THE CONCISE GUIDE TO PHARMACOLOGY 2013/14: LIGAND-GATED ION CHANNELS

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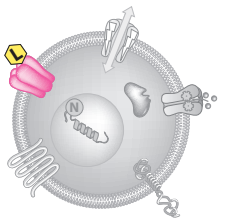

Abstract

The Concise Guide to PHARMACOLOGY 2013/14 provides concise overviews of the key properties of over 2000 human drug targets with their pharmacology, plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. The full contents can be found at http://onlinelibrary.wiley.com/doi/10.1111/bph.12444/full.

Ligand-gated ion channels are one of the seven major pharmacological targets into which the Guide is divided, with the others being G protein-coupled receptors, ion channels, catalytic receptors, nuclear hormone receptors, transporters and enzymes. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. A new landscape format has easy to use tables comparing related targets.

It is a condensed version of material contemporary to late 2013, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in previous Guides to Receptors and Channels. It is produced in conjunction with NC-IUPHAR and provides the official IUPHAR classification and nomenclature for human drug targets, where appropriate. It consolidates information previously curated and displayed separately in IUPHAR-DB and the Guide to Receptors and Channels, providing a permanent, citable, point-in-time record that will survive database updates.

An Introduction to Ligand-gated Ion Channels

Ligand-gated ion channels (LGICs) are integral membrane proteins that contain a pore which allows the regulated flow of selected ions across the plasma membrane. Ion flux is passive and driven by the electrochemical gradient for the permeant ions. The channels are opened, or gated, by the binding of a neurotransmitter to an orthosteric site(s) that triggers a conformational change that results in the conducting state. Modulation of gating can occur by the binding of endogenous, or exogenous, modulators to allosteric sites. LGICs mediate fast synaptic transmission, on a millisecond time scale, in the nervous system and at the somatic neuromuscular junction. Such transmission involves the release of a neurotransmitter from a pre-synaptic neurone and the subsequent activation of post-synaptically located receptors that mediate a rapid, phasic, electrical signal (the excitatory, or inhibitory, post-synaptic potential). However, In addition to their traditional role in phasic neurotransmission, it is now established that some LGICs mediate a tonic form of neuronal regulation that results from the activation of extra-synaptic receptors by ambient levels of neurotransmitter. The expression of some LGICs by non-excitable cells is suggestive of additional functions.

By convention, the LGICs comprise the excitatory, cation-selective, nicotinic acetylcholine (Millar and Gotti, 2009; Changeux, 2010), 5-HT_3 (Barnes *et al.*, 2009; Walstab *et al.*, 2010), ionotropic glutamate (Lodge, 2009; Traynelis *et al.*, 2010) and P2X receptors (Jarvis and Khakh, 2009; Surprenant and North, 2009) and the inhibitory, anion-selective, $GABA_A$ (Olsen and Sieghart, 2008; Belelli *et al.*, 2009) and glycine receptors (Lynch, 2009; Yevenes and Zeihofer, 2011). The nicotinic acetylcholine, 5-HT_3, $GABA_A$ and glycine receptors (and an additional zinc-activated channel) are pentameric structures and are frequently referred to as the Cys-loop receptors due to the presence of a defining loop of residues formed by a disulphide bond in the extracellular domain of their constituent subunits (Miller and Smart, 2010; Thompson *et al.*, 2010). However, the prokaryotic ancestors of these receptors contain no such loop and the term pentameric ligand-gated ion channel (pLGIC) is gaining acceptance in the literature (Hilf and Dutzler, 2009). The ionotropic

glutamate and P2X receptors are tetrameric and trimeric structures, respectively. Multiple genes encode the subunits of LGICs and the majority of these receptors are heteromultimers. Such combinational diversity results, within each class of LGIC, in a wide range of receptors with differing pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues. The LGICs thus present attractive targets for new therapeutic agents with improved discrimination between receptor isoforms and a reduced propensity for off-target effects. The development of novel, faster screening techniques for compounds acting on LGICs (Dunlop *et al.,* 2008) will greatly aid in the development of such agents.

Acknowledgements

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Conflict of interest

The authors state that there is no conflict of interest to disclose.

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List of records presented

5-HT_3 receptors

Overview: The 5-HT_3 receptor [nomenclature as agreed by the NC-IUPHAR Subcommittee on 5-hydroxytryptamine (serotonin) receptors [16]] is a ligand-gated ion channel of the Cys-loop family that includes the zinc-activated channels, 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 [2]. Five human 5-HT_3 receptor subunits have been cloned and homo-oligomeric assemblies of 5-HT_3A and hetero-oligomeric assemblies of 5-HT_3A and 5-HT_3B subunits have been characterised in detail. The 5-HT_3C (*HTR3C*, Q8WXA8), 5-HT_3D (*HTR3D*, Q70Z44) and 5-HT_3E (*HTR3E*, A5X5Y0) subunits [22,32], like the 5-HT_3B subunit, do not form functional homomers, but are reported to assemble with the 5-HT_3A subunit to influence its functional expression rather than pharmacological profile [13,34,49]. 5-HT_3A, -C, -D, and -E subunits also interact with the chaperone RIC-3 which predominantly enhances the surface expression of homomeric 5-HT_3A receptor [49]. The co-expression of 5-HT_3A and 5-HT_3C-E subunits has been demonstrated in human colon [21]. A recombinant hetero-oligomeric 5-HT_3AB receptor has been reported to contain two copies of the 5-HT_3A subunit and three copies of the 5-HT_3B subunit in the order B-B-A-B-A [3], but this is inconsistent with recent reports which show at least one A-A interface [25,47]. The 5-HT_3B subunit imparts distinctive biophysical properties upon hetero-oligomeric 5-HT_3AB versus homo-oligomeric 5-HT_3A recombinant receptors [8,10–11,19,23,37,40], influences the potency of channel blockers, but generally has only a modest effect upon the apparent affinity of agonists, or the affinity of antagonists ([5], but see [7,9–10]) which may be explained by the orthosteric binding site residing at an interface formed between 5-HT_3A subunits [25,47]. However, 5-HT_3A and 5-HT_3AB receptors differ in their allosteric regulation by some general anaesthetic agents, small alcohols and indoles [17,38–39]. The potential diversity of 5-HT_3 receptors is increased by alternative splicing of the genes HTR3A and E [6,14,31,33–34]. In addition, the use of tissue-specific promoters driving expression from different transcriptional start sites has been reported for the *HTR3A*, *HTR3B, HTR3D* and *HTR3E* genes, which could result in 5-HT_3 subunits harbouring different N-termini [19,31,48]. To date, inclusion of the 5-HT_3A subunit appears imperative for 5-HT_3 receptor function.

Channels

Nomenclature	5-HT_3A	5-HT_3AB
Subunits	5-HT3A (*HTR3A*, P46098)	5-HT3A, 5-HT3B (*HTR3B*, O95264)
Selective agonists (EC_{50})	SR57227A (~$4x10^{-7}$ M), meta-chlorphenylbiguanide ($1.6x10^{-6}$ – $4x10^{-6}$ M) [4,8,24,28–29], 2-methyl-5-HT ($2.5x10^{-6}$ – $3.1x10^{-6}$ M) [4,8,24,28], 1-phenylbiguanide ($8x10^{-5}$ M) [4]	–
Selective antagonists (IC_{50})	(S)-zacopride (Ki $1x10^{-9}$ M) [5], granisetron (Ki ~$1.5x10^{-9}$ – $2.5x10^{-9}$ M) [15,28], tropisetron (Ki $1.5x10^{-9}$ – $3x10^{-9}$ M) [24,28], ondansetron (Ki ~$5x10^{-9}$ – $1.5x10^{-8}$ M) [5,15,28]	–
Channel Blockers (IC_{50})	picrotoxinin ($1.1x10^{-5}$ M) [42], TMB-8 ($1.176x10^{-5}$ M) [41], diltiazem ($2.1x10^{-5}$ M) [42], bilobalide ($4.7x10^{-4}$ M) [42], ginkgolide B ($7.3x10^{-4}$ M) [42]	picrotoxinin ($6.3x10^{-5}$ M) [43], bilobalide ($3.1x10^{-3}$ M) [43], ginkgolide B ($3.9x10^{-3}$ M) [43]
Radioligands (K_d)	[^{3}H]ramosetron (Antagonist) ($1.5x10^{-10}$ M) [28], [^{3}H]GR65630 (Antagonist) ($2.56x10^{-9}$ – $4.8x10^{-10}$ M) [12,24], [^{3}H]granisetron (Antagonist) ($1.2x10^{-9}$ M) [5,15], [^{3}H](S)-zacopride (Antagonist) ($2x10^{-9}$ M) [35], [^{3}H]LY278584 (Antagonist) ($3.08x10^{-9}$ M) [1]	–
Functional characteristics	γ = 0.4-0.8 pS [+ 5-HT3B, γ = 16 pS]; inwardly rectifying current [+ 5-HT3B, rectification reduced]; nH 2-3 [+ 5-HT3B 1-2]; relative permeability to divalent cations reduced by co-expression of the 5-HT3B subunit	γ = 0.4-0.8 pS [+ 5-HT3B, γ = 16 pS]; inwardly rectifying current [+ 5-HT3B, rectification reduced]; nH 2-3 [+ 5-HT3B 1-2]; relative permeability to divalent cations reduced by co-expression of the 5-HT3B subunit

Comments: Although not a selective antagonist, methadone displays multimodal and subunit-dependent antagonism of 5-HT_3 receptors [9]. Similarly, TMB-8, diltiazem, picrotoxin, bilobalide and ginkgolide B are not selective for 5-HT_3 receptors (*e.g.* [43]). The anti-malarial drugs mefloquine and quinine exert a modestly more potent block of 5-HT_3A versus 5-HT_3AB receptor-mediated responses [46]. Known better as a partial agonist of nicotinic acetylcholine $\alpha4\beta2$ receptors, varenicline is also an agonist of the 5-HT_3A receptor [26]. Human [4,28], rat [18], mouse [27], guinea-pig [24] ferret [30] and canine [20] 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 [36,44–45,50]).

