Acetylcholine (nicotinic)

Overview: Nicotinic acetylcholine receptors are members of the Cys-loop family of transmitter-gated ion channels that includes the $GABA_A$, strychnine-sensitive glycine and $5\text{-}HT_3$ receptors. All nicotinic receptors are formed as pentamers of subunits. Genes (ENSF00000000049) encoding a total of 17 subunits (α1–10, β1–4, δ, ε and γ) have been identified. All subunits are of mammalian origin with the exception of α8 (avian). Each subunit possesses four 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 loops 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, has revealed the binding site in detail (reviewed by Karlin, 2002, Smit *et al*., 2003, Sine & Engel, 2006). 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). 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 coexpressed with at least two other subunits. The α6 subunit can form a functional receptor when coexpressed 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, and 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, coassembly 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
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	$[^3H]/[^{125}I]$-α-bungarotoxin	$[^3H]/[^{125}I]$-epibatidine (hα2β4, 42 pM; rα2β2, 10 pM; rα2β4, 87 pM), $[^3H]$-cytisine	$[^3H]/[^{125}I]$-epibatidine (hα3β2, 7 pM; hα3β4, 230 pM; rα3β2, 14 pM, rα3β4, 300 pM), $[^3H]$-cytisine
Functional characteristics	$\alpha(1)_2\beta\gamma\delta$: P_{Ca}/P_{Na} = 0.16–0.2, P_f = 2.1%; $\alpha(1)_2\beta\varepsilon\delta$: P_{Ca}/P_{Na} = 0.65–1.38, P_f = 4.1–4.2%	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 (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†	$(\alpha7)_5$: 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)	$(\alpha7)_5$: α-bungarotoxin, methyllycaconitine, α-conotoxin ImI
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	$(\alpha7)_5$: Bgt > MLA > (+)-Tc† > atr > DHβE
Channel blockers	—	Mecamylamine, hexamethonium	—
Probes	$[^3H]/[^{125}I]$-epibatidine (hα4β2, 10–33 pM; hα4β4, 187 pM; rα4β2, 30 pM, rα4β4, 85 pM), $[^3H]$-cytisine, $[^3H]$-nicotine	$[^3H]$-epibatidine (native chick cα6β4*, 35 pM)	$[^3H]/[^{125}I]$-α-bungarotoxin ($(h\alpha7)_5$, 700–800 pM), $[^3H]$-methyllycaconitine (native rα7*, 1.9 nM)
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%

PSAB-OFB also activates $5\text{-}HT_3$ receptors

Nomenclature	**α8* (avian)**	**α9***	**α10***
Previous names	Neuronal, α-bungarotoxin-sensitive	—	—
Potency order of commonly used agonists	$(\alpha 8)_5$: cyt ~ nic ⩾ ACh > DMPP	$(\alpha 9)_5$: cho > ACh > sub > car	ACh
Selective antagonists	—	$(\alpha 9)_5$: α-bungarotoxin, strychnine, nicotine, muscarine	α10α9: α-bungarotoxin, strychnine, nicotine, muscarine
Commonly used antagonists	$(\alpha 8)_5$: Bgt > atr ⩾ (+)-Tc ⩾ str	$(\alpha 9)_5$: 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	[^{3}H]/[^{125}I]-α-bungarotoxin	[^{3}H]/[^{125}I]-α-bungarotoxin	—
Functional characteristics	—	α9: $P_{Ca}/P_{Na} = 9$; α9α10: $P_{Ca}/P_{Na} = 9$	—

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/noncompetitive 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: **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**, cytosine; **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**, (E)-*N*-methyl-4-(3-pyridinyl)-3-butene-1-amine; **TC-2559**, also known as (RJR-2403), (E)-*N*-methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine; **(+)-Tc**, (+)-tubocurarine

