride; **PSAB-OFP**, (*R*)-(−)-5′phenylspiro[1-azabicyclo[2.2.2] octane-3,2′-(3′H)furo[2,3-b]pyridine; str, strychnine; **sub**, suberyldicholine; **sux**, succinylcholine; **TC-2403**, (RJR-2403),(E)-*N*-methyl-4-(3-pyridinyl)-3-butene-1-amine; **TC-2559**, (E)-*N*-methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine

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$GABA_A$ (γ-aminobutyric acid)

Overview: The $GABA_A$ receptor is a transmitter-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT_3 and strychnine-sensitive glycine receptors. The receptor exists as a pentamer of 4TM subunits that form an intrinsic anion channel. Sequences of six α, three β, three γ one δ, three ρ, one ε, one π and one θ $GABA_A$ receptor subunits (Ensembl gene family ID ENSF00000000053) have been reported in mammals (Barnard, 2000; Korpi *et al.*, 2002; Whiting, 2003; Sieghart, 2006). The π-subunit is restricted to reproductive tissue. Alternatively spliced versions of α4- and α6- (both not functional) α5-, β2-, β3- and γ2-subunits exist. In addition, three ρ-subunits, (ρ1–3) function as either homo- or hetero-oligomeric assemblies (Zhang *et al.*, 2001). Although receptors formed from ρ-subunits have sometimes been termed $GABA_C$ receptors (Zhang, 2001), they represent a subpopulation of $GABA_A$ receptor, classed as the $GABA_{A0r}$ subtype, under NC-IUPHAR recommendations (Barnard *et al.*, 1998). Many $GABA_A$ receptor subtypes contain α-, β- and γ-subunits with the likely stoichiometry 2α.2β.1γ (Korpi *et al.*, 2002, Fritschy and Brünig, 2003). It is thought that the majority of $GABA_A$ receptors harbour a single type of α- and β-subunit variant. The α1β2γ2 hetero-oligomer constitutes the largest population of $GABA_A$ receptors in the CNS, followed by the α2β3γ2 and α3β3γ2 isoforms. Receptors that incorporate the α4- α5-or α6-subunit, or the β1-, γ1-, γ3-, δ-, ε- and θ-subunits, are less numerous, but they may nonetheless serve important functions. For example, extrasynaptically located receptors that contain α6- and δ-subunits in cerebellar granule cells, or an α4- and δ-subunit in dentate gyrus granule cells and thalamic neurones, mediate a non-desensitizing tonic current that is important for neuronal excitability in response to ambient concentrations of GABA (see Mody and Pearce, 2004; Semyanov, 2004; Farrant and Nusser, 2005; Walker and Semyanov, 2008). The α- and β-subunits contribute to the GABA binding site and both the α- and γ-subunits are required for the benzodiazepine (BZ) site. The particular α-and γ-subunit isoforms exhibit marked effects on recognition and/or efficacy at the BZ site. Thus, receptors incorporating either α4- or α6-subunits are not recognised by 'classical' benzodiazepines, such as flunitrazepam. A variety of proteins that associate with the large intracellular M3-M4 loop of $GABA_A$ receptor subunits influence the trafficking, cell surface expression, internalisation and function of the receptor (Chen and Olsen, 2007). It is beyond the scope of this supplement to discuss the pharmacology of individual GABA receptor isoforms in detail; such information can be gleaned in the reviews by Barnard *et al*. (1998), Frolund *et al*. (2002), Korpi *et al*. (2002), Krogsgaard-Larsen *et al*. (2002), Johnston (2005), Sieghart (2006) and Möhler (2007). Agents that discriminate between α-subunit isoforms are noted in the table and additional agents that demonstrate selectivity between receptor isoforms are indicated in the text below.

The classification of $GABA_A$ receptors has been addressed by NC-IUPHAR (Barnard *et al.*, 1998), but is currently under review (R.W. Olsen, NC-IUPHAR $GABA_A$ receptor sub-committee chair, personal communication). The existing scheme utilizes subunit structure and receptor function as the basis for classification. In view of the fact that a benzodiazepine (BZ) binding site is not unique to the $GABA_A$ receptor, and that certain receptor isoforms (i.e. those incorporating α4- or α6-subunits) are insensitive to classical benzodiazepines it is recommended that the term '$GABA_A$/benzodiazepine receptor complex' should no longer be used and be replaced by '$GABA_A$ receptor'. The term benzodiazepine receptor itself is contentious because receptors should generally be named to reflect their endogenous ligand and many discriminatory ligands acting at this site are generally not benzodiazepines (e.g. zolpidem, an imidazopyridine). Here, the term 'BZ site of the $GABA_A$ receptor' is adopted as one of the two alternatives proposed by NC-IUPHAR.

