The Concise Guide to PHARMACOLOGY 2015/16

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THE CONCISE GUIDE TO PHARMACOLOGY 2015/16: Ligand-gated ion channels

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Abstract

The Concise Guide to PHARMACOLOGY 2015/16 provides concise overviews of the key properties of over 1750 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.13350/full. Ligand-gated ion channels are one of the eight major pharmacological targets into which the Guide is divided, with the others being: ligand-gated ion channels, voltage-gated ion channels, other ion channels, nuclear hormone receptors, catalytic receptors, enzymes and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The Concise Guide is published in landscape format in order to facilitate comparison of related targets. It is a condensed version of material contemporary to late 2015, which is presented in greater detail and constantly updated on the website www.guidetopharmacology.org, superseding data presented in the previous Guides to Receptors & Channels and the Concise Guide to PHARMACOLOGY 2013/14. 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 GRAC and provides a permanent, citable, point-in-time record that will survive database updates.

Conflict of Interest

The authors state that there are no conflicts of interest to declare.

Overview: 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. These channels are open, 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 neuron 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 [48, 236], 5-HT3 [20, 353], ionotropic glutamate [208, 338] and P2X receptors [158, 321] and the inhibitory, anion-selective, GABAA [25, 264] and glycine receptors [215, 373]. The nicotinic acetylcholine, 5-HT3, GABAA 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 [238, 327]. 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 [133]. 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 combinatorial 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 [88] will greatly aid in the development of such agents.

**Family structure**

| S871 | 5-HT3 receptors |
| S873 | Acid-sensing (proton-gated) ion channels (ASICs) |
| S875 | Epithelial sodium channels (ENaC) |
| S877 | GABA_A receptors |

| S882 | Glycine receptors |
| S885 | Ionotropic glutamate receptors |
| S891 | P3 receptor |
| S892 | Nicotinic acetylcholine receptors |
| S896 | P2X receptors |
| S898 | Ryanodine receptor |
| S900 | ZAC |

**5-HT3 receptors**

**Ligand-gated ion channels → 5-HT3 receptors**

**Overview:** The 5-HT3 receptor (nomenclature as agreed by the NC-IUPHAR Subcommittee on 5-Hydroxytryptamine (serotonin) receptors [145]) 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 [20]. Five human 5-HT3 receptor subunits have been cloned and homo-oligomeric assemblies of 5-HT3A and hetero-oligomeric assemblies of 5-HT3A and 5-HT3B subunits have been characterised in detail. The 5-HT3C (HTR3C, Q8WXB8), 5-HT3D (HTR3D, Q70244) and 5-HT3E (HTR3E, Q5X8Y0) subunits [173, 256], like the 5-HT3B subunit, do not form functional homomers, but are reported to assemble with the 5-HT3A subunit to influence its functional expression rather than pharmacological profile [136, 258, 352]. 5-HT3A, -C, -D, and -E subunits also interact with the chaperone RIC-3 which predominantly enhances the surface expression of homomeric 5-HT3A receptor [352]. The co-expression of 5-HT3A and 5-HT3C-E subunits has been demonstrated in human colon [170]. A recombinant hetero-oligomeric 5-HT3AB receptor has been reported to contain two copies of the 5-HT3A subunit and three copies of the 5-HT3B subunit in the order B-B-A-B-A [23], but this is inconsistent with recent reports which show at least one A-A interface [207, 331]. The 5-HT3B subunit imparts distinctive biophysical properties upon hetero-oligomeric 5-HT3AB versus homo-oligomeric 5-HT3A recombinant receptors [68, 86, 124, 160, 178, 277, 317], influences the potency of channel blockers, but generally has only a modest effect upon the apparent affinity of agonists, or the affinity of antagonists ([36], but see [67, 71, 86]) which may be explained by the orthosteric binding site residing at an interface formed between 5-HT3A subunits [207, 331]. However, 5-HT3A and 5-HT3AB receptors differ in their allostatic regulation by some general anaesthetic agents, small alcohols and indoles [146, 293, 314]. The potential diversity of 5-HT3 receptors is increased by alternative splicing of the genes HTR3A and E [39, 139, 255, 257, 258]. In addition, the use of tissue-specific promoters driving expression from different transcriptional start sites has been reported for theHTR3A, HTR3B, HTR3D and HTR3E genes, which could result in 5-HT3 subunits harbouring different N-termini [160, 255, 339]. To date, inclusion of the 5-HT3A subunit appears imperative for 5-HT3 receptor function.