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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 (ENSF00000000053) have been reported in mammals (Barnard, 2000; Korpi *et al*., 2002). 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 (see Barnard, 2000). In addition, three ρ-subunits (ρ1–3) function as either homo- or hetero-oligomeric assemblies (Bormann & Feigenspan, 2000; 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 proposals (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 & Brünig, 2003). It is thought that the majority of GABA$_A$ receptors harbour a single type of α- and β-subunit variant. The $\alpha1\beta2\gamma2$ hetero-oligomer constitutes the largest population of GABA$_A$ receptors in the CNS, followed by the $\alpha2\beta3\gamma2$ and $\alpha3\beta3\gamma2$ 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 nondesensitising tonic current that is important for neuronal excitability in response to ambient concentrations of GABA (see Mody & Pearce, 2004; Semyanov *et al*., 2004; Farrant & Nusser, 2005). 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. 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) and Johnston (2005). 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). The proposed scheme utilises 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, 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
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 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), α5IA (α5 selective *versus* α1, α2 and α3 subunit-containing receptors *via* greater inverse agonist efficacy, RY024 (α5 selective *via* high affinity)
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 subunit, 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
BDZ 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 low affinity for α4- or α6-subunits), [^{18}F]-fluoroethylflumazenil
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 is a partial agonist at receptors with the subunit composition $\alpha4\beta3\gamma2$, but elicits currents in excess of those evoked by GABA at the $\alpha4\beta3\delta$ receptor where GABA itself is a low efficacy agonist (Brown *et al*., 2002; Bianchi & MacDonald, 2003). Recent data suggest that the presence of the γ subunit within the heterotromeric complex reduces the efficacy and potency of agonists (Stórustovu & 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 & Lambert 2005). 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 pictrotoxinin 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 nonanaesthetic compounds have been identified (see Belelli *et al*., 1999; Krazowski *et al*., 2000; Thompson & Wafford, 2001; Hemmings *et al*., 2005). 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 $\beta2/\beta3$- 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 coassembled with $\beta2/\beta3$-, but not β1-subunit (see Korpi *et al*., 2002); La^{3+} (potentiates responses mediated by $\alpha1\beta3\gamma2$L receptors, weakly inhibits $\alpha6\beta3\gamma2$L receptors, and strongly blocks $\alpha6\beta3\delta$ and $\alpha4\beta3\delta$ receptors (Saxena *et al*., 1997; Brown *et al*., 2002)); ethanol (selectively potentiates responses mediated by $\alpha4\beta3\delta$ and $\alpha6\beta3\delta$ receptors *versus* receptors in which β2 replaces β3, or γ replaces δ (Wallner *et al*., 2003, but see also Borghese *et al*., 2006)). 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 & 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-triazol[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-4*H*-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-4*H*-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; **THIP**, also known as gaboxadol; **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-ylmethoxy)-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 (TM1, TM3 and TM4), a channel lining re-entrant 'p-loop' (MD2) located between TM1 and TM3 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), Yamakura & Shimoji (1999), Jane *et al.* (2000), Huettner (2003) and Cull-Candy & Leszkiewicz (2004). 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 receptors has been addressed by NC-IUPHAR (Lodge & Dingledine, 2000). The proposed scheme, which recommends a revised nomenclature for ionotropic glutamate receptor subunits, is adopted here. Commonly used alternative appellations are indicated in parenthesis.

