TRANSMITTER-GATED CHANNELS

Acetylcholine (nicotinic)

Overview: Nicotinic acetylcholine receptors are members of the cys-loop superfamily 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. 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 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). 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*. α5 and β3 subunits lack function when expressed 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
Potency order of commonly used agonists	$(\alpha1)_2\beta1\varepsilon\delta$: 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-conotoxins GI and MI, pancuronium	—	α3β2: α-conotoxin MII (also blocks α6β2*) α3β4: α-conotoxin AuIB
Commonly used antagonists	$(\alpha1)_2\beta1\gamma\delta$ (embryonic): Bgt > pan > (+)-Tc (high-affinity α1/δ binding site, low-affinity α/γ site) $(\alpha1)_2\beta1\varepsilon\delta$ (adult): 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
Radioligands 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} ~ 0.3 $\alpha(1)_2\beta\varepsilon\delta$: P_{Ca}/P_{Na} ~ 0.9	α2β2: P_{Ca}/P_{Na} ~ 1.5	α3β2: P_{Ca}/P_{Na} ~ 1.5; α3β4: P_{Ca}/P_{Na} ~ 1.0, fractional calcium flux = 2.7%

Nomenclature	**α4***	**α6***	**α7***
Previous names	Neuronal, α-bungarotoxin-insensitive	—	Neuronal, α-bungarotoxin-sensitive
Selective agonists	α4β2: TC-2559 (Chen *et al*., 2003), RJR-2403 (Papke *et al*., 2000), ABT-594 (Donnelly-Roberts *et al*., 1998)	—	AR-R17779 (Mullen *et al*., 2000), choline, PASB-OFP (Broad *et al*., 2002)
Potency order of commonly used agonists	α4β2: epi > ana-a > nic = cyt† > DMPP > ACh 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 (Dowell *et al*., 2003) α6β2*: 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	—
Radioligands K_d	[^{3}H]/[^{125}I]-epibatidine (hα4β2, 10–33 pM; hα4β4, 187 pM; rα4β2, 30 pM; rα4β4, 85 pM), 5-iodo-A-85380 (hα4* 12 pM), [^{3}H]-cytisine, [^{3}H]-nicotine	[^{3}H]-epibatidine (native chick cα6β4*, 35 pM)	[^{3}H]/[^{125}I]-αbungarotoxin, ($(h\alpha7)_5$ 700–800 pM) [^{3}H]-methyllycaconitine, (native rα7*, 1.9 nM)
Functional characteristics	α4β2: P_{Ca}/P_{Na} ~ 1.5, fractional calcium flux = 2.6% α4β4: fractional calcium flux = 1.5%	—	P_{Ca}/P_{Na} ~ 6–20, fractional calcium flux = 11.4%

Nomenclature	**α8* (avian)**	**α9***	**α10***
Previous names	Neuronal, α-bungarotoxin-sensitive	—	—
Selective agonists	—	—	—
Potency order of commonly used agonists	$(\alpha8)_5$: cyt ~ nic ⩾ ACh > DMPP	$(\alpha9)_5$: cho > ACh > sub > car	ACh
Selective antagonists	—	$(\alpha9)_5$: α-bungarotoxin, strychnine, nicotine, muscarine	α10α9: α-bungarotoxin, strychnine, nicotine, muscarine
Commonly used antagonists	$(\alpha8)_5$: Bgt > atr ⩾ (+)-Tc ⩾ str	$(\alpha9)_5$: Bgt > MLA > str ~ tropisetron > (+)-TC > bic ⩾ atr ~ epi > mec > DHβE > cyt > nic > mus	α10α9: Bgt > tropisetron = str > (+)-Tc > bic = atr > nic > mus
Channel blockers	—	—	—
Radioligands K_d	$[^3H]/[^{125}I]$-α-bungarotoxin	$[^3H]/[^{125}I]$-α-bungarotoxin	—
Functional characteristics	—	$P_{Ca}/P_{Na} \sim 80$	—

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**, 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**, hexamethenium; **mec**, mecamylamine; **MLA**, methyllycaconitine; **mus**, muscarine; **nic**, nicotine; **OH-GTS-21**, 3-(4-hydroxy, 2-methoxy)benzylidine anabaseine; **pan**, pancuronium; **PSAB-OFP**, (*R*)-(−)-5′phenylspiro[1-azabicyclo[2.2.2] octane-3,2'-(3'H)furo[2,3-b]pyridine; **RJR-2403**, (*E*)-*N*-methyl-4-(3-pyridinyl)-3-butene-1-amine; **str**, strychnine; **sub**, suberyldicholine; **sux**, succinylcholine; **(+)-Tc**, (+)-tubocurarine; **TC-2559**, (*E*)-*N*-methyl-4-[3-(5-ethoxypyridin)yl]-3-buten-1-amine **5-iodo-A-85380**, 5-iodo-3-(2(*S*)-azetidinylmethoxy)pyridine