| Nomenclature | 5-HT3AB |
|--------------|---------|
| Subunits     | 5-HT3A, 5-HT3B |
| Functional Characteristics | $\gamma = 0.4-0.8$ pS [$+ 5$-HT3B, rectification reduced]; $n_+ ^{2-3} [+ 5$-HT3B 1-2]; relative permeability to divalent cations reduced by co-expression of the 5-HT3B subunit |

| Nomenclature | 5-HT3A |
|--------------|---------|
| Subunits     | 5-HT3A |
| Functional Characteristics | $\gamma = 0.4-0.8$ pS [$+ 5$-HT3B, $\gamma = 16$ pS]; inwardly rectifying current [$+ 5$-HT3B, rectification reduced]; $n_+ ^{2-3} [+ 5$-HT3B 1-2]; relative permeability to divalent cations reduced by co-expression of the 5-HT3B subunit |
### Subunits

| Nomenclature | 5-HT₃AB |
|--------------|---------|
| Selective agonists | – |
| Antagonists | – |
| Channel blockers | picrotoxin (pIC₅₀ 4.2) [326], bilobalide (pIC₅₀ 2.5) [326], ginkgolide B (pIC₅₀ 2.4) [326] |
| Labelled ligands | – |

### Nomenclature

| Subunit | HTR3A, HTR3B, HTR3C, HTR3D, HTR3E |
|---------|----------------------------------|
| Nomenclature | 5-HT₃A, 5-HT₃B, 5-HT₃C, 5-HT₃D, 5-HT₃E |
| HGNC, UniProt | HTR3A, P46098, HTR3B, Q95264, HTR3C, Q8WXA8, HTR3D, Q7QZ44, HTR3E, AXS5Y0 |
| Functional Characteristics | γ = 0.4–0.8 pS [5-HT₃B, γ = 16 pS]; inwardly rectifying current [5-HT₃B, rectification reduced]; n₁₂ = 2–3 [5-HT₃B 1–2]; relative permeability to divalent cations reduced by co-expression of the 5-HT₃B subunit |
| Antagonists | – |
| Selective antagonists | – |
| Channel blockers | picrotoxin (pIC₅₀ 5) [325], TMB-8 (pIC₅₀ 4.9) [320], diltiazem (pIC₅₀ 4.7) [325], bilobalide (pIC₅₀ 3.3) [325], ginkgolide B (pIC₅₀ 3.1) [325] |
| Labelled ligands | – |

### Comments:

Quantitative data in the table refer to homooligomeric assemblies of the human 5-HT₃A subunit, or the receptor native to human tissues. Significant changes introduced by co-expression of the 5-HT₃B subunit are indicated in parenthesis. Although not a selective antagonist, methadone displays multimodal and subunit-dependent antagonism of 5-HT₃ receptors [71]. Similarly, TMB-8, diltiazem, picrotoxin, bilobalide and ginkgolide B are not selective for 5-HT₃ receptors (e.g., [326]). The anti-malarial drugs mefloquine and quinine exert a modestly more potent block of 5-HT₃A versus 5-HT₃AB receptor-mediated responses [328]. Known better as a partial agonist of the 5-HT₃A receptor [213], Human [24, 241], rat [151], mouse [224], guinea-pig [196] ferret [243] and canine [162] orthologues of the 5-HT₃A receptor subunit have been cloned that exhibit intraspecies variations in receptor pharmacology. Notably, most ligands display significantly reduced affinities at the guinea-pig 5-HT₃ receptor in comparison with other species. In addition to the agents listed in the table, native and recombinant 5-HT₃ receptors are subject to allosteric modulation by extracellular divalent cations, alcohols, several general anaesthetics and 5-hydroxy- and halide-substituted indoles (see reviews [272, 329, 330, 353]).
Acid-sensing (proton-gated) ion channels (ASICs)

Ligand-gated ion channels → Acid-sensing (proton-gated) ion channels (ASICs)