NMDA receptors: NMDA receptors assemble as heteromers that may be drawn from GLU_{N1} (NMDA-R1, NR1, GluRζ1), GLU_{N2A} (NMDA-R2A, NR2A, GluRε1), GLU_{N2B} (NMDA-R2B, NR2B, GluRε2), GLU_{N2C} (NMDA-R2C, NR2C, GluRε3), GLU_{N2D} (NMDA-R2D, NR2D, GluRε4), GLU_{N3A} (NMDA-R3A) and GLU_{N3B} (NMDA-R3B) subunits. Alternative splicing can generate eight isoforms of GLU_{N1} with differing pharmacological properties. Various splice variants of $GLU_{N2B,2C,2D}$ and GLU_{N3A} have also been reported. Activation of NMDA receptors requires the binding of two agonists, glutamate to the S1 and S2 regions of the GLU_{N2} subunit and glycine to S1 and S2 regions of the GLU_{N1} subunit (Erreger *et al.*, 2004; Chen & Wyllie, 2006). The minimal requirement for efficient functional expressional of NMDA receptors *in vitro* is a di-heteromeric assembly of GLU_{N1} and at least one GLU_{N2} subunit variant, as a dimer of heterodimers arrangement (Furukawa *et al.*, 2005; Mayer, 2006). However, more complex tri-heteromeric assemblies, incorporating multiple subtypes of GLU_{N2} subunit, or GLU_{N3} 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 ($GLU_{N2A} = GLU_{N2B} > GLU_{N2C} = GLU_{N2D}$), PPDA ($GLU_{N2C} = GLU_{N2D} > GLU_{N2B} = GLU_{N2A}$, Feng *et al.*, 2004), NVP-AAM077 ($GLU_{N2A} > GLU_{N2C} > GLU_{N2D} > GLU_{N2B}$, Auberson *et al.*, 2002; Feng *et al.*, 2004; but see Frizelle *et al.*, 2006), conantokin-G ($GLU_{N2B} > GLU_{N2D} = GLU_{N2C} = GLU_{N2A}$)
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, ketamine, phencyclidine, memantine, amantidine
Probes	
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 & Shimoji, 1999; Cull-Candy & 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 sulfate potentiates di-heteromeric assemblies of GLU_{N1}/GLU_{N2A} and GLU_{N1}/GLU_{N2B} subunits, but inhibits receptors assembled as GLU_{N1}/GLU_{N2C}, or GLU_{N1}/GLU_{N2D}, heteromers (Malayev *et al.*, 2002). Tonic proton blockade of NMDA receptor function is alleviated by polyamines and the inclusion of exon 5 within GLU_{N1} 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 GLU_{N1} and GLU_{N2C} subunits are unusually insensitive to proton blockade. Ifenprodil, its analogue CP101606, haloperidol, felbamate and Ro84304 discriminate between recombinant NMDA receptors assembled from GLU_{N1} and either GLU_{N2A}, or GLU_{N2B}, subunits by acting as selective, non-competitive, antagonists of hetero-oligomers incorporating GLU_{N2B}. LY233536 is a competitive antagonist that also displays selectivity for GLU_{N2B} over GLU_{N2A} subunit-containing receptors. Similarly, CGP61594 is a photoaffinity label that interacts selectively with receptors incorporating GLU_{N2B} *versus* GLU_{N2A}, GLU_{N2D} and, to a lesser extent, GLU_{N2C} subunits. Conversely, the voltage-independent component of NMDA receptor inhibition by Zn^{2+} is most pronounced for receptors that contain the GLU_{N2A} *versus* GLU_{N2B} subunit. In addition to influencing the pharmacological profile of the NMDA receptor, the identity of the GLU_{N2} subunit co-assembled with GLU_{N1} is an important determinant of biophysical properties that include sensitivity to block by Mg^{2+}, single-channel conductance and channel deactivation time (Cull-Candy & Leszkiewicz, 2004). Incorporation of the GLU_{N3A} subunit into tri-heteromers containing GLU_{N1} and GLU_{N2} 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 GLU_{N3B} in tri-heteromers. The expression of GLU_{N3A}, or GLU_{N3B}, with GLU_{N1} alone is reported to form 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).