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$GABA_A$ receptors

Overview: The $GABA_A$ receptor is a ligand-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, $5\text{-}HT_3$ and strychnine-sensitive glycine receptors. $GABA_A$ receptor-mediated inhibition within the CNS occurs by fast synaptic transmission, sustained tonic inhibition and temporally intermediate events that have been termed '$GABA_A$, slow' [9]. $GABA_A$ receptors exist as pentamers of 4TM subunits that form an intrinsic anion selective channel. Sequences of six α, three β, three γ, one δ, three ρ, one ε, one π and one θ $GABA_A$ receptor subunits (gene family ID ENSF00000000053) have been reported in mammals [36–37,42,44]. The π-subunit is restricted to reproductive tissue. Alternatively spliced versions of many subunits exist (e.g. α4- and α6- (both not functional) α5-, β2-, β3- and γ2), along with RNA editing of the α3 subunit [12]. The three ρ-subunits, (ρ1-3) function as either homo- or hetero-oligomeric assemblies [10,55]. Receptors formed from ρ-subunits, because of their distinctive pharmacology that includes insensitivity to bicuculline, benzodiazepines and barbiturates, have sometimes been termed $GABA_C$ receptors [55], but they are classified as $GABA_A$ receptors by NC-IUPHAR on the basis of structural and functional criteria [3,36–37].

Many $GABA_A$ receptor subtypes contain α-, β- and γ-subunits with the likely stoichiometry 2α.2β.1γ [26,36]. It is thought that the majority of $GABA_A$ receptors harbour a single type of α- and β -subunit variant. The α1β2γ2 hetero-oligomer constitutes the largest population of $GABA_A$ receptors in the CNS, followed by the α2β3γ2 and α3β3γ2 isoforms. Receptors that incorporate the α4- α5-or α6-subunit, or the β1-, γ1-, γ3-, δ-, ε- and θ-subunits, are less numerous, but they may nonetheless serve important functions. For example, extrasynaptically located receptors that contain α6- and δ-subunits in cerebellar granule cells, or an α4- and δ-subunit in dentate gyrus granule cells and thalamic neurones, mediate a tonic current that is important for neuronal excitability in response to ambient concentrations of GABA [4,13,32,40,45]. GABA binding occurs at the β+/α- subunit interface and the homologous γ+/α- subunits interface creates the benzodiazepine site. A second site for benzodiazepine binding has recently been postulated to occur at the α+/β- interface ([38]; reviewed by [43]). The particular α-and γ-subunit isoforms exhibit marked effects on recognition and/or efficacy at the benzodiazepine site. Thus, receptors incorporating either α4- or α6-subunits are not recognised by 'classical' benzodiazepines, such as flunitrazepam (but see [104]). The trafficking, cell surface expression, internalisation and function of $GABA_A$ receptors and their subunits are discussed in detail in several recent reviews [61,70,81,101] but one point worthy of note is that receptors incorporating the γ2 subunit (except when associated with α5) cluster at the postsynaptic membrane (but may distribute dynamically between synaptic and extrasynaptic locations), whereas as those incorporating the d subunit appear to be exclusively extrasynaptic.

NC-IUPHAR [53,86] class $GABA_A$ receptors according to their subunit structure, pharmacology and receptor function. Currently, eleven native $GABA_A$ receptors are classed as conclusively identified (*i.e.*, α1β2γ2, α1βγ2, α3βγ2, α4βγ2, α4β2δ, α4β3δ, α5βγ2, α6βγ2, α6β2δ, α6β3δ and ρ) with further receptor isoforms occurring with high probability, or only tentatively [86–87]. It is beyond the scope of this Guide to discuss the pharmacology of individual $GABA_A$ receptor isoforms in detail; such information can be gleaned in the reviews [53,66,71,76,78,83,86–87,92] and [51–52]. Agents that discriminate between α-subunit isoforms are noted in the table and additional agents that demonstrate selectivity between receptor isoforms, for example via β-subunit selectivity, are indicated in the text below. The distinctive agonist and antagonist pharmacology of ρ receptors is summarised in the table and additional aspects are reviewed in [60,72,84,105].

Subunits

Nomenclature	α1	α2	α3	α4	α5	α6
HGNC, UniProt	*GABRA1*, P14867	*GABRA2*, P47869	*GABRA3*, P34903	*GABRA4*, P48169	*GABRA5*, P31644	*GABRA6*, Q16445
Agonists	isoguvacine [GABA site] (Full agonist), isonipecotic acid [GABA site], muscimol [GABA site] (Full agonist), piperidine-4-sulphonic acid [GABA site] (Full agonist), THIP [GABA site]					
Selective antagonists	bicuculline [GABA site], gabazine [GABA site]					
Channel Blockers	picrotoxin, TBPS					
Endogenous allosteric regulators	5α-pregnan-3α-ol-20-one (Potentiation), tetrahydrodeoxycorticosterone (Potentiation), Zn^{2+} (Inhibition)					

Nomenclature	α1	α2	α3	α4	α5	α6
Allosteric Regulators [benzodiazepine site]	α3IA (Inverse agonist), α5IA (Inverse agonist), bretazenil (Full agonist), diazepam (Full agonist), DMCM (Inverse agonist), flumazenil (Antagonist), flunitrazepam (Full agonist), MRK016 (Inverse agonist), Ro154513 (Inverse agonist), Ro194603 (Inverse agonist), Ro4938581 (Inverse agonist), TP003 (Antagonist), TPA023 (Antagonist)	α3IA (Inverse agonist), α5IA (Inverse agonist), bretazenil (Full agonist), diazepam (Full agonist), DMCM (Inverse agonist), flumazenil (Antagonist), flunitrazepam (Full agonist), MRK016 (Inverse agonist), ocinaplon (Partial agonist), Ro154513 (Inverse agonist), Ro194603 (Inverse agonist), Ro4938581 (Inverse agonist), TP003 (Antagonist), ZK93426 (Antagonist)	α5IA (Inverse agonist), bretazenil (Full agonist), diazepam (Full agonist), DMCM (Inverse agonist), flumazenil (Antagonist), flunitrazepam (Full agonist), MRK016 (Inverse agonist), ocinaplon (Partial agonist), Ro154513 (Inverse agonist), Ro4938581 (Inverse agonist), ZK93426 (Antagonist)	flumazenil (Partial agonist, low affinity)	α3IA (Inverse agonist), bretazenil (Full agonist), diazepam (Full agonist), DMCM (Inverse agonist), flumazenil (Antagonist), flunitrazepam (Full agonist), ocinaplon (Partial agonist), Ro154513 (Inverse agonist), Ro194603 (Inverse agonist), TP003 (Antagonist), TPA023 (Antagonist), ZK93426 (Antagonist)	bretazenil (Full agonist), flumazenil (Partial agonist, low affinity)
Selective allosteric regulators [benzodiazepine site]	indiplon (Full agonist, high affinity), L838417 (Antagonist), ocinaplon (Full agonist), zaleplon (Full agonist, high affinity), ZK93426 (Antagonist), zolpidem (Full agonist, high affinity)	L838417 (Partial agonist), TPA023 (Partial agonist, low efficacy)	α3IA (higher affinity), L838417 (Partial agonist), Ro194603 (Inverse agonist, higher affinity), TP003 (Partial agonist, high efficacy), TPA023 (Partial agonist, low efficacy)	bretazenil (Full agonist), Ro154513 (Full agonist)	α5IA (Inverse agonist), L655708 (Inverse agonist, high affinity), L838417 (Partial agonist), MRK016 (Inverse agonist), Ro4938581 (Inverse agonist, higher affinity), RY024 (Inverse agonist, high affinity)	Ro154513 (Full agonist)
Radioligands (K_d)	[^{11}C]flumazenil [benzodiazepine site], [^{18}F]fluoroethylflumazenil [benzodiazepine site], [^{35}S]TBPS [anion channel], [^{3}H]CGS8216 [benzodiazepine site], [^{3}H]flunitrazepam [benzodiazepine site], [^{3}H]gabazine [GABA site], [^{3}H]muscimol [GABA site], [^{3}H]zolpidem [benzodiazepine site]					
Comment	Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [77]					

Comments: isonipectoic acid is a relatively high efficacy agonist at the GABA binding site of α4 and α6 subunits. Diazepam and flunitrazepam are not active at α4- or α6-subunits. [^{11}C]flumazenil is a low affinity ligand at the benzodiazepine site of α4 and α6 subunits. [^{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).