Overview: Acid-sensing ion channels (ASICs) are members of a superfamily of proteins that include the epithelial Na+ channel (ENaC), the FMRF-amide activated channel of invertebrates, the degenerins (DEG) of Caenorhabditis elegans, channels in Drosophila melanogaster and ‘orphan’ channels that include BLINaC. ASIC subunits contain two TM domains and assemble as homo- or hetero-trimers to form proton-gated, voltage-insensitive, Na+ permeable, channels (reviewed in [119]). Splice variants of ASIC1 [provisionally termed ASIC1a (ASIC, ASICα, BNaC2a) [349], ASIC1b (ASICβ, BNaC2β) [54] and ASIC1b2 (ASIC(2)) [340]; note that ASIC1a is also permeable to Ca2+] and ASIC2 [provisionally termed ASIC2a (MDEG1, BNaC1α, BNC1α) [109, 284, 350] and ASIC2b (MDEG2, BNaC1β) [205]] have been cloned. Unlike ASIC2a (listed in table), heterologous expression of ASIC2b alone does not support H+-gated currents. A third member, ASIC3 (DRASIC, TNaC1) [348], has been identified. A fourth mammalian member of the family (ASIC4/SPASIC) does not support a proton-gated channel in heterologous expression systems and is reported to down regulate the expression of ASIC1a and ASIC3 [5, 80, 120]. ASIC channels are primarily expressed in central and peripheral neurons including nociceptors where they participate in neuronal sensitivity to acidosis. They have also been detected in taste receptors (ASIC1-3), photoreceptors and retinal cells (ASIC1-3), cochlear hair cells (ASIC1b), testis (hASIC3), pituitary gland (ASIC4), lung epithelial cells (ASIC1a and -3), urothelial cells, adipose cells (ASIC3), vascular smooth muscle cells (ASIC1-3), immune cells (ASIC1, -3 and -4) and bone (ASIC1-3). The activation of ASIC1a within the central nervous system contributes to neuronal injury caused by focal ischemia and to axonal degeneration in autoimmune inflammation in a mouse model of multiple sclerosis. However, activation of ASIC1a can terminate seizures. Peripheral ASIC3-containing channels play a role in post-operative pain. Further proposed roles for centrally and peripherally located ASICs are reviewed in and [203]. The relationship of the cloned ASICs to endogenously expressed proton-gated ion channels is becoming established. Acid-sensing ion channels, ion selectivity, pH-sensitive and sensitivity to blockers that resemble some of the native proton activated currents recorded from neurones [15, 22, 94, 205].
ASIC1

Nomenclature

 ASIC1a: γ 14pS
 pNa/PK = 5-13, pNa/Pca = 2.5
 rapid activation rate (5.8-13.7 ms), rapid
 inactivation rate (1.2-4 s) @ pH 7.4
 ASIC1b: γ 19 pS
 pNa/PK = 14.0, pNa/Pca (transient component)
 rapid activation rate (9.9 ms), rapid inactivation
 rate (0.9-1.7 s) @ pH 6.0, slow recovery (4.4-7.7
 s) @ pH 7.4

Endogenous activators

 Extrinsic H+ (ASIC1a) (pEC50 ~ 6.2–6.8),
 Extrinsic H+ (ASIC1b) (pEC50 ~ 5.1–6.2)

Activators

 –

Channel blockers

 psalmotoxin 1 (ASIC1a) (pEC50 ~ 9), Zn2+ (ASIC1a)
 (pEC50 ~ 8.2), Pb2+ (ASIC1b) (pEC50 ~ 5.8),
 A-317567 (ASIC1a) (pEC50 ~ 5.7) [87] – Rat, Pb2+
 (ASIC1a) (pEC50 ~ 5.4), amiloride (ASIC1a) (pEC50
 S), benzamil (ASIC1a) (pEC50 S),
 ethylisopropylamiloride (ASIC1a) (pEC50 S),
 nafamostat (ASIC1a) (pIC50 ~ 4.9), amiloride
 (ASIC1b) (pEC50 4.6–4.7), flurbiprofen (ASIC1a)
 (pEC50 3.5) [345] – Rat, ibuprofen (ASIC1a)
 (pEC50 ~ 3.5), Ni2+ (ASIC1a) (pEC50 ~ 3.2)

Labelled ligands

 [125I]psalmotoxin 1 (ASIC1a) (pKd 9.7)

Comments

 ASIC1a and ASIC1b are also blocked by
 diarylamidines (IC50 3 μM for ASIC1a)