Nomenclature	$GABA_A$
Ensembl Gene family ID	ENSF00000000053
Selective agonists (GABA site)	Muscimol, isoguvacine, THIP (gaboxadol); piperidine-4-sulphonic acid (low efficacy at α4 and α6 subunits), isonipecotic acid (α4 and α6 subunit selective *via* relatively high efficacy)
Selective antagonists (GABA site)	Bicuculline, gabazine (SR95531)
Selective agonists (BZ site)	Diazepam (not α4- or α6-subunits), flunitrazepam (not α4- or α6-subunits), zolpidem, zaleplon and indiplon (α1 subunit selective *via* high affinity), ocinaplon (α1 subunit selective as essentially a full agonist versus partial agonist at α2, α3 and α5 subunit-containing receptors), L838417 (α2, α3 and α5 subunit selective as a partial agonist versus antagonist at α1-subunit-containing receptors), Ro154513 (selective for α4- and α6-subunit-containing receptors as an agonist versus inverse agonist at α1-, α2-, α3- and α5-subunit-containing receptors), TP003 (selective for α3-subunit-containing receptors as a high efficacy partial agonist versus essentially antagonist activity at α1- α2- and α5-subunit-containing receptors), TPA023 (selective for α2- and α3-subunit-containing receptors as a low efficacy partial agonist versus essentially antagonist activity at α1- and α5-subunit-containing receptors)
Selective antagonists (BZ site)	Flumazenil (low affinity for α4- or α6-subunits), ZK93426, L838417 (α1 subunit selective *via* antagonist activity versus partial agonist at α2-, α3- and α5-subunit subunit containing receptors)
Inverse agonists (BZ site)	DMCM, Ro194603, α3IA (α3 selective *via* higher affinity and greater inverse agonist activity versus α1, α2 and α5-subunit containing receptors), L655708 (α5 selective *via* high affinity), RY024 (α5 selective *via* high affinity), α5IA (α5 selective versus α1, α2 and α3-subunit containing receptors *via* greater inverse agonist efficacy)
Endogenous allosteric modulators	5α-pregnan-3α-ol-20-one (potentiation), tetrahydrodeoxycorticosterone (potentiation) Zn^{2+} (potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a γ subunit reduces inhibitory potency, Krishek *et al.*, 1998), extracellular protons (subunit dependent activity, Krishek *et al.*, 1996)
Channel blockers	Picrotoxin, TBPS
Probes	
GABA site	[^{3}H]muscimol, [^{3}H]gabazine (SR95531)
BZ site	[^{3}H]Flunitrazepam (not α4- or α6-subunit), [^{3}H]zolpidem (α1-subunit selective), [^{3}H]L655708 (α5-subunit selective), [^{3}H]RY80 (α5-subunit selective), [^{3}H]Ro154513 [selectively labels α4- and α6-subunit-containing receptors in the presence of a saturating concentration of a 'classical' benzodiazepine (e.g. diazepam)], [^{3}H]CGS8216, [^{11}C]flumazenil (PET ligand with low affinity for α4- or α6-subunits), [^{18}F]fluoroethylflumazenil (PET ligand)
Anion channel	[^{35}S]TBPS

The potency and efficacy of many GABA agonists varies between receptor $GABA_A$ receptor isoforms (Frolund *et al.*, 2002; Krogsgaard-Larsen *et al.*, 2002). For example, THIP (gaboxadol) is a partial agonist at receptors with the subunit composition α4β3γ2, but elicits currents in excess

of those evoked by GABA at the α4β3δ receptor where GABA itself is a low efficacy agonist (Brown *et al*., 2002; Bianchi and MacDonald, 2003). Recent data suggests that the presence of the γ subunit within the heterotrimeric complex reduces the potency and efficacy of agonists (Stórustovu and Ebert, 2006). The $GABA_A$ receptor contains distinct allosteric sites that bind barbiturates and endogenous (e.g. 5α-pregnan-3α-ol-20-one) and synthetic (e.g. alphaxalone) neuroactive steroids in a diastereo- or enantio-selective manner (see Belelli and Lambert, 2005; Herd *et al*., 2007; Hosie *et al*., 2007). Picrotoxinin and TBPS act at an allosteric site within the chloride channel pore to negatively regulate channel activity; negative allosteric regulation by γ-butyrolactone derivatives also involves the picrotoxinin site, whereas positive allosteric regulation by such compounds is proposed to occur at a distinct locus. Many intravenous (e.g. etomidate, propofol) and volatile (e.g. halothane, isoflurane) anaesthetics and alcohols also exert a regulatory influence upon $GABA_A$ receptor activity. Specific amino acid residues within $GABA_A$ receptor α- and β-subunits that influence allosteric regulation by anaesthetic and non-anaesthetic compounds have been identified (see Belelli *et al*., 1999; Krazowski *et al*., 2000; Thompson and Wafford, 2001; Hemmings *et al*., 2005; Hosie *et al*., 2007). An array of natural products including flavonoid and terpenoid compounds exert varied actions at $GABA_A$ receptors (reviewed in detail by Johnston, 2005).