AMPA and Kainate receptors: AMPA receptors assemble as homomers, or heteromers, that may be drawn from GLU_{A1} (GluR1, GluRA, GluR-A, GluR-K1), GLU_{A2} (GluR2, GluRB, GluR-B, GluR-K2), GLU_{A3} (GluR3, GluRC, GluR-C, GluR-K3), or GLU_{A4} (GluR4, GluRD, GluR-D) subunits. Homotetramers formed from GLU_{A2} subunits express relatively poorly due to their retention within the endoplasmic reticulum (see Bredt & Nicoll, 2003). Functional kainate receptors can be expressed as homomers of GLU_{K5} (GluR5, GluR-5, EAA3), GLU_{K6} (GluR6, GluR-6, EAA4), or GLU_{K7} (GluR7, GluR-7, EAA5) subunits. GLU_{K5-7} subunits are also capable of assembling into heterotetramers (see Lerma, 2003). Two additional kainate receptor subunits, GLU_{K1} (KA1, KA-1, EAA1) and GLU_{K2} (KA2, KA-2, EAA2), when expressed individually, form high affinity binding sites for kainate, but lack function (see Huettner, 2003). GLU_{K1} and GLU_{K2} can form heteromers when co-expressed with GLU_{K5-7} subunits (Lerma, 2003). RNA encoding the GLU_{A2} 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 GLU_{A2} 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 GLU_{A2} (Seeburg & Hartner, 2003). GLU_{K5} and GLU_{K6}, but not other kainate receptor subunits, are similarly edited and broadly similar functional characteristics apply to kainate receptors lacking either an RNA edited GLU_{K5}, or GLU_{K6}, 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) GLU_{A1-4} 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 GLU_{K5-7} 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, (*S*)-5-iodowillardiine, (2*S*,4*R*)-4-methyl glutamate (SYM2081), LY339434, domoic acid (except homomeric GLU_{K7}), kainite
Selective antagonists	NBQX, ATPO, LY293558, GYKI53655/LY300168 (active isomer GYKI53784/LY303070) (non-competitive)	UBP296 (More *et al*., 2004), LY294486, LY382884, NS3763 (non-competitive, Christensen *et al*., 2004)
Channel blockers	Intracellular polyamines, extracellular argiotoxin, extracellular Joro toxin, (all subtype selective)	Intracellular polyamines (subtype selective)
Probes	[^{3}H]-AMPA, [^{3}H]-CNQX	[^{3}H]-Kainate, [^{3}H]-(2*S*,4*R*)-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: pyrroliddones (piracetam, aniracetam); benzothiazides (cyclothiazide); benzylpiperidines (CX-516 (BDP-12), CX-546) and biarylpropylsulfonamides (LY392098, LY404187 and LY503430) (O'Neill *et al*., 2004). Activation of kainate receptors by AMPA shows subunit dependency (e.g. heteromers containing GLU_{K6} and GLU_{K2} subunits are sensitive; homomers assembled from the GLU_{K6} subunit, or GLU_{K7} subunit, are insensitive). Quinoxalinediones such as CNQX and NBQX show limited selectivity between AMPA and kainate receptors. LY293558 also has kainate (GLU_{K5}) receptor activity. ATPO is a potent competitive antagonist of AMPA receptors, has a weaker antagonist action at kainate receptors comprising GLU_{K5} subunits, but is devoid of activity at kainate receptors formed from GLU_{K6} or GLU_{K6}/GLU_{K2} subunits. The pharmacological activity of ATPO resides with the (*S*)-enantiomer. ATPA, UBP296, LY294486, LY339434, LY382884 and (*S*)-5-iodowillardiine interact selectively with kainate receptors containing a GLU_{K5} subunit. (2*S*,4*R*)-4-methyl glutamate (SYM2081) is equipotent in activating (and desensitizing) GLU_{K5} and GLU_{K6} 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-methyl glutamate and LY339434 have agonist activity at NMDA receptors. (2*S*,4*R*)-4-methyl glutamate is also an inhibitor of the glutamate transporters EAAT1 and EAAT2.

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*,4α*R*,6*R*,8α*R*-6-[2-(1(2)*H*-tetrazol-5yl)ethyl]-decahydroisoquinoline-3-carboxylate; **LY294486**, (3*SR*,4α*RS*,6*SR*,8*RS*)-6-([{(1*H*-tetrazol-5yl)methyl}oxy]methyl)-1,2,3,4α,5,6,7,8,8α-decahydroisoquinolone-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-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; **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; **PEAQX**, 5-phosphonomethyl-1,4-dihydroquinoxaline-2,3-dione, also known as NVP-AAM077; **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; **UBP296**, (*RS*)-3-2-carboxybenzyl)willardiine

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Glycine receptors

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 $5\text{-}HT_3$ receptors. Structurally and functionally, the glycine receptor is most closely related to the $GABA_A$ receptor. The receptor is expressed either as a homopentamer of α subunits, or a complex now thought to harbour 2α and 3β subunits (Grudzinska *et al*., 2005; Betz & 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) 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) and α3 (α3S and α3L) subunits and by RNA editing of the α3 subunit (Meier *et al*., 2005). 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. It also anchors the receptor, *via* an amphipathic sequence within the intracellular loop region, to gephyrin, a cytoskeletal attachment protein, that binds to tubulin and thus clusters and anchors hetero-oligomeric receptors to the synapse (see Moss and Smart, 2001; Kirsch, 2006). G-protein βγ subunits enhance the open state probability of native and recombinant glycine receptors most probably *via* a direct association (Yevenes *et al*., 2003).