 ASIC2

 Nomenclature

 ASIC2: γ 10.4-13.4 pS
 pNa/PK = 10, pNa/Pca = 20
 rapid activation rate, moderate inactivation rate
 (3.3-5.5 s) @ pH 5

Endogenous activators

 Extracellular H+ (pEC50 ~ 4.1–5)

Activators

 –

Channel blockers

 amiloride (pEC50 4.6), A-317567 (pEC50 ~ 4.5),
 nafamostat (pEC50 ~ 4.2), Cd2+ (pEC50 ~ 3)

Labelled ligands

 –

Comments

 ASIC2 is also blocked by diarylamidines

ASIC3

 Nomenclature

 ASIC3: γ 13-15 pS;
 biphase response consisting of rapidly
 inactivating transient and sustained
 components:
 very rapid activation (~5 ms) and inactivation
 (0.4 s);
 fast recovery (0.4-0.6 s) @ pH 7.4, transient
 component partially inactivated at pH 7.2

Endogenous activators

 Extracellular H+ (transient component) (pEC50
 ~ 6.2–6.7), Extracellular H+ (sustained
 component) (pEC50 ~ 3.5–4.3)

Activators

 –

Channel blockers

 GMQ (largely non-desensitizing; at pH 7.4)
 (pEC50 ~ 3), aracine (at pH 7.4) (pEC50 ~ 2.9),
 agmatine (at pH 7.4) (pEC50 ~ 2)

Labelled ligands

 APETx2 (transient component only) (pIC50 7.2),
 nafamostat (transient component) (pEC50
 ~ 5.6), A-317567 (pEC50 ~ 5), amiloride
 (transient component only - sustained
 component enhanced by 200μM amiloride at
 pH 4) (pIC50 4.2–4.8), Cd2+ (pEC50 4.4), Zn2+
 (pEC50 4.2), aspirin (sustained component)
 (pEC50 4) [345], diclofenac (sustained
 component) (pEC50 4), salicylic acid
 (sustained component) (pEC50 3.6)

Comments

 ASIC3 is also blocked by diarylamidines

Acid-sensing (proton-gated) ion channels (ASICs)
Zn$^{2+}$ indicating complex biphasic actions of the divalent [60]. Nitric oxide potentiates submaximal currents activated by H$^+$ mediated by ASIC1a, ASIC1b, ASIC2a and ASIC3 [42]. Ammonium activates ASIC channels (most likely ASIC1a) in midbrain dopaminergic neurones; that may be relevant to neuronal disorders associated with hyperammonemia [278]. The positive modulation of homomeric, heteromeric and native ASIC channels by the peptide FMRFamide and related substances, such as neuropeptides FF and SF, is reviewed in detail in [204]. Inflammatory conditions and particular pro-inflammatory mediators induce overexpression of ASIC-encoding genes, enhance ASIC currents [223], and in the case of arachidonic acid directly activate the channel [75, 310]. The sustained current component mediated by ASIC3 is potentiated by hypertonic solutions in a manner that is synergistic with the effect of arachidonic acid [75]. Selective activation of ASIC3 by GMQ at a site separate from the proton binding site is potentiated by mild acidosis and reduced extracellular Ca$^{2+}$ [376].

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Epithelial sodium channels (ENaC)

Ligand-gated ion channels → Epithelial sodium channels (ENaC)

Overview: The epithelial sodium channels (ENaC) mediate sodium reabsorption in the aldosterone-sensitive distal part of the nephron and the collecting duct of the kidney. ENaC is found on other tight epithelial tissues such as the Airways, distal colon and exocrine glands. ENaC activity is tightly regulated in the kidney by aldosterone, angiotensin II (AGT, P01019), vasopressin (AVP, P01185), insulin (INS, P01308) and glucocorticoids; this fine regulation of ENaC is essential to maintain sodium balance between daily intake and urinary excretion of sodium, circulating volume and blood pressure. ENaC expression is also vital for clearance of foetal lung fluid, and to maintain air-surface-liquid [147, 209]. Sodium reabsorption is suppressed by the ‘potassium-sparing’ diuretics amiloride and triamterene. ENaC is a heteromultimeric channel made of homologous αβ and γ subunits. The primary structure of αENaC subunit was identified by expression cloning [43]; β and γ ENaC were identified by functional complementation of the α subunit [44]. Each ENaC subunit contains 2 TM α helices connected by a large extracellular loop and short cytoplasmic amino- and carboxy-termini. The stoichiometry of the epithelial sodium channel in the kidney and related epithelia is, by homology with the structurally related channel ASIC1a, thought to be a heterotrimer of 1α:1β:1γ subunits [114].