In addition to the agents listed in the table, modulators of $GABA_A$ receptor activity that exhibit subunit dependent activity include: salicylidene salicylhydrazide (negative allosteric modulator selective for β1- versus β2-, or β3-subunit-containing receptors (Thompson *et al*., 2004)); loreclezole, etomidate, tracazolate and mefenamic acid (positive allosteric modulators with selectivity for β2/β3- over β1-subunit-containing receptors, see Korpi *et al*. (2002)); tracazolate (intrinsic efficacy, i.e. potentiation, or inhibition, is dependent upon the identity of the γ1–3-, δ-, or ε-subunit co-assembed with α1- and β1-subunits (Thompson *et al*., 2002)); amiloride (selective blockade of receptors containing an α6-subunit (Fisher, 2002)); frusemide (selective blockade of receptors containing an α6-subunit co-assembled with β2/β3-, but not β1-subunit (see Korpi *et al*. (2002)); La^{3+} (potentiates responses mediated by α1β3γ2L receptors, weakly inhibits α6β3γ2L receptors, and strongly blocks α6β3δ and α4β3δ receptors (Saxena *et al*., 1997, Brown *et al*., 2002)); ethanol (selectively potentiates responses mediated by α4β3δ and α6β3δ receptors versus receptors in which β2 replaces β3, or γ replaces δ (Wallner *et al*., 2006, but see also Korpi *et al*., 2007)). It should be noted that the apparent selectivity of some positive allosteric modulators (e.g. neurosteroids such as 5α-pregnan-3α-ol-20-one for δ-subunit-containing receptors (e.g. α1β3δ) may be a consequence of the unusually low efficacy of GABA at this receptor isoform (Bianchi *et al*., 2003).

A subpopulation of retinal GABA receptors (activated by trans-4-aminocrotonic acid) assembled from ρ subunits is bicuculline-insensitive and gates Cl^- channels that are insensitive to barbiturates and benzodiazepines and selectively blocked by TPMPA. Isoguvacine and piperidine-4-sulphonic acid do not activate $GABA_A$ receptors assembled from ρ subunits, and THIP is a moderately potent antagonist. Receptors formed from ρ subunits have often been found to be insensitive to neuroactive steroids, but relatively high concentrations of such compounds can modulate the activity of the ρ1 subunit in a stereoselective manner, 5α-pregnanes potentiating, and 5β-pregnanes inhibiting, responses elicited by low concentrations of GABA (Morris and Amin, 2004). Although these receptors have sometimes been termed $GABA_C$ receptors (see Zhang *et al*., 2001), this appellation is not endorsed by NC-IUPHAR and they are currently viewed as a sub-class of $GABA_A$ receptor. This position is strengthened by the observation that single amino acid mutations can impart some typical features of $GABA_A$ receptor pharmacology upon the $GABA_{A0r}$ subtype (Belelli *et al*., 1999; Walters *et al*., 2000).

Abbreviations: **α3IA**, 6-(4-pyridyl)-5-(4-methoxyphenyl)-3-carbomethoxy-1-methyl-1*H*-pyridin-2-one; **α5IA**, 3-(5-methylisoxazol-3-yl)-6-[(1-methyl-1,2,3-triazol-4-yl)methyloxy]-1,2,4-triazolo[3,4-*a*]phthalazine; **CGS8216**, 2-phenylpyrazolo[4,3-c]quinolin-3(5)-one; **DMCM**, methy-6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate; **L655708**, ethyl(s)-(11,12,13,13a-tetrahydro-7-methoxy-9-oxo)-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate; **L838417**, 7-*tert*-butyl-3-(2,5-difluoro-phenyl)-6-(2-methyl-2*H*-[1,2,4]triazol-3-ylmethoxy)-[1,2,4]triazolo[4,3-b]pyridazine; **Ro154513**, ethyl-8-azido-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4] benzodiazepine-3-carboxylate; **Ro194603**, imidazo[1,5-a]1,4-thienodiazepinone; **RY024**, *tert*-butyl-8-ethynyl-5,6-dihydro-5-methyl-6-oxo-4H-imidazol[1,5-α][1,4]benzodiazepine-3-carboxylate; **RY80**, ethyl-8-acetylene-5, 6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5a][1,4]benzodiazepine-3-carboxylate; **SR95531**, 2-(3′-carboxy-2′-propyl)-3-amino-6-*p*-methoxyphenylpyridazinium bromide; **TBPS**, *tert*-butylbicyclophosphorothionate; **TP003**, 4,2′-difluro-5′-[8-fluro-7-(1-hydroxy-1-methylethyl)imidazo[1,2-á]pyridine-3-yl]biphenyl-2-carbonitrile; **TPA023**, 7-(1,1-dimethylethyl)-6-(2-ethyl-2*H*-1,2,4-triazol-3-yl-methoxy)-3-(2-fluorphenyl)-1,2,4-triazolo[4,3-*b*]pyridazine; **TPMPA**, (1,2,5,6-tetrahydropyridine-4-yl)methylphosphinic acid; **ZK93423**, 6-benzyloxy-4-methoxymethy-β-carboline-3-carboxylate ethyl ester; **ZK93426**, 5-isopropyl-4-methyl-β-carboline-3-carboxylate ethyl ester