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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 family ID ENSF00000000053) have been reported in mammals (Barnard, 2000; Korpi *et al*., 2002). The π subunit is restricted to reproductive tissue. Alternatively spliced versions of α6- (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). 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. The α- and β-subunits contribute to the GABA-binding site and both the α- and γ-subunits are required for the benzodiazepine (BDZ) site. The particular α and γ subunit isoforms exhibit marked effects on recognition and/or efficacy at the BDZ site. Thus, receptors incorporating either α4 or α6 subunits are not recognized by 'classical' benzodiazepines, such as flunitrazepam. It is beyond the scope of this supplement to discuss the pharmacology of individual receptor isoforms in detail; such information can be gleaned from the reviews by Barnard *et al*. (1998), Frolund *et al*. (2002), Korpi *et al*. (2002) and Krogsgaard-Larsen *et al*. (2002). 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 utilizes subunit structure and receptor function as the basis for classification. In view of the fact that a benzodiazepine (BDZ)-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 'BDZ site of the $GABA_A$ receptor' is adopted as one of the two alternatives proposed by NC-IUPHAR.

Nomenclature	**$GABA_A$**
Ensembl 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 (BDZ site)	Diazepam (not α4- or α6-subunits), flunitrazepam (not α4- or α6-subunits), zolpidem and zaleplon (α1 subunit selective *via* high affinity), L838417 (α2, α3 and α5 subunit selective *via* partial agonist activity),
Selective antagonists (BDZ site)	Flumazenil (low affinity for α4- or α6-subunits), L838417 (α1 subunit selective *via* antagonist activity) ZK93426
Inverse agonists (BDZ site)	DMCM, Ro194603, L655708 (α5 selective *via* high affinity), RY024 (α5 selective *via* high affinity)
Endogenous allosteric modulators	5α-pregnan-3α-ol-20-one (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
Radioligands	
GABA site	[^{3}H]-muscimol, [^{3}H]-gabazine (SR95531)
BDZ site	[^{3}H]-Flunitrazepam (not α4- or α6-subunits), [^{3}H]-zolpidem (α1 subunit selective), [^{3}H]-L655708 (α5 selective), [^{3}H]-Ro154513 [selectively labels α4 and α6 subunit-containing receptors in the presence of a saturating concentration of a non-radioactive 'classical' benzodiazepine (e.g. diazepam)], [^{3}H]-CGS8216
Anion channel	[^{35}S]-TBPS

The potency and efficacy of many GABA agonists vary between $GABA_A$ 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 $\alpha4\beta3\gamma2$, 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). 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 Lambert *et al*., 2003). 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).

In addition to the agents listed in the table, modulators of $GABA_A$ receptor activity that exhibit subunit-dependent activity include: loreclezole, etomidate, tracazolate and mefenamic acid (positive allosteric modulators with selectivity for $\beta2/\beta3$ over $\beta1$ subunit-containing receptors, see Korpi *et al*. (2002); tracazolate (intrinsic efficacy, that is, potentiation, or inhibition, is dependent upon the identity of the γ1–3, delta, or epsilon subunit co-assembled with α1 and $\beta1$ 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 $\beta2/\beta3$, but not $\beta1$, 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 $\alpha6\beta3\delta$ receptors (Saxena *et al*., 1997)). 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. $\alpha4\beta3\delta$) may be a consequence of the unusually low efficacy of GABA at this receptor isoform (Bianchi *et al*., 2003).

A bicuculline- and baclofen-insensitive site has been located in cerebellum using *cis*-4-aminocrotonic acid. A subpopulation of retinal GABA receptors (activated by *trans*-4-aminocrotonic acid) assembled from ρ subunits is similarly bicuculline-insensitive and gates Cl^- channels that are insensitive to barbiturates and benzodiazepines and selectively blocked by TPMPA. Isoguvacine, THIP and piperidine-4-sulphonic acid do not activate $GABA_A$ receptors assembled from ρ subunits. Receptors formed from ρ subunits have often been found to be insensitive to neuroactive steroids (see Bormann, 2000), but relatively high concentrations of such compounds can modulate the activity of the $\rho1$ subunit in a stereoselective manner, 5α-pregnanes potentiating, and 5β-pregnanes inhibiting, responses elicited by low concentrations of GABA. Although these receptors have sometimes been termed $GABA_C$ receptors (see Bormann, 2000; Zhang, 2001), they may represent a subpopulation of $GABA_A$ receptors, classed as the $GABA_{A0r}$ subtype, under NC-IUPHAR proposals (Barnard *et al*., 1998). This suggestion is strengthened by the observation that single amino-acid mutations can impart some features of $GABA_A$ receptor pharmacology upon the $GABA_{A0r}$ subtype (Belelli *et al*., 1999; Walters *et al*., 2000).