| Nomenclature | ENaCαβγ |
|--------------|---------|
| Subunits     | ENaC β, ENaC α, ENaC γ |

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Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13350/full
Subunits

| Nomenclature | ENaC α | ENaC β | ENaC δ | ENaC γ |
|--------------|--------|--------|--------|--------|
| HGNC, UniProt | SCNN1A, P37088 | SCNN1B, P51168 | SCNN1D, P51172 | SCNN1G, P51170 |

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GABA<sub>A</sub> receptors

Ligand-gated ion channels → GABA<sub>A</sub> receptors

Overview: The GABA<sub>A</sub> receptor is a ligand-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT<sub>3</sub>, and strychnine-sensitive glycine receptors. GABA<sub>A</sub> receptor-mediated inhibition within the CNS occurs by fast synaptic transmission, sustained tonic inhibition and temporally intermediate events that have been termed ‘GABA<sub>A</sub>, slow’ [45]. GABA<sub>A</sub> 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<sub>A</sub> receptor subunits have been reported in mammals [263, 264, 305, 307]. 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 [66]. The three ρ-subunits, (ρ1-3) function as either homo- or hetero-oligomeric assemblies [53, 380]. Receptors formed from ρ-subunits, because of their distinctive pharmacology that includes insensitivity to bicuculline, benzodiazepines and barbiturates, have sometimes been termed GABA<sub>C</sub> receptors [380]. But they are classified as GABA<sub>A</sub> receptors by NC-IUPHAR on the basis of structural and functional criteria [19, 263, 264].

Many GABA<sub>A</sub> receptor subtypes contain α-, β- and γ-subunits with the likely stoichiometry 2α2βδγ1γ [190, 264]. It is thought that the majority of GABA<sub>A</sub> receptors harbour a single type of α- and β-subunit variant. The α1β2γ2 hetero-oligomer constitutes the largest population of GABA<sub>A</sub> 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 [25, 96, 244, 301, 311]. GABA binding occurs at the β4/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 α5/β-interface [286]; reviewed by [306]. 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 [374]). The trafficking, cell surface expression, internalisation and function of GABA<sub>A</sub> receptors and their subunits are discussed in detail in several recent reviews [58, 153, 214, 343] 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 those incorporating the δ subunit appear to be exclusively extrasynaptic.

NC-IUPHAR [19, 264] class the GABA<sub>A</sub> receptors according to their subunit structure, pharmacology and receptor function. Currently, eleven native GABA<sub>A</sub> receptor classes are ascribed unambiguously to specific subunits (i.e., α1β2γ2, α1β1γ2, α3β2γ2, α4β2γ2, α4β3γ2, α5β2γ2, α6β2γ2, α6β3γ2 and ρ) with further receptor isoforms occurring with high probability, or only tentatively [263, 264]. It is beyond the scope of this Guide to discuss the pharmacology of individual GABA<sub>A</sub> receptor isoforms in detail; such information is available in the reviews [19, 104, 165, 190, 192, 249, 263, 264, 305] and [11, 12]. 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 [53, 166, 253, 380].
GABA<sub>A</sub> receptor α1 subunit
bicuculline [GABA site], gabazine [GABA site]

GABA<sub>A</sub> receptor α2 subunit
bicuculline [GABA site], gabazine [GABA site]

GABA<sub>A</sub> receptor α3 subunit
bicuculline [GABA site], gabazine [GABA site]

Channel blockers
TPBS, picrotoxin

Endogenous allosteric modulators
5α-pregn-3α-ol-20-one (Potentiation), Zn<sup>2+</sup> (Inhibition), tetrahydrodeoxycorticosterone (Potentiation)