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Glutamate (ionotropic)

Overview: The ionotropic glutamate receptors comprise members of the NMDA (*N*-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid) and kainate receptor classes, named originally according to their preferred, synthetic, agonist [see Dingledine *et al*. (1999) for a comprehensive review]. 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 in the reviews by Dingledine *et al*. (1999), Jane *et al*. (2000), Huettner (2003), Cull-Candy and Leszkiewicz (2004), Kew and Kemp (2005), Erreger *et al*. (2007) and Paoletti and Neyton (2007). 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 (G.L. Collingridge, NC-IUPHAR ionotropic glutamate receptor sub-committee chair, personal communication). The scheme developed recommends a revised nomenclature for ionotropic glutamate receptor subunits that is adopted here. Alternative appellations that have been used previously 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 expressional 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+} at resting potential.

Nomenclature	NMDA
Ensembl Gene family ID	ENSF00000000436
Selective agonists (glutamate site)	NMDA, aspartate, D,L(tetrazol-5-yl)glycine, homoquinolinic acid (partial agonist)
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 > GluN2C > GluN2D > GluN2B, Auberson *et al*., 2002; Feng *et al*., 2004; but see Frizelle *et al*., 2006), conantokin-G (GluN2B > GluN2D = GluN2C = GluN2A)
Selective agonists (glycine site)	Glycine, D-serine, (+)-HA966 (partial agonist)
Selective antagonists (glycine site)	5,7-Dichlorokynurenate, L689560, L701324, GV196771A
Channel blockers	Mg^{2+}, dizocilpine (MK801), ketamine, phencyclidine, memantine, amantidine, N^1-dansyl-spermine (GluN2A = GluN2B > > GluN2C = GluN2D),
Radioligands	
Glutamate site	[^{3}H]CPP, [^{3}H]CGS19755, [^{3}H]CGP39653
Glycine site	[^{3}H]Glycine, [^{3}H]L689560, [^{3}H]MDL105519
Cation channel	[^{3}H]Dizocilpine

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 (see Dingledine *et al*., 1999; Yamakura and Shimoji, 1999; Cull-Candy and Leszkiewicz, 2004). The receptor is also allosterically modulated, in both positive and negative directions, by endogenous neuroactive steroids in a subunit dependent manner. For example, pregnenolone sulphate potentiates di-heteromeric assemblies of GluN1/GluN2A and GluN1/GluN2B subunits, but inhibits receptors assembled as GluN1/GluN2C, or GluN1/GluN2D, heteromers (Malayev *et al*., 2002). 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 antagonist ifenprodil increases the fraction of receptors blocked by protons at ambient concentration. Inclusion of exon 5 also abolishes potentiation by polyamines and inhibition by Zn^{2+}. Receptors assembled from GluN1 and GluN2C subunits are unusually insensitive to proton blockade. Ifenprodil, its analogue 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. Conversely, the voltage-independent component of NMDA receptor inhibition by Zn^{2+} is most pronounced for receptors that contain the GluN2A *versus* GluN2B subunit. 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 channel deactivation time (Cull-Candy and Leszkiewicz, 2004). 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+}. 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). 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. Homotetramers formed from GluA2 subunits express relatively poorly due to their retention within the endoplasmic reticulum (see Bredt and Nicoll, 2003). Transmembrane AMPA receptor regulatory proteins (TARPs) act as auxiliary subunits to AMPA receptors and influence their trafficking, single channel conductance and gating (reviewed by Nicoll *et al*., 2006; Ziff, 2007). The nomenclature of kainate receptor subunits has been revised to provide a logical numerical sequence that harmonises with their gene names (G.L. Collingridge, personal communication). 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 (see Huettner, 2003). GluK4 and GluK5 can form heteromers when co-expressed with GluK1-3 subunits (Lerma, 2003). 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. Recombinant AMPA receptors lacking RNA edited GluA2 subunits are: (1) permeable to Ca^{2+}; (2) blocked by intracellular polyamines at depolarized potentials causing inward rectification; (3) blocked by extracellular argiotoxin and Joro spider toxins and (4) 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. 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-flurowillardiine	ATPA, desiherbaine, (s)-5-iodowillardiine, (2 s,4r)-4-methyl glutamate (SYM2081), LY339434, domoic acid (except homomeric GluK3), kainate
Selective antagonists	NBQX, ATPO, LY293558, GYKI53655/LY300168 (active isomer GYKI53784/LY303070) (noncompetitive)	UBP302 (More *et al*., 2004), UBP310 (Dolman *et al*., 2005), LY382884, LY466195 (Weiss *et al*., 2006) NS3763 (non-competitive, Christensen *et al*., 2004)
Channel blockers	Intracellular polyamines, extracellular argiotoxin, extracellular Joro toxin, (selective for channels lacking GluA2)	Intracellular polyamines (subtype selective)
Radioligands	[^{3}H]AMPA, [^{3}H]CNQX	[^{3}H]Kainate, [^{3}H](2 s,4r)-4-methyl glutamate