Nomenclature	β1	β2	β3	γ1	γ2	γ3
HGNC, UniProt	*GABRB1*, P18505	*GABRB2*, P47870	*GABRB3*, P28472	*GABRG1*, Q8NIC3	*GABRG2*, P18507	*GABRG3*, Q99928
Channel Blockers	picrotoxin, TBPS					
Comment	Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [77]					

Nomenclature	δ	ε	θ	π
HGNC, UniProt	*GABRD*, O14764	*GABRE*, P78334	*GABRQ*, Q9UN88	*GABRP*, O00591
Selective agonists	THIP [GABA site] (Full agonist)	–	–	–
Channel Blockers	picrotoxin, TBPS			
Comment	Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively			

Nomenclature	ρ1	ρ2	ρ3
HGNC, UniProt	*GABRR1*, P24046	*GABRR2*, P28476	*GABRR3*, A8MPY1
Agonists	isoguvacine [GABA site] (Partial agonist), muscimol [GABA site] (Partial agonist)		
Selective agonists	5-Me-IAA [GABA site] (Full agonist), (±)-*cis*-2-CAMP [GABA site] (Full agonist)		
Antagonists	isonipecotic acid [GABA site], piperidine-4-sulphonic acid [GABA site], THIP [GABA site]		
Selective antagonists	aza-THIP [GABA site], *cis*-3-ACPBPA [GABA site], *trans*-3-ACPBPA [GABA site], TPMPA [GABA site]		
Channel Blockers	picrotoxin, TBPS		
Comment	bicuculline is not active at these subunits		

Comments: The potency and efficacy of many GABA agonists vary between receptor $GABA_A$ receptor isoforms [66,73,78]. For example, THIP (gaboxadol) is a partial agonist at receptors with the subunit composition α4β3γ2, but elicits currents in excess of those evoked by GABA at the α4β3δ receptor where GABA itself is a low efficacy agonist [56,58]. The antagonists bicuculline and gabazine differ in their ability to suppress spontaneous openings of the $GABA_A$ receptor, the former being more effective [98]. The presence of the γ subunit within the heterotrimeric complex reduces the potency and efficacy of agonists [96]. 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 [55,68–69,100]. Picrotoxinin and TBPS act at an allosteric site within the chloride channel pore to negatively regulate channel activity; negative allosteric regulation by γ-butyrolactone derivatives also involves the picrotoxinin site, whereas positive allosteric regulation by such compounds is proposed to occur at a distinct locus. Many intravenous (*e.g.*, etomidate, propofol) and inhalational (*e.g.*, halothane, isoflurane) anaesthetics and alcohols also exert a regulatory influence upon $GABA_A$ receptor activity [57,85]. Specific amino acid residues within $GABA_A$ receptor α- and β-subunits that influence allosteric regulation by anaesthetic and non-anaesthetic compounds have been identified [67,69]. Photoaffinity labelling of distinct amino acid residues within purified $GABA_A$ receptors by the etomidate derivative, [^{3}H]azi-etomidate, has also been demonstrated [80] and this binding subject to positive allosteric regulation by anaesthetic steroids [79]. An array of natural products including flavonoid and terpenoid compounds exert varied actions at $GABA_A$ receptors (reviewed in detail in [71]).

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 [99]]; fragrent dioxane derivatives [positive allosteric modulators selective for β1- versus β2-, or β3-subunit-containing receptors [91]]; loreclezole, etomidate, tracazolate, mefenamic acid, etifoxine, stiripentol, valerenic acid amide [positive allosteric modulators with selectivity for β2/β3- over β1-subunit-containing receptors [65,74,76]]; tracazolate [intrinsic efficacy, *i.e.*, potentiation, or inhibition, is dependent upon the identity of the γ1-3-, δ-, or ε-subunit co-assembled with α1- and β1-subunits [97]]; amiloride [selective blockade of receptors containing an α6-subunit [64]]; furosemide [selective blockade of receptors containing an α6-subunit co-assembled with β2/β3-, but not β1-subunit [76]]; La^{3+} [potentiates responses mediated by α1β3γ2L receptors, weakly inhibits α6β3γ2L receptors, and strongly blocks α6β3δ and α4β3δ receptors [58,89]]; ethanol [selectively potentiates responses mediated by α4β3δ and α6β3δ receptors versus receptors in which β2 replaces β3, or γ replaces δ [103], but see also [75]]; DS1 and DS2 [selectively potentiate responses mediated by δ-subunit-containing receptors [102]]. 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 [54,56].

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Glycine receptors

Overview: The inhibitory glycine receptor [nomenclature as agreed by the NC-IUPHAR sub-committee on glycine receptors] is a member of the Cys-loop superfamily of transmitter-gated ion channels that includes the zinc activated channels, $GABA_A$, nicotinic acetylcholine and $5\text{-}HT_3$ receptors [121]. The receptor is expressed either as a homo-pentamer of α subunits, or a complex now thought to harbour 2α and 3β subunits [107,111], that contain an intrinsic anion channel. Four differentially expressed isoforms of the α-subunit (α1-α4) and one variant of the β-subunit (β1, *GLRB*, P48167) have been identified by genomic and cDNA cloning. Further diversity originates from alternative splicing of the primary gene transcripts for α1 ($\alpha1^{INS}$ and $\alpha1^{del}$), α2 (α2A and α2B), α3 (α3S and α3L) and β (βΔ7) subunits and by mRNA editing of the α2 and α3 subunit [109,124,128]. Both α2 splicing and α3 mRNA editing can produce subunits (*i.e.*, α2B and α3P185L) with enhanced agonist sensitivity. 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 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 contributes to agonist binding, reduces single channel conductance and alters pharmacology. The β-subunit also anchors the receptor, via an amphipathic sequence within the large intracellular loop region, to gephyrin. The latter is a cytoskeletal attachment protein that binds to a number of subsynaptic proteins involved in cytoskeletal structure and thus clusters and anchors hetero-oligomeric receptors to the synapse [116–117,126]. G-protein βγ subunits enhance the open state probability of native and recombinant glycine receptors by association with domains within the large intracellular loop [135–136]. Intracellular chloride concentration modulates the kinetics of native and recombinant glycine receptors [129]. Intracellular Ca^{2+} appears to increase native and recombinant glycine receptor affinity, prolonging channel open events, by a mechanism that does not involve phosphorylation [110].

Subunits

Nomenclature	α1	α2	α3
HGNC, UniProt	*GLRA1*, P23415	*GLRA2*, P23416	*GLRA3*, O75311
Selective agonists (potency order)	glycine > β-alanine > taurine	glycine > β-alanine > taurine	glycine > β-alanine > taurine
Selective antagonists (IC_{50})	HU-308 (weak inhibition), PMBA, strychnine, pregnenolone sulphate (K_i $1.9x10^{-6}$ M), tropisetron (K_i $8.4x10^{-5}$ M), ginkgolide X ($7.6x10^{-7}$ M), nifedipine ($3.3x10^{-6}$ M), bilobalide ($2x10^{-5}$ M), colchicine ($3.24x10^{-4}$ M)	PMBA, strychnine, pregnenolone sulphate (K_i $5.5x10^{-6}$ M), tropisetron (K_i $1.3x10^{-5}$ M), HU-210 ($9x10^{-8}$ M), WIN55212-2 ($2.2x10^{-7}$ M), HU-308 ($1.1x10^{-6}$ M), ginkgolide X ($2.8x10^{-6}$ M), bilobalide ($8x10^{-6}$ M), colchicine ($6.4x10^{-5}$ M), 5,7-dichlorokynurenic acid ($1.88x10^{-4}$ M)	strychnine, HU-210 ($5x10^{-8}$ M), HU-308 ($9.7x10^{-8}$ M), WIN55212-2 ($9.7x10^{-8}$ M), (12E,20Z,18S)-8-hydroxyvariabilin ($7x10^{-6}$ M), nifedipine ($2.92x10^{-5}$ M)
Channel Blockers (IC_{50})	cyanotriphenylborate ($1.3x10^{-6}$ M), ginkgolide B ($6x10^{-7}$ – $8x10^{-6}$ M), picrotin ($5.2x10^{-6}$ M), picrotoxinin ($5.1x10^{-6}$ M), picrotoxin ($6.3x10^{-6}$ M)	picrotoxinin ($4.1x10^{-7}$ M), picrotoxin ($2.3x10^{-6}$ M), ginkgolide B ($3.7x10^{-6}$ – $1.14x10^{-5}$ M), picrotin ($1.31x10^{-5}$ M), cyanotriphenylborate (>$2x10^{-5}$ M)	picrotoxin (block is weaker when β subunit is co-expressed), picrotoxinin ($4.3x10^{-7}$ M), ginkgolide B ($1.8x10^{-6}$ M), picrotin ($6x10^{-6}$ M)
Endogenous allosteric regulators	Extracellular H^+ (Inhibition, endogenous), Zn^{2+} (Potentiation, endogenous; not affected by β subunit co-expression) (EC_{50} $3.7x10^{-8}$ M), Cu^{2+} (Inhibition, endogenous; not affected by β subunit co-expression) (IC_{50} $4x10^{-6}$ – $1.5x10^{-5}$ M), Zn^{2+} (Inhibition, endogenous) (IC_{50} $1.5x10^{-5}$ M)	Zn^{2+} (Potentiation, endogenous; not affected by β subunit co-expression) (EC_{50} $5.4x10^{-7}$ M), Cu^{2+} (Inhibition, endogenous) (IC_{50} $1.7x10^{-5}$ M), Zn^{2+} (Inhibition, endogenous) (IC_{50} $3.6x10^{-4}$ M)	Cu^{2+} (Inhibition, endogenous) (IC_{50} $9x10^{-6}$ M), Zn^{2+} (Inhibition, endogenous) (IC_{50} $1.5x10^{-4}$ M)
Selective allosteric regulators	anandamide (Potentiation) (EC_{50} $3.8x10^{-8}$ M), HU-210 (Potentiation) (EC_{50} $2.7x10^{-7}$ M), Δ^9-tetrahydrocannabinol (Potentiation, ~1500% potentiation) (EC_{50} ~$3x10^{-6}$ M)	Δ^9-tetrahydrocannabinol (Potentiation, ~230% potentiation) (EC_{50} ~$1x10^{-6}$ M)	Δ^9-tetrahydrocannabinol (Potentiation, ~1500% potentiation) (EC_{50} ~$5x10^{-6}$ M)
Radioligands (K_d)	[^{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)