Abbreviations: **CGS8216**, 2-phenylpyrazolo[4,3-c]quinolin-3(5)-one; **DMCM**, methyl-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-2H-[1,2,4]triazol-3-ylmethoxy)-[1,2,4]triazolo[4,3-b]pyridazine; **Ro154513**, methyl-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; **SR95531**, 2-(3′-carboxy-2′-propyl)-3-amino-6-*p*-methoxyphenylpyridazinium bromide; **TBPS**, *tert*-butylbicyclophosphorothionate; **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 propionic 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 Madden, 2002). 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), Cull-Candy *et al*. (2001) and Huettner (2003). 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, GluRξ1), 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 (one nonfunctional) of GLU_{N1} with differing pharmacological properties. Various splice variants of $GLU_{N2B,2C,2D}$ and GLU_{N3A} have also been reported (see Cull-Candy *et al*., 2001). Activation of NMDA receptors requires the binding of two agonists, glutamate to the GLU_{N2} subunit and glycine to the GLU_{N1} subunit. The minimal requirement for efficient functional expressional of NMDA receptors *in vitro* is a diheteromeric assembly of GLU_{N1} and at least one GLU_{N2} subunit variant, most likely in a dimer of dimers arrangement (Madden, 2002). However, more complex triheteromeric 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 family ID	ENSF00000000436
Selective agonists (glutamate site)	Aspartate, NMDA, D,L(tetrazol-5-yl)glycine, homoquinolinic acid
Selective antagonists (glutamate site)	D-AP5, CGS19755, CGP37849, LY233053, D-CCPene (GLU_{N2A} = GLU_{N2B} > GLU_{N2C} = GLU_{N2D}), 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 (MK801), ketamine, phencyclidine, memantine, amantidine
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 & Shimoji, 1999; Cull-Candy *et al*., 2001). 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 diheteromeric 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 noncompetitive antagonist ifenprodil increases the fraction of receptors blocked by protons at ambient concentration. 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, noncompetitive, antagonists of heterooligomers 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 *et al*., 2001). Incorporation of the GLU_{N3A} subunit into triheteromers 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 triheteromers.

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 Heuttner, 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. 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 family ID	ENSF00000000118	ENSF00000000118
Selective agonists	AMPA, (S)-5-flurowillardiine	ATPA, LY339434, LY382884, (2S,4R)-4-methyl glutamate (SYM2081), domoic acid (except homomeric GLU_{K7}), kainate
Selective antagonists	NBQX, ATPO, LY293558, GYKI53655/LY300168 (active isomer GYKI 53784/LY303070) (noncompetitive)	LY294486
Channel blockers	Intracellular polyamines, extracellular argiotoxin, extracellular Joro toxin (all subtype selective)	Intracellular polyamines (subtype selective)
Radioligands	[^{3}H]-AMPA, [^{3}H]-CNQX	[^{3}H]-Kainate, [^{3}H-](2S,4R)-4-methyl glutamate]

All AMPA receptors are additionally activated by kainate (and domoate) with relatively low potency (EC_{50} 100 μM). 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, 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, LY294486, LY339434, LY382884 and (S)-5-iodowillardiine interact selectively with kainate receptors containing a GLU_{K5} subunit. (2S,4R)-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 (2S,4R)-4-methyl glutamate and LY339434 have agonist activity at NMDA receptors. (2S,4R)-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,** (1S,2S)-1-4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol; **CPP**, (±)-2-carboxypiperazine-4-yl)propyl-1-phosphonic acid; **D-AP5,** D(2)-2-amino-5-phosphonopentanoate; **D-CCPene**, 3-(2-carboxypiperazine-4-yl)-propenyl-1-phosphonic 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**, 3S,4αR,6R,8αR-6-[2-(1(2)H-tetrazol-5yl)ethyl]-decahydroisoquinoline-3-carboxylate; **LY294486**, (3SR,4αRS,6SR,8RS)-6-([{(1H-tetrazol-5yl)methyl}oxy]methyl)-1,2,3,4α,5,6,7,8,8α-decahydroisoquinolone-3-carboxylic acid; **LY339434**, (2S,4R,6*E*)-2-amino-4-carboxy-7-(2-naphthyl)hept-6-enoic acid; **LY382884**, (3S, 4aR, 6S, 8aR)-6-((4-carboxyphenyl)methyl-1,2,3,4,4a,5,6,7,8,8a-decahydro isoquinoline-3-carboxylic acid; **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; **Ro8-4304**, 4-3-[4-(4-fluro-phenyl-)3,6-dihydro-2*H*-pyridin-1-yl]-2-hydroxy-propoxy-benzamide