All AMPA receptors are additionally activated by kainate (and domoate) with relatively low potency ($EC_{50} \sim 100\,\mu M$). AMPA receptor activity is potentiated by several classes of agent that are not tabulated above including: pyrrolidones (piracetam, aniracetam); benzothiazides (cyclothiazide); benzylpiperidines [CX-516 (BDP-12), CX-546] and biarylpropylsulfonamides (LY392098, LY404187 and LY503430) (O'Neill *et al*., 2004; O'Neill and Witkin, 2007). Activation of kainate receptors by AMPA shows subunit dependency (*e.g.* heteromers containing GluK2- and GluK5-subunits are sensitive; homomers assembled from the GluK2 subunit, or GluK3 subunit, are insensitive). Quinoxalinediones such as CNQX and NBQX show limited selectivity between AMPA and kainate receptors. LY293558 also has kainate (GluK1) receptor activity. 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. ATPA, desiherbaine, UBP296, UBP310, LY339434, LY382884 LY466195 and (s)-5-iodowillardiine interact selectively with kainate receptors containing a GluK1 subunit. (2s,4r)-4-methyl glutamate (SYM2081) is equipotent in activating (and desensitising) GluK1 and GluK2 receptor isoforms and, *via* the induction of desensitisation at low concentrations, has been used as a functional antagonist of kainate receptors. Both (2 s,4r)-4-methyl glutamate and LY339434 have agonist activity at NMDA receptors. (2 s,4r)-4-methyl glutamate 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 neither a function receptor, nor binding site for glutamate receptor ligands, when expressed solely, or in combination with other ionotropic glutamate receptor subunits, in transfected cells (Yuzaki, 2003).

Abbreviations: AMPA, (*RS*)-α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic 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-methylphosphono-3-pentanoic acid; **CGP39653**, (*RS*)-(*E*)-2-amino-4-propylphosphono-3-pentanoic acid; **CGS19755**, 4-phosphonomethyl-2-piperidinecarboxylic 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**, (±)-2-carboxypiperazine-4-yl)propyl-1-phosphonic acid; **CX-516**; 1-(quinoxalin-6-ylcarbonyl)piperidine; CX-546, 1-(1,4-benzodioxan-6-ylcarbonyl)piperidine; **D-AP5**, D(2)-2-amino-5-phosphonopentanoate; **D-CCPene**, 3-(2-carboxypiperazine-4-yl)-propenyl-1-phosponic acid; **GV196771A**, *E*-4, 6-dichloro-3-(2-oxo-1-phenyl-pyrrolidin-3-ylidenemethyl)-1*H*-indole-2-carboxylic acid; **GYKI53655**, 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-(3N-methylcarbamate)-2,3-benzodiazepine, also known as LY300168; **GYKI53784**, (-)1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3-methylcarbamoyl-2,3-benzodiazepine, also known as LY303070; **HA966**, 3-amino-1-hydroxypyrrolid-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*(1)-4-[(2*H*-tetrazole-5yl)methyl]piperidine-2-carboxylic acid; **LY233536**, (RS)-6-(1*H*-tetrazol-5-ylmethyl)decahydraisoquinoline-3-carboxylic acid; **LY293558**, 3 *S*,4*aR*,6*R*, 8*aR*-6-[2-(1(2)H-tetrazol-5yl)ethyl]-decahydroisoquinoline-3-carboxylate; **LY339434**, (2 *S*,4*R*, 6*E*)-2-amino-4-carboxy-7-(2-naphthyl)hept-6-enoic acid; **LY382884**, (3*S*, 4*aR*, 6*S*, 8*aR*)-6-((4-carboxyphenyl)methyl-1,2,3,4,4a,5,6,7,8, 8a-decahydro isoquinoline-3-carboxylic acid; **LY392098**, **propane-2-sulfonic acid [2-(4- thiophen-3-yl-phenyl)-propyl]-amide; LY404187**, Propane-2-sulfonic acid [2-(4′-cyano-biphenyl-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; **NBQX**, 6-nitro-7-sulfamoyl-benz(*f*)quinoxaline-2,3-dione; **NS3763**, 5-carboxyl-2, 4-di-benzamido-benzoic acid; **NVP-AAM077**, **(*R*)-[(*S*)-1-(4-bromo-phenyl)-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-fluro-phenyl-)3, 6-dihydro-2*H*-pyridin-1-yl]-2-hydroxy-propoxy-benzamide; **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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Glycine