Comments: Data in the table refer to homo-oligomeric assemblies of the α-subunit, significant changes introduced by co-expression of the β1 subunit are indicated in parenthesis. Not all glycine receptor ligands are listed within the table, but some that may be useful in distinguishing between glycine receptor isoforms are indicated (see detailed view pages for each subunit: α1, α2, α3, α4, β). pregnenolone sulphate, tropisetron and colchicine, for example, although not selective antagonists of glycine receptors, are included for this purpose. strychnine is a potent and selective competitive glycine receptor antagonist with affinities in the range 5–15 nM. RU5135 demonstrates comparable potency, but additionally blocks $GABA_A$ receptors. There are conflicting reports concerning the ability of cannabinoids to inhibit [119], or potentiate and at high concentrations activate [106,108,112,131–132] glycine receptors. Nonetheless, cannabinoid analogues may hold promise in distinguishing between glycine receptor subtypes [132]. In addition, potentiation of glycine receptor activity by cannabinoids has been claimed to contribute to cannabis-induced analgesia relying on Ser296/307 (α1/α3) in M3 [131]. Several analogues of muscimol and piperidine act as agonists and antagonists of both glycine and $GABA_A$ receptors. picrotoxin acts as an allosteric inhibitor that appears to bind within the pore, and shows strong selectivity towards homomeric receptors. While its components, picrotoxinin and picrotin, have equal potencies at α1 receptors, their potencies at α2 and α3 receptors differ modestly and may allow some distinction between different receptor types [133]. Binding of picrotoxin within the pore has been demonstrated in the crystal structure of the related *C. elegans* GluCl Cys-loop receptor [113]. In addition to the compounds listed in the table, numerous agents act as allosteric regulators of glycine receptors (comprehensively reviewed in [118,120,130,137]). 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 [125]. The effect of Zn^{2+} is somewhat mimicked by Ni^{2+}. Endogenous Zn^{2+} is essential for normal glycinergic neurotransmission mediated by α1 subunit-containing receptors [114]. 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 enhance glycine receptor function although whether this occurs by a direct allosteric action at the receptor [123], or through G protein βγ subunits [134] is debated. Recent crystal structures of the bacterial homologue, GLIC, have identified transmembrane binding pockets for both anaesthetics [127] and alcohols [115]. 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 (which may occur within the femtomolar range at the homomeric glycine α1 receptor), or inhibition, depending upon the subunit composition of the receptor and the concentrations of the modulator and glycine employed. Potentiation and inhibition by tropeines involves different binding modes [122]. Additional tropeines, including atropine, modulate glycine receptor activity.

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Ionotropic glutamate receptors

Overview: The ionotropic glutamate receptors comprise members of the NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid) and kainate receptor classes, named originally according to their preferred, synthetic, agonist [149,174,197]. Receptor heterogeneity within each class arises from the homo-oligomeric, or hetero-oligomeric, assembly of distinct subunits into cation-selective tetramers. Each subunit of the tetrameric complex comprises an extracellular amino terminal domain (ATD), an extracellular ligand binding domain (LBD), three transmembrane domains composed of three membrane spans (M1, M3 and M4), a channel lining re-entrant 'p-loop' (M2) located between M1 and M3 and an intracellular carboxy- terminal domain (CTD) [166,169,177,181,197]. The X-ray structure of a homomeric ionotropic glutamate receptor (GluA2 – see below) has recently been solved at 3.6Å resolution [194] and although providing the most complete structural information current available may not representative of the subunit arrangement of, for example, the heteromeric NMDA receptors [167]. It is beyond the scope of this supplement to discuss the pharmacology of individual ionotropic glutamate receptor isoforms in detail; such information can be gleaned from [144,148–149,153,164–165,168,184–186,197–198]. Agents that discriminate between subunit isoforms are, where appropriate, noted in the tables and additional compounds that distinguish between receptor isoforms are indicated in the text below.

The classification of glutamate receptor subunits has been recently been re-addressed by NC-IUPHAR [146]. The scheme developed recommends a revised nomenclature for ionotropic glutamate receptor subunits that is adopted here.

AMPA and Kainate receptors AMPA receptors assemble as homomers, or heteromers, that may be drawn from GluA1, GluA2, GluA3 and GluA4 subunits. Transmembrane AMPA receptor regulatory proteins (TARPs) of class I (i.e. γ2, γ3, γ4 and γ8) act, with variable stoichiometry, as auxiliary subunits to AMPA receptors and influence their trafficking, single channel conductance gating and pharmacology (reviewed in [154,163,179,195]). Functional kainate receptors can be expressed as homomers of GluK1, GluK2 or GluK3 subunits. GluK1-3 subunits are also capable of assembling into heterotetramers (*e.g.* GluK1/K2; [171,188–189]). Two additional kainate receptor subunits, GluK4 and GluK5, when expressed individually, form high affinity binding sites for kainate, but lack function, but can form heteromers when expressed with GluK1-3 subunits (*e.g.* GluK2/K5; reviewed in [165,188–189]). Kainate receptors may also exhibit 'metabotropic' functions [171,191]. As found for AMPA receptors, kainate receptors are modulated by auxiliary subunits (Neto proteins, [172,188]). An important function difference between AMPA and kainate receptors is that the latter require extracellular Na+ and Cl^- for their activation [141,190]. RNA encoding the GluA2 subunit undergoes extensive RNA editing in which the codon encoding a p-loop glutamine residue (Q) is converted to one encoding arginine (R). This Q/R site strongly influences the biophysical properties of the receptor. Recombinant AMPA receptors lacking RNA edited GluA2 subunits are: (1) permeable to Ca^{2+}; (2) blocked by intracellular polyamines at depolarized potentials causing inward rectification (the latter being reduced by TARPs); (3) blocked by extracellular argiotoxin and Joro spider toxins and (4) demonstrate higher channel conductances than receptors containing the edited form of GluA2 [162,192]. GluK1 and GluK2, but not other kainate receptor subunits, are similarly edited and broadly similar functional characteristics apply to kainate receptors lacking either an RNA edited GluK1, or GluK2, subunit [171,188]. Native AMPA and kainate receptors displaying differential channel conductances, Ca^{2+} permeabilites and sensitivity to block by intracellular polyamines have been identified [147,162,173]. GluA1-4 can exist as two variants generated by alternative splicing (termed 'flip' and 'flop') that differ in their desensitization kinetics and their desensitization in the presence of cyclothiazide which stabilises the nondesensitized state. TARPs also stabilise the non-desensitized conformation of AMPA receptors and facilitate the action of cyclothiazide [179]. Splice variants of GluK1-3 also exist which affects their trafficking [171,188].