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), ginkgolide B (IC_{50} = 0.6 μM + β = 0.18 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), Zn^{2+} (IC_{50} = 15 μM)	Strychnine, PMBA, picrotoxin (+β weakens block), ginkgolide B (IC_{50} = 3.7 μM + β = 0.14 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), Zn^{2+} (IC_{50} = 360 μM)	Strychnine, picrotoxin (+β weakens block), ginkgolide B (IC_{50} = 1.8 μM + β = 0.55 μM), αEMBTL (+β converts block to potentiation), Zn^{2+} (IC_{50} = 150 μM)
Selective potentiators	αEMBTL, Zn^{2+} (EC_{50} = 37 nM)	Zn^{2+} (EC_{50} = 540 nM)	(αEMBTL *reduces* α3-mediated responses)
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 coexpression of the β1 subunit (ENSG00000109738) 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 of 5–15 nM. RU5135 demonstrates comparable potency, but additionally blocks $GABA_A$ receptors. Both the endocannabinoids, anandamide and 2-arachidonylglycerol, block neuronal glycine receptors at physiological concentrations (Lozavaya *et al*., 2005). Several analogues of muscimol and piperidine act as agonists and antagonists of both glycine and $GABA_A$ receptors. Picrotoxin acts as an allosteric inhibitor with strong selectivity towards homomeric receptors composed of α subunits and its components, picrotoxinin and picrotin, have similar inhibitory potencies (reviewed by Lynch, 2004). 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). 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+}. α1 subunit channel function is more sensitive (by ~15-fold) to potentiation by Zn^{2+} compared to α2, irrespective of the presence of the β subunit. 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 $5\text{-}HT_3$ receptor antagonist tropisetron (ICS 205–930), which may evoke potentiation 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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5-Hydroxytryptamine$_3$

Overview: The 5-HT$_3$ receptor (nomenclature as agreed by 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. Three 5-HT$_3$ receptor subunits (5-HT$_{3A}$, 5-HT$_{3B}$ and 5-HT$_{3C}$) have been cloned, but only 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. Putative *HTR3D* and *HTR3E* genes have also been described (Niesler *et al.*, 2003) but there is presently no evidence that they encode *bone fide* 5-HT$_3$ receptor subunits that are functional. The hetero-oligomeric receptor has recently 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, homo- and hetero-oligomeric 5-HT$_3$ receptors differ in their allosteric regulation by some general anaesthetic agents (Solt *et al.*, 2005). The diversity of 5-HT$_3$ receptors is increased by alternative splicing of the 5-HT$_{3A}$ subunit. Variants of the human 5-HT$_{3B}$ subunit that differ in the extracellular N-terminal domain have been postulated to exist in the intestine and brain due to alternative promoters within *HTR$_{3B}$* gene that initiate transcription at different start sites (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$_{50}$)	2-Methyl-5-HT (5.3–5.5), 3-chlorophenyl-biguanide (5.4–5.7)
Selective antagonists (pIC$_{50}$)	Granisetron (9.5), ondansetron (9.5), tropisetron (9.2)
Channel blockers	Diltiazem, TMB-8, picrotoxin [+5-HT$_{3B}$ potency reduced, Das & Dillon, 2003]
Probes	[^{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]; relative permeability to divalent cations reduced by coexpression 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 coexpression of the 5-HT$_{3B}$ subunit are indicated in parenthesis. Human (Belelli *et al.*, 1995; Miyaki *et al.*, 1995), rat (Isenberg *et al.*, 1993), mouse (Maricq *et al.*, 1991), guinea-pig (Lankiewicz *et al.*, 1998) and ferret (Mochizuki *et al.*, 2000) 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; Peters *et al.*, 1997 and Lovinger, 1999).

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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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, 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-$\beta\gamma$-meATP, $\alpha\beta$-meATP	—	$\alpha\beta$-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)	—

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)

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. $\alpha\beta$-meATP); suramin and PPADS are non-selective antagonists at $rP2X_{1-3,5}$ 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). Some recombinant P2X receptors expressed to high density bind [^{35}S]-ATPγS and [^{3}H]-$\alpha\beta$-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; **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; **KN-62**, 1-(*N,O*-bis[5-isoquinolinesulphonyl]-*N*-methyl-l-tyrosyl)-4-phenylpiperazine; **NF023**, 8,8′-(carbonylbis[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; **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 channel)

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 is 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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