Overview: The inhibitory glycine receptor (provisional nomenclature adopted here classifies glycine receptor isoforms by their α-subunit) is a member of the Cys-loop superfamily of transmitter-gated ion channels that includes the $GABA_A$, nicotinic acetylcholine and 5-HT_3 receptors. Structurally and functionally, the glycine receptor is most closely related to the $GABA_A$ receptor. The receptor is expressed either as a homo-pentamer of α subunits, or a complex now thought to harbour 2α and 3β subunits (Grudzinska *et al*., 2005; Betz and Laube, 2006), that contain an intrinsic Cl^- channel. Four differentially expressed isoforms of the α-subunit (α1-α4) and one variant of the β-subunit (β1, ENSG00000109738) have been identified by genomic and cDNA cloning. Further diversity originates from alternative splicing of the primary gene transcripts for α1 ($\alpha1^{INS}$ and $\alpha1^{del}$), α2 (α2A and α2B), α3 (α3S and α3L) and β (βΔ7) subunits and by mRNA editing of the α3 subunit (Meier *et al*., 2005; Oertel *et al*., 2007). In particular, the α2B subunit has a 2–4 fold higher sensitivity to glycine, β-alanine and taurine. Predominantly, the mature form of the receptor contains α1 (or α3) and β subunits while the immature form is mostly composed of only α2 subunits. RNA transcripts encoding the α4-subunit have not been detected in adult humans. The α4-subunit may be a pseudogene in man and is not tabulated here. The N-terminal domain of the α-subunit contains both the agonist and strychnine binding sites that consist of several discontinuous regions of amino acids. Inclusion of the β-subunit in the pentameric glycine receptor reduces single channel conductance and alters pharmacology and contributes to agonist binding. It also anchors the receptor, *via* an amphipathic sequence within the large intracellular loop region, to gephyrin. The latter is a cytoskeletal attachment protein that binds to a number of subsynaptic proteins involved in cytoskeletal structure and thus clusters and anchors hetero-oligomeric receptors to the synapse (see Moss and Smart, 2001; Kirsch, 2006; Kneussel and Loebrich, 2007). G-protein βγ subunits enhance the open state probability of native and recombinant glycine receptors by association with domains within the large intracellular loop (Yevenes *et al*., 2003, 2006). Intracellular Ca^{2+} appears to increase native and recombinant glycine receptor affinity, prolonging channel open events, by a mechanism that does not involve phosphorylation (Fucile *et al*., 2000).

Nomenclature	α1	α2	α3
Ensembl ID	ENSG00000145888	ENSG00000101958	ENSG00000145451
Selective agonists (potency order)	Glycine > β-alanine > taurine	Glycine > β-alanine > taurine	Glycine > β-alanine > taurine
Selective antagonists and modulators with subunit selectivity	Strychnine, PMBA, picrotoxin (+β weakens block), picrotoxinin (IC_{50} = 5.1 μM + β = 27 μM), picrotin (IC_{50} = 5.2 μM + β = 27 μM), ginkgolide B (IC_{50} = 0.6–8.0 μM + β = 0.18–2.5 μM), bilobalide (IC_{50} = 20 μM + β = 204 μM), pregnenolone sulphate (K_i = 1.9 μM; + β = 2.7 μM), tropisetron (K_i = 84 μM; + β = 44 μM), colchicine (IC_{50} = 324 μM)	Strychnine, PMBA, picrotoxin (+β weakens block), picrotoxinin (IC_{50} = 0.41 μM), picrotin (IC_{50} = 13.1 μM), ginkgolide B (IC_{50} = 3.7–11.4 μM + β = 0.14–0.8 μM), bilobalide (IC_{50} = 8 μM + β = 50 μM), pregnenolone sulphate (K_i = 5.5 μM; + β = 10.1 μM), tropisetron (K_i = 13 μM; + β = 5.4 μM), colchicine (IC_{50} = 64 μM), DCKA (IC_{50} = 188 μM)	Strychnine, picrotoxin (+β weakens block), picrotoxinin (IC_{50} = 0.43 μM + β = 8.9 μM), picrotin (IC_{50} = 6.0 μM + β = 24 μM),ginkgolide B (IC_{50} = 1.8 μM + β = 0.55 μM), αEMBTL (+β converts block to potentiation)
Selective potentiators	αEMBTL		(αEMBTL *reduces* α3-mediated responses)
Endogenous potentiators (EC_{50})	Zn^{2+} (37 nM) (not affected by β)	Zn^{2+} (540 nM) (not affected by β)	
Endogenous inhibitors (IC_{50})	Zn^{2+} (15 μM; + β = 13 μM), Cu^{2+} (4 μM), H^+	Zn^{2+} (360 μM; + β = 180 μM)	Zn^{2+} (150 μM)
Channel blockers (IC_{50})	cyanotriphenylborate (1.3 μM + β = 2.8 μM)	cyanotriphenylborate (≫ 20 μM; + β = 7.5 μM)	
Probes	[^{3}H]strychnine	[^{3}H]strychnine	[^{3}H]strychnine
Functional characteristics	γ = 86 pS (main state) (+β = 44 pS)	γ = 111 pS (main state) (+β = 54 pS)	γ = 105 pS (main state) (+β = 48)