Subunits

Nomenclature	GluA1	GluA2	GluA3	GluA4
HGNC, UniProt	*GRIA1*, P42261	*GRIA2*, P42262	*GRIA3*, P42263	*GRIA4*, P48058
Agonists	AMPA (Full agonist), (*S*)-5-fluorowillardiine (Full agonist)			
Selective antagonists	ATPO, GYKI53655, GYKI53784 (active isomer, non-competitive), LY293558, NBQX			
Channel Blockers	extracellular argiotoxin, extracellular joro toxin	extracellular argiotoxin	extracellular argiotoxin, extracellular joro toxin	extracellular argiotoxin, extracellular joro toxin
Allosteric Regulators	aniracetam (Positive), CX516 (Positive), CX546 (Positive), cyclothiazide (Positive), IDRA-21 (Positive), LY392098 (Positive), LY404187 (Positive), LY503430 (Positive), piracetam (Positive), S18986 (Positive)			
Radioligands (K_d)	[^{3}H]AMPA, [^{3}H]CNQX			
Comment	piracetam and aniracetam are examples of pyrrolidinones. cyclothiazide, S18986, and IDRA-21 are examples of benzothiadiazides. CX516 and CX546 are examples of benzylpiperidines. LY392098, LY404187 and LY503430 are examples of biarylpropylsulfonamides. Also blocked by intracellular polyamines			

Nomenclature	GluK1	GluK2	GluK3	GluK4	GluK5
HGNC, UniProt	*GRIK1*, P39086	*GRIK2*, Q13002	*GRIK3*, Q13003	*GRIK4*, Q16099	*GRIK5*, Q16478
Agonists (EC_{50})	8-deoxy-neodysiherbaine (Full agonist), ATPA (Full agonist), domoic acid (Full agonist), dysiherbaine (Full agonist), (*S*)-4-AHCP (Full agonist), (*S*)-5-iodowillardiine, kainate (Full agonist), LY339434 (Full agonist), SYM2081 (Full agonist)	domoic acid (Full agonist), dysiherbaine (Full agonist), kainate (Full agonist), SYM2081 (Full agonist)	dysiherbaine (Full agonist), kainate (Full agonist, low potency), SYM2081 (Full agonist)	domoic acid (Full agonist), dysiherbaine (Full agonist), kainate (Full agonist), SYM2081 (Full agonist)	domoic acid (Full agonist), dysiherbaine (Full agonist), kainate (Full agonist), SYM2081 (Full agonist)
Selective antagonists (IC_{50})	2,4-epi-neodysiherbaine, ACET, LY382884, LY466195, MSVIII-19, NS3763 (non-competitive), UBP302, UBP310	2,4-epi-neodysiherbaine	–	–	–
Allosteric Regulators	concanavalin A (Positive)	concanavalin A (Positive)	–	–	–
Radioligands (K_d)	[^{3}H](2S,4R)-4-methylglutamate, [^{3}H]kainate, [^{3}H]UBP310 ($2.1x10^{-8}$ M) [138]	[^{3}H](2S,4R)-4-methylglutamate, [^{3}H]kainate	[^{3}H](2S,4R)-4-methylglutamate, [^{3}H]kainate, [^{3}H]UBP310 ($5.6x10^{-7}$ M) [138]	[^{3}H](2S,4R)-4-methylglutamate, [^{3}H]kainate	[^{3}H](2S,4R)-4-methylglutamate, [^{3}H]kainate
Comment	–	Intracellular polyamines are subtype selective channel blockers (GluK3 >> GluK2)	domoic acid and concanavalin A are inactive at the GluK3 subunit. Intracellular polyamines are subtype selective channel blockers (GluK3 >> GluK2)	–	–

Comments: *AMPA and Kainate receptors* All AMPA receptors are additionally activated by kainate (and domoic acid) with relatively low potency, (EC_{50} ~ 100 μM). Inclusion of TARPs within the receptor complex increases the potency and maximal effect of kainate [163,179]. AMPA is weak partial agonist at GluK1 and at heteromeric assemblies of GluK1/GluK2, GluK1/GluK5 and GluK2/GluK5 [165]. Quinoxalinediones such as CNQX and NBQX show limited selectivity between AMPA and kainate receptors. LY293558 also has kainate (GluK1) receptor activity as has GYKI53655 (GluK3 and GluK2/GluK3) [165]. ATPO is a potent competitive antagonist of AMPA receptors, has a weaker antagonist action at kainate receptors comprising GluK1 subunits, but is devoid of activity at kainate receptors formed from GluK2 or GluK2/GluK5 subunits. The pharmacological activity of ATPO resides with the (S)-enantiomer. ACET and UBP310 may block GluK3, in addition to GluK1 [138,187]. (2S,4R)-4-methylglutamate (SYM2081) is equipotent in activating (and desensitising) GluK1 and GluK2 receptor isoforms and, via the induction of desensitisation at low concentrations, has been used as a functional antagonist of kainate receptors. Both (2*S*,4*R*)-4-methylglutamate and LY339434 have agonist activity at NMDA receptors. (2S,4R)-4-methylglutamate is also an inhibitor of the glutamate transporters EAAT1 and EAAT2.

Delta subunits GluD1 (*GRID1*, Q9ULK0) and GluD2 (*GRID2*, O43424) comprise, on the basis of sequence homology, an 'orphan' class of ionotropic glutamate receptor subunit. They do not form a functional receptor when expressed solely, or in combination with other ionotropic glutamate receptor subunits, in transfected cells [199]. However, GluD2 subunits bind D-serine and glycine and GluD2 subunits carrying the mutation A654T form a spontaneously open channel that is closed by D-serine [182].

NMDA receptors NMDA receptors assemble as obligate heteromers that may be drawn from GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A and GluN3B subunits. Alternative splicing can generate eight isoforms of GluN1 with differing pharmacological properties. Various splice variants of GluN2B, 2C, 2D and GluN3A have also been reported. Activation of NMDA receptors containing GluN1 and GluN2 subunits requires the binding of two agonists, glutamate to the S1 and S2 regions of the GluN2 subunit and glycine to S1 and S2 regions of the GluN1 subunit [145,152]. The minimal requirement for efficient functional expression of NMDA receptors *in vitro* is a di-heteromeric assembly of GluN1 and at least one GluN2 subunit variant, as a dimer of heterodimers arrangement in the extracellular domain [157,167,177]. However, more complex tri-heteromeric assemblies, incorporating multiple subtypes of GluN2 subunit, or GluN3 subunits, can be generated *in vitro* and occur *in vivo*. The NMDA receptor channel commonly has a high relative permeability to Ca^{2+} and is blocked, in a voltage-dependent manner, by Mg^{2+} such that at resting potentials the response is substantially inhibited.

Nomenclature	GluN1	GluN2A	GluN2B	GluN2C
HGNC, UniProt	*GRIN1*, Q05586	*GRIN2A*, Q12879	*GRIN2B*, Q13224	*GRIN2C*, Q01098
Endogenous agonists	D-aspartate [glutamate site], D-serine [glycine site], glycine [glycine site], L-aspartate [glutamate site]	D-aspartate [glutamate site] (low potency), D-serine [glycine site] (low potency), glycine [glycine site] (low potency), L-aspartate [glutamate site] (low potency)	D-aspartate [glutamate site] (intermediate potency), D-serine [glycine site] (intermediate potency), glycine [glycine site] (intermediate potency), L-aspartate [glutamate site] (intermediate potency)	D-aspartate [glutamate site] (intermediate potency), D-serine [glycine site] (intermediate potency), glycine [glycine site] (intermediate potency), L-aspartate [glutamate site] (intermediate potency)
Agonists	(+)-HA966 [glycine site] (Partial agonist), homoquinolinic acid [glutamate site] (Partial agonist), (*RS*)-(tetrazol-5-yl)glycine [glutamate site] (Full agonist), NMDA [glutamate site] (Full agonist)	(+)-HA966 [glycine site] (Partial agonist, low potency), homoquinolinic acid [glutamate site] (partial agonist), (*RS*)-(tetrazol-5-yl)glycine [glutamate site] (Full agonist, low potency), NMDA [glutamate site] (Full agonist, low potency)	(+)-HA966 [glycine site] (Partial agonist), homoquinolinic acid [glutamate site] (Full agonist, high potency), (*RS*)-(tetrazol-5-yl)glycine [glutamate site] (Full agonist, intermediate potency), NMDA [glutamate site] (Full agonist, intermediate potency)	homoquinolinic acid [glutamate site] (partial agonist), (*RS*)-(tetrazol-5-yl)glycine [glutamate site] (Full agonist, intermediate potency), NMDA [glutamate site] (Full agonist, intermediate potency)
Selective antagonists	5,7-dichlorokynurenic acid [glycine site], GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site]	5,7-dichlorokynurenic acid [glycine site], CGP37849 [glutamate site], CGS19755 [glutamate site], conantokin-G [glutamate site] (low potency), d-AP5 [glutamate site], d-CCPene [glutamate site] (high potency), GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], NVP-AAM077 [glutamate site] (high potency (human), but weakly selective for rat GluN2A versus GluN2B) [139,155-156,183], UBP141 [glutamate site] (low potency) [180]	5,7-dichlorokynurenic acid [glycine site], CGP37849 [glutamate site], CGS19755 [glutamate site], conantokin-G [glutamate site] (high potency), d-AP5 [glutamate site], d-CCPene [glutamate site] (high potency), GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], NVP-AAM077 [glutamate site] (low potency (human), but weakly selective for rat GluN2A versus GluN2B) [139,155–156,183], UBP141 [glutamate site] (low potency) [180]	5,7-dichlorokynurenic acid [glycine site], CGP37849 [glutamate site], CGS19755 [glutamate site], conantokin-G [glutamate site] (intermediate potency), d-AP5 [glutamate site], d-CCPene [glutamate site] (intermediate potency), GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], UBP141 [glutamate site] (intermediate potency) [180]
Channel Blockers	–	amantidine (GluN2C = GluN2D ≥ GluN2B ≥ GluN2A), ketamine, memantine (GluN2C ≥ GluN2D ≥ GluN2B > GluN2A), Mg^{2+} (GluN2A = GluN2B > GluN2C = GluN2D), MK-801, N^1-dansyl-spermine (GluN2A = GluN2B >> GluN2C = GluN2D), phencyclidine		
Radioligands (K_d)	[^{3}H]CGP39653 [glutamate site], [^{3}H]CGP61594 [glycine site] ([^{3}H]CGP61594 is a photoaffinity ligand), [^{3}H]CGS19755 [glutamate site], [^{3}H]CPP [glutamate site], [^{3}H]glycine [glycine site], [^{3}H]L689560 [glycine site], [^{3}H]MDL105519 [glycine site], [^{3}H]MK-801 [cation channel]			