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Glycine

Overview: The inhibitory glycine receptor 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- (α subunit) or hetero- (3α:2β subunits) pentameric assembly containing an intrinsic Cl^- channel. Four differentially expressed isoforms of the α-subunit ($\alpha1-\alpha4$) and one variant of the β-subunit ($\beta1$) have been identified by genomic and cDNA cloning. Further diversity originates from alternative splicing of the $\alpha1$, $\alpha2$ and $\alpha3$ subunits. In addition, a rat specific $\alpha2$ subunit variant (termed $\alpha2$*) demonstrates greatly reduced affinity towards glycine and strychnine. Predominantly, the mature form of the receptor contains $\alpha1$ (or $\alpha3$) and β subunits, while the immature form is mostly composed of only $\alpha2$ subunits. RNA transcripts encoding the $\alpha4$ subunit have not been detected in adult humans. The $\alpha4$ 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 Kneussel & Betz, 2000; Moss & Smart, 2001). There is no NC-IUPHAR recommendation for the classification of glycine receptors. The provisional nomenclature adopted here classifies glycine receptor isoforms according to their α-subunit.

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), 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), 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), αEMBTL (+β converts block to potentiation)
Selective potentiators	αEMBTL		(αEMBTL *reduces* α3-mediated responses)
Channel blockers (IC_{50})	Cyanotriphenylborate (1.3 μM + β = 2.8 μM), BN52021 (270 nM)	Cyanotriphenylborate (> > 20 μM; +β = 7.5 μM)	
Radioligands	[^{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 $\beta1$ 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 the most potent and selective competitive glycine receptor antagonist with affinities in the range 5–15 nM. Several analogues of muscimol and piperidine act as agonists and antagonists of both glycine and $GABA_A$ receptors. Picrotoxin has been reported to block the chloride channel of glycine receptors (Pribilla *et al*., 1992) or, by contrast, to act as a competitive antagonist (Lynch *et al*., 1995). Picrotoxin shows strong selectivity towards homomeric receptors composed of α subunits (Pribilla *et al*., 1992; Lynch *et al*., 1995), and its components, picrotoxinin and picrotin, have similar inhibitory potencies. In addition to the compounds listed in the table, numerous agents act as allosteric regulators of glycine receptors (reviewed by Rajendra *et al*., 1997; Laube *et al*., 2002). Zn^{2+} acts through distinct binding sites of high and low affinity to allosterically enhance channel function at low (< 10 μM) concentrations and inhibit responses at higher (> 50–100 μM) concentrations. The effect of Zn^{2+} is mimicked by Ni^{2+}. 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 $\alpha1$ or $\alpha2$ subunits, or hetero-oligomers of $\alpha1/\beta$ or $\alpha2/\beta$ subunits, is differentially affected by the 5-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 (Maksay *et al*., 1999; Supplisson & Chesnoy-Marchais, 2000). Additional tropienes, including atropine, modulate glycine receptor activity.

Abbreviations: **αEMBTL**, α-ethyl,α-methyl-γ-thiobutyrolactone; **BN52021**, (±)-*trans*-2,5-bis(3,4,5-trimethoxyphenyl)-1,3-dioxolane; **DCKA**, dichlorokynurenic acid; **PMBA**, 3-[2′-phosphonomethyl[1,1′-biphenyl]-3-yl]alanine

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

Overview: The 5-HT$_3$ receptor (nomenclature as agreed by NC-IUPHAR Subcommittee on 5-hydroxytryptamine (serotonin) receptors (Hoyer *et al*., 1994) and subsequently revised (Hartig *et al*., 1996)) 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 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 *bona fide* 5-HT$_3$ receptor subunits that are functional. 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), 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). The diversity of 5-HT$_3$ receptors is increased by alternative splicing of the 5-HT$_{3A}$ subunit.

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
Radioligands	[^{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 co-expression of the 5-HT$_{3B}$ subunit

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; 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 the reviews by Lambert *et al*., 1995; Parker *et al*., 1996; Peters *et al*., 1997; 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) transmitter-gated channels conducting Na^+, K^+ and Ca^{2+}, with two putative transmembrane 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 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 form pores permeable to low molecular weight solutes (Surprenant *et al*., 1996).

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)	—	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)

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 nonselective 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). 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; **$\alpha\beta$-meATP**, $\alpha\beta$-methylene-adenosine 5′-triphosphate; **$\beta\gamma$-meATP**, $\beta\gamma$-methylene-adenosine 5′-triphosphate; **NF023**, 8,8′-(carbonylbis[imino-3,1-phenylene carbonylimino])bis-1,3,5-naphthalenetrisulphonic acid; **PPADS**, pyridoxalphosphate-6-azophenyl-2′,4′-disulphonate; **TNP-ATP**, 2′,3′-*O*-(2,4,6-trinitrophenyl)-ATP

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