Data in the table refer to homo-oligomeric assemblies of the α-subunit, significant changes introduced by co-expression of the β1 subunit are indicated in parenthesis. Not all glycine receptor ligands are listed within the table, but those that may be useful in distinguishing between glycine receptor isoforms are indicated. Pregnenolone sulphate, tropisetron and colchicine, for example, although not selective antagonists of glycine receptors, are included for this purpose. Strychnine is a potent and selective competitive glycine receptor antagonist with affinities in the range 5–15 nM. RU5135 demonstrates comparable potency, but additionally blocks $GABA_A$ receptors. There are conflicting reports concerning the ability of cannabinoids to inhibit (Lozovaya *et al*., 2005), or potentiate (Hejazi *et al*., 2006), glycine receptor function. Several analogues of muscimol and piperidine act as agonists and antagonists of both glycine and $GABA_A$ receptors. Picrotoxin acts as an allosteric inhibitor that appears to bind within the pore, and shows strong selectivity towards homomeric receptors. While its components, picrotoxinin and picrotin, have equal potencies at α1 receptors, their potencies at α2 and α3 receptors differ and allow a distinction between such homo-oligomeric assemblies (Yang *et al*., 2007). In addition to the compounds listed in the table, numerous agents act as allosteric regulators of glycine receptors (comprehensively reviewed by Laube *et al*., 2002, Lynch, 2004 and Webb and Lynch, 2007). Zn^{2+} acts through distinct binding sites of high- and low-affinity to allosterically enhance channel function at low (<10 μM) concentrations and inhibits responses at higher concentrations in a subunit selective manner (Miller *et al*., 2005). The effect of Zn^{2+} is somewhat mimicked by Ni^{2+}. Endogenous Zn^{2+} is essential for normal glycinergic neurotransmission mediated by α1 subunit-containing receptors (Hirzel *et al*., 2006). Elevation of intracellular Ca^{2+} produces fast potentiation of glycine receptor-mediated responses. Dideoxyforskolin (4 μM) and tamoxifen (0.2–5 μM) both potentiate responses to low glycine concentrations (15 μM), but act as inhibitors at higher glycine concentrations (100 μM). Additional modulatory agents that enhance glycine receptor function include inhalational, and several intravenous general anaesthetics (e.g. minaxolone, propofol and pentobarbitone) and certain neurosteroids. Ethanol and higher order *n*-alcohols also act allosterically to enhance glycine receptor function. Solvents inhaled as drugs of abuse (e.g. toluene, 1-1-1-trichloroethane) may act at sites that overlap with those recognising alcohols and volatile anaesthetics to produce potentiation of glycine receptor function. The function of glycine receptors formed as homomeric complexes of α1 or α2 subunits, or hetero-oligomers of α1/β or α2/β subunits, is differentially affected by the 5-HT_3 receptor antagonist tropisetron (ICS 205–930)

which may evoke potentiation (which may occur within the femtomolar range at the homomeric glycine α1 receptor), or inhibition, depending upon the subunit composition of the receptor and the concentrations of the modulator and glycine employed. Additional tropienes, including atropine, modulate glycine receptor activity.

Abbreviations: αEMBTL, α-ethyl, α-methyl-γ-thiobutyrolactone; **DCKA**, dichlorokynurenic acid; **PMBA**, 3-[2′-phosphonomethyl[1,1′-biphenyl]-3-yl]alanine; **RU5135**, 3α-hydroxy-16-imino-5β-17-azaandrostan-11-one

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P2X

Overview: P2X receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on P2X Receptors, Khakh *et al*., 2001) are putative trimeric (Jiang *et al*., 2003; Nicke *et al*., 1998) transmitter-gated channels, gating primarily Na^+, K^+ and Ca^{2+}, exceptionally $Cl^-$with two putative TM domains per subunit, where the endogenous ligand is ATP. The relationship of many of the cloned receptors to endogenously expressed receptors is not yet established. The Nomenclature Subcommittee has recommended that for P2X receptors, structural criteria should be the initial criteria for nomenclature where possible. Functional P2X receptors exist as polymeric transmitter-gated channels; the native receptors may occur as either homopolymers (e.g. $P2X_1$ in smooth muscle) or heteropolymers (e.g. $P2X_2$:$P2X_3$ in the nodose ganglion). $P2X_7$ receptors have been shown to form functional homopolymers which, in turn, activate pores permeable to low molecular weight solutes (Donnelly-Roberts *et al*., 2004).

Nomenclature	$P2X_1$	$P2X_2$	$P2X_3$	$P2X_4$
Ensembl ID	ENSG00000108405	ENSG00000177026	ENSG00000109991	ENSG00000135124
Selective agonists	L-βγ-meATP, αβ-meATP	—	αβ-meATP	—
Selective antagonists	TNP-ATP (pIC_{50} 8.9, Virginio *et al*., 1998), Ip_5I (pIC_{50} 8.5), NF023 (pIC_{50} 6.7); NF449 (pIC_{50} 6.3, Kassack *et al*., 2004)	—	TNP-ATP (pIC_{50} 8.9, Virginio *et al*., 1998), A317491 (7.5, Jarvis *et al*., 2002), RO3 (pIC_{50} 7.5, Ford *et al*., 2006)	—

A317491 and RO3 also block the $P2X_2$:$P2X_3$ heteromultimer (Ford *et al*., 2006; Jarvis *et al*., 2002).