Nomenclature	GluN2D
HGNC, UniProt	*GRIN2D*, O15399
Endogenous agonists	D-aspartate [glutamate site] (GluN2D > GluN2C = GluN2B > GluN2A), D-serine [glycine site] (GluN2D > GluN2C > GluN2B > GluN2A), glycine [glycine site] (GluN2D > GluN2C > GluN2B > GluN2A), L-aspartate [glutamate site] (GluN2D = GluN2B > GluN2C = GluN2A)
Agonists	homoquinolinic acid [glutamate site] (Full agonist, GluN2B ≥ GluN2A ≥ GluN2D > GluN2C; partial agonist at GluN2A and GluN2C), (*RS*)-(tetrazol-5-yl)glycine [glutamate site] (Full agonist, GluN2D > GluN2C = GluN2B > GluN2A), NMDA [glutamate site] (Full agonist, GluN2D > GluN2C > GluN2B > GluN2A)
Selective antagonists	5,7-dichlorokynurenic acid [glycine site], CGP37849 [glutamate site], CGS19755 [glutamate site], conantokin-G [glutamate site] (GluN2B > GluN2D = GluN2C = GluN2A), d-AP5 [glutamate site], d-CCPene [glutamate site] (GluN2A = GluN2B > GluN2C = GluN2D), GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], UBP141 [glutamate site] (GluN2D ≥ GluN2C > GluN2A ≥ GluN2B) [180]
Channel Blockers	amantidine (GluN2C = GluN2D ≥ GluN2B ≥ GluN2A), ketamine, memantine (GluN2C ≥ GluN2D ≥ GluN2B > GluN2A), Mg^{2+} (GluN2A = GluN2B > GluN2C = GluN2D), MK-801, N^1-dansyl-spermine (GluN2A = GluN2B >> GluN2C = GluN2D), phencyclidine
Radioligands	[^{3}H]CGP39653 [glutamate site], [^{3}H]CGP61594 [glycine site] ([^{3}H]CGP61594 is a photoaffinity ligand), [^{3}H]CGS19755 [glutamate site], [^{3}H]CPP [glutamate site], [^{3}H]glycine [glycine site], [^{3}H]L689560 [glycine site], [^{3}H]MDL105519 [glycine site], [^{3}H]MK-801 [cation channel]

Comments: Potency orders unreferenced in the table are from [144,150,153,170,186,197]. 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 [148–149,197]. Voltage-independent inhibition by Zn^{2+} binding with high affinity within the ATD is highly subunit selective (GluN2A >> GluN2B > GluN2C ≥ GluN2D; [186,197]). The receptor is also allosterically modulated, in both positive and negative directions, by endogenous neuroactive steroids in a subunit dependent manner [161,176]. Tonic proton blockade of NMDA receptor function is alleviated by polyamines and the inclusion of exon 5 within GluN1 subunit splice variants, whereas the non-competitive antagonists ifenprodil and CP101606 (traxoprodil) increase the fraction of receptors blocked by protons at ambient concentration. Inclusion of exon 5 also abolishes potentiation by polyamines and inhibition by Zn^{2+} that occurs through binding in the ATD [196]. Ifenprodil, CP101606, haloperidol, felbamate and Ro8-4304 discriminate between recombinant NMDA receptors assembled from GluN1 and either GluN2A, or GluN2B, subunits by acting as selective, non-competitive, antagonists of heterooligomers incorporating GluN2B through a binding site at the ATD GluN1/GluN2B subunit interface [167]. LY233536 is a competitive antagonist that also displays selectivity for GluN2B over GluN2A subunit-containing receptors. Similarly, CGP61594 is a photoaffinity label that interacts selectively with receptors incorporating GluN2B versus GluN2A, GluN2D and, to a lesser extent, GluN2C subunits. TCN 201 and TCN 213 have recently been shown to block GluN2A NMDA receptors selectively by a mechanism that involves allosteric inhibition of glycine binding to the GluN1 site [140,151,159,178]. In addition to influencing the pharmacological profile of the NMDA receptor, the identity of the GluN2 subunit co-assembled with GluN1 is an important determinant of biophysical properties that include sensitivity to block by Mg^{2+}, single-channel conductance and maximal open probablity and channel deactivation time [148,152,158]. Incorporation of the GluN3A subunit into tri-heteromers containing GluN1 and GluN2 subunits is associated with decreased single-channel conductance, reduced permeability to Ca^{2+} and decreased susceptibility to block by Mg^{2+} [142,160]. Reduced permeability to Ca^{2+} has also been observed following the inclusion of GluN3B in tri-heteromers. The expression of GluN3A (*GRIN3A*, Q8TCUS), or GluN3B (*GRIN3B*, O60391), with GluN1 alone forms, in *Xenopus laevis* oocytes, a cation channel with unique properties that include activation by glycine (but not NMDA), lack of permeation by Ca^{2+} and resistance to blockade by Mg^{2+} and NMDA receptor antagonists [143]. The function of heteromers composed of GluN1 and GluN3A is enhanced by Zn^{2+}, or glycine site antagonists, binding to the GluN1 subunit [175]. Zn^{2+} also directly activates such complexes. The co-expression of GluN1, GluN3A and GluN3B appears to be required to form glycine-activated receptors in mammalian cell hosts [193].

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Nicotinic acetylcholine receptors

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 [201,229,235–236,241]. All nicotinic receptors are pentamers in which each of the five subunits contains four α-helical transmembrane domains. Genes (Ensembl family ID ENSF00000000049) encoding a total of 17 subunits (α1-10, β1-4, γ, δ and ε) have been identified [224]. All subunits with the exception of α8 (present in avian species) have been identified in mammals. All α subunits possess two tandem cysteine residues near to the site involved in acetylcholine binding, and subunits not named α lack these residues [229]. The orthosteric ligand binding site is formed by residues within at least three peptide domains on the α subunit (principal component), and three on the adjacent subunit (complementary component). nAChRs contain several allosteric modulatory sites. One such site, for positive allosteric modulators (PAMs) and allosteric agonists, has been proposed to reside within an intrasubunit cavity between the four transmembrane domains [215,243]; see also [220]). The high resolution crystal structure of the molluscan acetylcholine binding protein, a structural homologue of the extracellular binding domain of a nicotinic receptor pentamer, in complex with several nicotinic receptor ligands (*e.g.*[208]) and the crystal structure of the extracellular domain of the α1 subunit bound to α-bungarotoxin at 1.94 Å resolution [213], has revealed the orthosteric binding site in detail (reviewed in [209,224,234–235]). Nicotinic receptors at the somatic neuromuscular junction of adult animals have the stoichiometry $(\alpha1)_2\beta1\delta\varepsilon$, whereas an extrajunctional $(\alpha1)_2\beta1\gamma\delta$ receptor predominates in embryonic and denervated skeletal muscle and other pathological states. Other nicotinic receptors are assembled as combinations of α(2-6) and &beta(2-4) subunits. For α2, α3, α4 and β2 and β4 subunits, pairwise combinations of α and β (*e.g.* α3β4 and α4β2) are sufficient to form a functional receptor *in vitro*, but far more complex isoforms may exist *in vivo* (reviewed in [217–218,229]). There is strong evidence that the pairwise assembly of some α and β subunits can occur with variable stoichiometry [*e.g.* $(\alpha4)_2(\beta2)_2$ or $(\alpha4)_3(\beta2)_2$] which influences the biophysical and pharmacological properties of the receptor [229]. α5 and β3 subunits lack function when expressed alone, or pairwise, but participate in the formation of functional hetero-oligomeric receptors when expressed as a third subunit with another α and β pair [e.g. α4α5αβ2, α4αβ2β3, α5α6β2, see [229] for further examples]. 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 [242]. The α7, α8, and α9 subunits form functional homo-oligomers, but can also combine with a second subunit to constitute a hetero-oligomeric assembly (*e.g.* α7β2 and α9α10). 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. Comprehensive listings of nicotinic receptor subunit combinations identified from recombinant expression systems, or *in vivo*, are given in [229]. In addition, numerous proteins interact with nicotinic ACh receptors modifying their assembly, trafficking to and from the cell surface, and activation by ACh (reviewed by [203,223,228]).

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 [226]. 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 – see also [212]).

Subunits

Nomenclature	α1*	α2*	α3*
HGNC, UniProt	*CHRNA1*, P02708	*CHRNA2*, Q15822	*CHRNA3*, P32297
Commonly used antagonists	$(\alpha1)_2\beta1\gamma\delta$ and $(\alpha1)_2\beta1\delta\varepsilon$: α-bungarotoxin > pancuronium > vecuronium > rocuronium > (+)-tubocurarine (IC_{50} = 43 - 82 nM)	α2β2: DHβE (K_B = 0.9 μM), (+)-tubocurarine (K_B = 1.4 μM); α2β4: DHβE (K_B = 3.6 μM), (+)-tubocurarine (K_B = 4.2 μM)	α3β2: DHβE (K_B = 1.6 μM, IC_{50} = 2.0 μM), (+)-tubocurarine (K_B = 2.4 μM); α3β4: DHβE (K_B = 19 μM, IC_{50} = 26 μM), (+)-tubocurarine (K_B = 2.2 μM)
Selective agonists	succinylcholine (Full agonist, selective for $(\alpha1)_2\beta1\gamma\delta$)	–	–
Selective antagonists	α-bungarotoxin, α-conotoxin GI, α-conotoxin MI, pancuronium, waglerin-1 (selective for $(\alpha1)_2\beta1\delta\varepsilon$)	–	α-conotoxin AuIB (α3β4), α-conotoxin-GIC (α3β2), α-conotoxin MII (α3β2), α-conotoxin PnIA (α3β2), α-conotoxin TxIA (α3β2)
Selective channel blockers (IC_{50})	gallamine ($(\alpha1)_2\beta1\gamma\delta$ and $(\alpha1)_2\beta1\delta\varepsilon$) (~$1\times10^{-6}$ M), mecamylamine ($(\alpha1)_2\beta1\delta\varepsilon$) (~$1.5\times10^{-6}$ M)	hexamethonium, mecamylamine	A-867744 (α3β4) [227], hexamethonium (α3β2), hexamethonium (α3β4), NS1738 (α3β4) [237], mecamylamine (α3β4) (3.9×10^{-7} M), mecamylamine (α3β2) (7.6×10^{-6} M)
Selective allosteric regulators	–	LY2087101 (Positive) [206]	–

Nomenclature	α1*	α2*	α3*
Radioligands (K_d)	[^{125}I]α-bungarotoxin, [^{3}H]α-bungarotoxin	[^{3}H]cytisine, [^{125}I]epibatidine (α2β2) ($1x10^{-11}$ – $2.1x10^{-11}$ M - Rat), [^{3}H]epibatidine (α2β2) ($1x10^{-11}$ – $2.1x10^{-11}$ M - Rat), [^{125}I]epibatidine (α2β4) ($4.2x10^{-11}$ M), [^{3}H]epibatidine (α2β4) ($4.2x10^{-11}$ M), [^{125}I]epibatidine (α2β4) ($8.4x10^{-11}$ – $8.7x10^{-11}$ M - Rat), [^{3}H]epibatidine (α2β4) ($8.4x10^{-11}$ – $8.7x10^{-11}$ M - Rat)	[^{3}H]cytisine, [^{125}I]epibatidine (α3β2) ($7x10^{-12}$ M), [^{3}H]epibatidine (α3β2) ($7x10^{-12}$ M), [^{125}I]epibatidine (α3β2) ($1.4x10^{-11}$ – $3.4x10^{-11}$ M - Rat), [^{3}H]epibatidine (α3β2) ($1.4x10^{-11}$ – $3.4x10^{-11}$ M - Rat), [^{125}I]epibatidine (α3β4) ($2.3x10^{-10}$ M), [^{3}H]epibatidine (α3β4) ($2.3x10^{-10}$ M), [^{125}I]epibatidine (α3β4) ($2.9x10^{-10}$ – $3.04x10^{-10}$ M - Rat), [^{3}H]epibatidine (α3β4) ($2.9x10^{-10}$ – $3.04x10^{-10}$ M - Rat)
Functional characteristics	$(α1)_2βγδ$: P_{Ca}/P_{Na} = 0.16 - 0.2, P_f = 2.1 – 2.9%; $(α1)_2βδε$: P_{Ca}/P_{Na} = 0.65 – 1.38, P_f = 4.1 – 7.2%	α2β2: P_{Ca}/P_{Na} ~ 1.5	α3β2: P_{Ca}/P_{Na} = 1.5; α3β4: P_{Ca}/P_{Na} = 0.78 - 1.1, P_f = 2.7 – 4.6%

Nomenclature	α4*	α6*	α7*
HGNC, UniProt	*CHRNA4*, P43681	*CHRNA6*, Q15825	*CHRNA7*, P36544
Commonly used antagonists	α4β2: DHβE (K_B = 0.1 μM; IC_{50} = 0.08 - 0.9 μM), (+)-tubocurarine (K_B = 3.2 μM, IC_{50} = 34 μM); α4β4: DHβE (K_B = 0.01 μM, IC_{50} = 0.19 – 1.2 μM), (+)-tubocurarine (K_B = 0.2 μM, IC_{50} = 50 μM)	α6/α3β2β3 chimera: DHβE (IC_{50} = 1.1 μM)	$(α7)_5$: DHβE (IC_{50} = 8 - 20 μM); $(α7)_5$: (+)-tubocurarine (IC_{50} = 3.1 μM)
Selective agonists	TC-2403 (Full agonist, α4β2) [232], TC-2559 (Full agonist, α4β2) [211]	–	4BP-TQS (Full agonist, 4BP-TQS is an allosteric agonist) [215], A-582941 (Full agonist, $(α7)_5$) [204], PHA-543613 (Full agonist, $(α7)_5$) [239], PHA-709829 (Full agonist, $(α7)_5$) [200], PNU-282987 (Full agonist, $(α7)_5$) [205], TC-5619 (Full agonist, $(α7)_5$) [219]
Selective antagonists	–	α-conotoxin MII (α6β2*), α-conotoxin MII [H9A, L15A] (α6β2β3), α-conotoxin PIA (α6/α3β2β3 chimera)	α-bungarotoxin ($(α7)_5$), α-conotoxin ArIB ($(α7)_5$), α-conotoxin ImI ($(α7)_5$), methyllycaconitine ($(α7)_5$)
Selective channel blockers (IC_{50})	A-867744 (α4β2) [227], NS1738 (α4β2) [237], mecamylamine (α4β4) ($3.3x10^{-7}$ – $4.9x10^{-6}$ M), mecamylamine (α4β2) ($3.6x10^{-6}$ – $4.1x10^{-6}$ M), hexamethonium (α4β2) ($6.8x10^{-6}$ – $2.9x10^{-5}$ M), hexamethonium (α4β4) ($9.1x10^{-5}$ M)	mecamylamine (α6/α3β2β3 chimera) ($1.1x10^{-5}$ M), hexamethonium (α6/α3β2β3 chimera) ($9.1x10^{-5}$ M)	mecamylamine ($(α7)_5$) ($1.56x10^{-5}$ M)
Selective allosteric regulators	LY2087101 (Positive, potentiates α4β2 and α4β4) [206], NS9283 (Positive, α4β2 and α4β4) [225]	–	A-867744 (Positive, $(α7)_5$:Type 2; also blocks α3β4 and α4β2) [227], JNJ1930942 (Positive, $(α7)_5$:Type 1/2) [214], LY2087101 (Positive, $(α7)_5$:Type 1) [206], NS1738 (Positive, $(α7)_5$:Type 1; also blocks α3β4 and α4β2) [237], PNU-120596 (Positive, $(α7)_5$:Type 2) [221]