Nomenclature	$P2X_5$	$P2X_6$	$P2X_7$
Other names	—	—	P_{2Z}
Ensembl ID	ENSG00000083454	ENSG00000099957	ENSG00000089041
Selective antagonists	—	—	Brilliant Blue G (pIC_{50} 8.0, Jiang *et al*., 2000), decavanadate (pA_2 7.4, Michel *et al*., 2006a), KN62 (Gargett and Whiley, 1997), A438079 (pIC_{50} 6.9, Donnelly-Roberts and Jarvis, 2007)

Agonists listed show selectivity within recombinant P2X receptors of *ca*. one order of magnitude. Several P2X receptors (particularly $P2X_1$ and $P2X_3$) may be inhibited by desensitisation using stable agonists (e.g. αβ-meATP); suramin and PPADS are non-selective antagonists at r & $hP2X_{1-3,5}$ and $hP2X_4$, but not $rP2X_{4,6,7}$ (Buell *et al*., 1996), and can also inhibit ATPase activity (Crack *et al*., 1994). Ip_5I is inactive at $rP2X_2$, an antagonist at $rP2X_3$ (pIC_{50} 5.6) and enhances agonist responses at $rP2X_4$ (King *et al*., 1999). Antagonist potency of NF023 at recombinant $P2X_2$, $P2X_3$ and $P2X_5$ is two orders of magnitude lower than that at $P2X_1$ receptors (Soto *et al*., 1999). The $P2X_7$ receptor may be inhibited in a non-competitive manner by the protein kinase inhibitors KN-62 and chelerythrine (Shemon *et al*., 2004), while the p38 MAP kinase inhibitor SB202190 shows a species-dependent non-competitive action (Donnelly-Roberts *et al*., 2004; Michel *et al*., 2006b). The pH-sensitive dye used in culture media, phenol red, is also reported to inhibit $P2X_1$ and $P2X_3$ containing channels (King *et al*., 2005). Some recombinant P2X receptors expressed to high density bind [^{35}S]-ATPγS and [^{3}H]-αβ-meATP, although the latter can also bind to 5′-nucleotidase (Michel *et al*., 1995).

Abbreviations: A317491, 5-({[3-phenoxybenzyl][(1*S*)-1,2,3,4-tetrahydro-1-naphthalenyl]amino}carbonyl)-1,2,4-benzenetricarboxylic acid; **A438079**, 3-(5-(2,3-dichlorophenyl)-1*H*-tetrazol-1-yl) methyl pyridine; **ATPγS**, adenosine 5′-(3-thio)triphosphate; **Ip_5I**, diinosine-5′,5′′-pentaphosphate; ***αβ*-meATP**, αβ-methylene-adenosine 5′-triphosphate; **βγ-meATP**, βγ-methylene-adenosine 5′-triphosphate; **KN62**, 1-(*N*,*O*-*bis*[5-isoquinolinesulphonyl]-*N*-methyl-L-tyrosyl)-4-phenylpiperazine; **NF023**, 8,8′-(carbonyl*bis*[imino-3,1-phenylene carbonylimino])bis-1,3,5-naphthalenetrisulfonic acid; **NF449**, 4,4′,4′′,4′′′-(carbonylbis[imino-5,1,3-benzenetriyl-bis{carbonylimino}])tetrakisbenzene-1,3-disulfonic acid octasodium salt; **PPADS**, pyridoxalphosphate-6-azophenyl-2′,4′-disulphonate; **RO3**, 5-(methyl[2-methylethyl-4,5-dimethoxyphenyl]-2,4pyridinediamine; **SB202190**, 4-[4-(4-fluorophenyl)-5-pyridin-4-yl-1*H*-imidazol-2-yl]phenol; **TNP-ATP**, 2′,3′-*O*-(2,4,6-trinitrophenyl)-ATP

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ZAC (Zinc-activated)

Overview: The zinc-activated channel (ZAC, provisional nomenclature and alternatively termed L2) is a recently identified member of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT_3, $GABA_A$ and strychnine-sensitive glycine receptors (Davies *et al*., 2003; Houtani *et al*., 2005). The channel is likely to exist as a homopentamer of 4TM subunits that form an intrinsic cation selective channel displaying constitutive activity that can be blocked by (+)-tubocurarine (Davies *et al*., 2003). ZAC is present in the human, chimpanzee, dog, cow and opossum genomes, but is functionally absent from mouse or rat genomes (Davies *et al*., 2003; Houtani *et al*., 2005).

Nomenclature	ZAC
Ensembl ID	ENSG00000186919
Selective agonists (pEC_{50})	Zn^{2+} (3.3)
Selective antagonists (pIC_{50})	(+)-Tubocurarine (5.2)
Functional characteristics	Outwardly rectifying current (both constitutive and evoked by Zn^{2+})

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