Nomenclature	α4*	α6*	α7*
Radioligands (K_d)	[^{125}I]epibatidine (α4β2) (1x10^{-11} – 3.3x10^{-11} M), [^{3}H]epibatidine (α4β2) (1x10^{-11} – 3.3x10^{-11} M), [^{3}H]cytisine (α4β2) (1x10^{-10} M - Rat), [^{3}H]cytisine (α4β4) (1x10^{-10} M), [^{125}I]epibatidine (α4β4) (1.87x10^{-10} M), [^{3}H]epibatidine (α4β4) (1.87x10^{-10} M), [^{125}I]epibatidine (α4β2) (3x10^{-10} – 4.6x10^{-10} M - Rat), [^{3}H]epibatidine (α4β2) (3x10^{-10} – 4.6x10^{-10} M - Rat), [^{3}H]nicotine (α4β2) (4x10^{-10} M - Rat), [^{3}H]cytisine (α4β2) (4.3x10^{-10} – 6.3x10^{-10} M), [^{125}I]epibatidine (α4β4) (8.5x10^{-10} – 9.4x10^{-10} M - Rat), [^{3}H]epibatidine (α4β4) (8.5x10^{-10} – 9.4x10^{-10} M - Rat)	[^{125}I]α-conotoxin MII, [^{3}H]epibatidine (native α6β4*) (3.5x10^{-11} M - Chicken)	[^{3}H]epibatidine ($(α7)_5$) (6x10^{-13} M), [^{3}H]A-585539 (native α7) (7x10^{-11} M) [202], [^{3}H]AZ11637326 ($(α7)_5$) (2.3x10^{-10} M) [216], [^{125}I]α-bungarotoxin ($(α7)_5$) (7x10^{-10} – 5x10^{-9} M), [^{3}H]α-bungarotoxin ($(α7)_5$) (7x10^{-10} – 5x10^{-9} M), [^{3}H]methyllycaconitine (native α7*) (1.9x10^{-9} M - Rat)
Functional characteristics	α4β2: P_{Ca}/P_{Na} = 1.65, P_f = 2.6 – 2.9%; α4β4: P_f = 1.5 – 3.0 %	–	P_{Ca}/P_{Na} = 6.6-20, P_f = 8.8 - 11.4%

Nomenclature	α8 (avian)*	α9*
HGNC, UniProt	–	*CHRNA9*, Q9UGM1
Commonly used antagonists	$(α8)_5$: α-bungarotoxin > atropine ≥ (+)-tubocurarine ≥ strychnine	$(α9)_5$: α-bungarotoxin > methyllycaconitine > strychnine ~ tropisetron > (+)-tubocurarine; α9α10: α-bungarotoxin > tropisetron = strychnine > (+)-tubocurarine
Selective antagonists (IC_{50})	–	α-bungarotoxin (α9α10), α-bungarotoxin ($(α9)_5$), α-conotoxin RgIA (α9α10), muscarine (α9α10), muscarine ($(α9)_5$), nicotine (α9α10), nicotine ($(α9)_5$), strychnine (α9α10), strychnine ($(α9)_5$)
Radioligands (K_d)	[^{3}H]epibatidine ($(α8)_5$) (2x10^{-10} M), [^{125}I]α-bungarotoxin (native α8*) (5.5x10^{-9} M), [^{3}H]α-bungarotoxin (native α8*) (5.5x10^{-9} M)	[^{125}I]α-bungarotoxin, [^{3}H]α-bungarotoxin, [^{3}H]methyllycaconitine (α9α10) (7.5x10^{-9} M)
Functional characteristics	–	$(α9)_5$: P_{Ca}/P_{Na} = 9; α9α10: P_{Ca}/P_{Na} = 9, P_f = 22%

Comments: Commonly used agonists of nACh receptors that display limited discrimination in functional assays between receptor subtypes include A-85380, cytisine, DMPP, epibatidine, nicotine and the natural transmitter, acetylcholine (ACh). A summary of their profile across differing receptors is provided in [218] and quantitative data across numerous assay systems are summarized in [222]. Quantitative data presented in the table for commonly used antagonists and channel blockers for human receptors studied under voltage-clamp are from [207,210,230–231,233,240]. Type I PAMs increase peak agonist-evoked responses but have little, or no, effect on the rate of desensitization of α7 nicotinic ACh receptors whereas type II PAMs also cause a large reduction in desensitization (reviewed in [238]).

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P2X receptors

Overview: P2X receptors (nomenclature as agreed by NC-IUPHAR Subcommittee on P2X Receptors, [246,261]) have a trimeric topology [257,260,270] with two putative TM domains, gating primarily Na^+, K^+ and Ca^{2+}, exceptionally Cl^-. 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.* P2X1 in smooth muscle) or heteropolymers (*e.g.* P2X2:P2X3 in the nodose ganglion and P2X1:P2X5 in mouse cortical astrocytes, [265]). P2X2, P2X4 and P2X7 receptors have been shown to form functional homopolymers which, in turn, activate pores permeable to low molecular weight solutes [276]. The hemi-channel pannexin-1 has been implicated in the pore formation induced by P2X7 [272], but not P2X2 [245], receptor activation.

Subunits

Nomenclature	P2X1	P2X2	P2X3	P2X4	P2X5	P2X6	P2X7
HGNC, UniProt	*P2RX1*, P51575	*P2RX2*, Q9UBL9	*P2RX3*, P56373	*P2RX4*, Q99571	*P2RX5*, Q93086	*P2RX6*, O15547	*P2RX7*, Q99572
Agonists	αβ-meATP (Full agonist), BzATP (Full agonist), L-βγ-meATP (Full agonist)	–	αβ-meATP (Full agonist), BzATP (Full agonist)	–	–	–	–
Antagonists (IC_{50})	TNP-ATP (~$1.3x10^{-9}$ M) [277], Ip_5I (~$3.2x10^{-9}$ M), NF023 (~$2x10^{-7}$ M), NF449 (~$5x10^{-7}$ M) [259]	–	TNP-ATP (~$1.3x10^{-9}$ M) [277], AF353 (~$1x10^{-8}$ M) [253], A317491 (~$3.1x10^{-8}$ M) [256], RO3 (~$3.1x10^{-8}$ M) [251]	–	–	–	decavanadate (pA_2 = 7.4) [269], A804598 (~$1x10^{-8}$ M), brilliant blue G (~$1x10^{-8}$ M) [258], A839977 (~$2x10^{-8}$ M) [248,250,254], A740003 (~$4x10^{-8}$ M), A438079 (~$1.25x10^{-7}$ M) [248]
Selective allosteric regulators	MRS 2219 (Positive) [255]	–	–	ivermectin (Positive) (Rat) [262]	–	–	AZ11645373 (Negative) [267,275], chelerythrine (Negative) [273], ivermectin (Positive) [271], KN62 (Negative) [252,273]
Comment	–	–	–	–	–	–	Effects of the allosteric modulators at P2X7 receptors are species-dependent

Comments: A317491 and RO3 also block the P2X2:P2X3 heteromultimer [251,256]. NF449, A317491 and RO3 are more than 10-fold selective for P2X1 and P2X3 receptors, respectively.

Agonists listed show selectivity within recombinant P2X receptors of *ca*. one order of magnitude. A804598, A839977, A740003 and A438079 are at least 10-fold selective for P2X7 receptors and show similar affinity across human and rodent receptors [248,250,254].

Several P2X receptors (particularly P2X1 and P2X3) may be inhibited by desensitisation using stable agonists (*e.g.* αβ-meATP); suramin and PPADS are non-selective antagonists at r & hP2X1–3,5 and hP2X4, but not rP2X4,6,7 [244], and can also inhibit ATPase activity [247]. Ip_5I is inactive at rP2X2, an antagonist at rP2X3 (pIC_{50} 5.6) and enhances agonist responses at rP2X4 [263]. Antagonist potency of NF023 at recombinant P2X2, P2X3 and P2X5 is two orders of magnitude lower than that at P2X1 receptors [274]. The P2X7 receptor may be inhibited in a non-competitive manner by the protein kinase inhibitors KN62 and chelerythrine [273], while the p38 MAP kinase inhibitor GTPγS and the cyclic imide AZ11645373 show a species-dependent non-competitive action [249,267–268,275]. The pH-sensitive dye used in culture media, phenol red, is also reported to inhibit P2X1 and P2X3 containing channels [264]. Some recombinant P2X receptors expressed to high density bind [^{35}S]ATPγS and [^{3}H]αβ-meATP, although the latter can also bind to 5′-nucleotidase [266]. [^{3}H]A317491 and [^{3}H]A804598 have been used as high affinity antagonist radioligands for P2X3 (and P2X2/3) and P2X7 receptors, respectively [250].

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ZAC

Overview: The zinc-activated channel [ZAC, nomenclature as agreed by the NC-IUPHAR Subcommittee for the zinc activated channel] is a member of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT_3, $GABA_A$ and strychnine-sensitive glycine receptors [278–279]. The channel is likely to exist as a homopentamer of 4TM subunits that form an intrinsic cation selective channel displaying constitutive activity that can be blocked by (+)-tubocurarine. ZAC is present in the human, chimpanzee, dog, cow and opossum genomes, but is functionally absent from mouse, or rat, genomes [278–279].

Subunits

Nomenclature	HGNC, UniProt	Endogenous agonists (EC_{50})	Selective antagonists (IC_{50})	Functional characteristics	Comment
ZAC	*ZACN*, Q401N2	Zn^{2+} (Selective) ($5x10^{-4}$ M) [278]	(+)-tubocurarine ($6.3x10^{-6}$ M) [278]	Outwardly rectifying current (both constitutive and evoked by Zn^{2+})	Although tabulated as an antagonist, it is possible that (+)-tubocurarine acts as a channel blocker

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