Nomenclature
GABA<sub>A</sub> receptor α1 subunit
clonazepam (Positive) (pK<sub>I</sub> 8.9) [285], flunitrazepam [benzodiazepine site] (Positive) (pK<sub>I</sub> 8.3) [122], diazepam [benzodiazepine site] (Positive) (pK<sub>I</sub> 7.8) [285], alprazolam [benzodiazepine site] (Positive) (pEC<sub>50</sub> 7.4) [6], α3IA [benzodiazepine site] (Inverse agonist), α5IA [benzodiazepine site] (Inverse agonist), DMCM [benzodiazepine site] (Inverse agonist), MRK016 [benzodiazepine site] (Inverse agonist), RO4938581 [benzodiazepine site] (Inverse agonist), Ro15-4513 [benzodiazepine site] (Inverse agonist), Ro19-4603 [benzodiazepine site] (Inverse agonist), TP003 [benzodiazepine site] (Antagonist), TPA023 [benzodiazepine site] (Antagonist), bretabenil [benzodiazepine site] (Full agonist), flumazenil [benzodiazepine site] (Partial agonist)

Selective allosteric modulators
zolpidem (Positive) (pK<sub>I</sub> 7.4–7.7) [123, 299], L838417 [benzodiazepine site] (Antagonist), ZK93426 [benzodiazepine site] (Antagonist), indiplon [benzodiazepine site] (Full agonist), oacinaplon [benzodiazepine site] (Full agonist)

Labelled ligands
[<sup>11</sup>C]Flumazenil [benzodiazepine site] (Allosteric modulator, Antagonist), [<sup>18</sup>F]Fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator, Antagonist), [<sup>35</sup>S]TPBS [anion channel] (Channel blocker), [<sup>3</sup>H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [<sup>3</sup>H]Flunitrazepam [benzodiazepine site] (Allosteric modulator, Positive), [<sup>3</sup>H]Gabazine [GABA site] (Antagonist), [<sup>3</sup>H]Muscimol [GABA site] (Agonist), [<sup>3</sup>H]Zolpidem [benzodiazepine site] (Allosteric modulator, Positive)

Comments
Zn<sup>2+</sup> is an endogenous allosteric regulator and causes potent inhibition of receptors formed by binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [191]

Clonazepam (Positive) (pK<sub>I</sub> 8.9) [285], flunitrazepam [benzodiazepine site] (Positive) (pK<sub>I</sub> 8.3) [122], diazepam [benzodiazepine site] (Positive) (pK<sub>I</sub> 7.8) [285], alprazolam [benzodiazepine site] (Positive) (pEC<sub>50</sub> 7.4) [6], α3IA [benzodiazepine site] (Inverse agonist), α5IA [benzodiazepine site] (Inverse agonist), DMCM [benzodiazepine site] (Inverse agonist), MRK016 [benzodiazepine site] (Inverse agonist), RO4938581 [benzodiazepine site] (Inverse agonist), Ro15-4513 [benzodiazepine site] (Inverse agonist), Ro19-4603 [benzodiazepine site] (Inverse agonist), TP003 [benzodiazepine site] (Antagonist), TPA023 [benzodiazepine site] (Antagonist), bretabenil [benzodiazepine site] (Full agonist), flumazenil [benzodiazepine site] (Partial agonist)

Selective allosteric modulators
zolpidem (Positive) (pK<sub>I</sub> 7.4–7.7) [123, 299], L838417 [benzodiazepine site] (Antagonist), ZK93426 [benzodiazepine site] (Antagonist), indiplon [benzodiazepine site] (Full agonist), oacinaplon [benzodiazepine site] (Full agonist)

Labelled ligands
[<sup>11</sup>C]Flumazenil [benzodiazepine site] (Allosteric modulator, Antagonist), [<sup>18</sup>F]Fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator, Antagonist), [<sup>35</sup>S]TPBS [anion channel] (Channel blocker), [<sup>3</sup>H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [<sup>3</sup>H]Flunitrazepam [benzodiazepine site] (Allosteric modulator, Positive), [<sup>3</sup>H]Gabazine [GABA site] (Antagonist), [<sup>3</sup>H]Muscimol [GABA site] (Agonist)

Comments
Zn<sup>2+</sup> is an endogenous allosteric regulator and causes potent inhibition of receptors formed by binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [191]

Clonazepam (Positive) (pK<sub>I</sub> 8.9) [285], flunitrazepam [benzodiazepine site] (Positive) (pK<sub>I</sub> 8.3) [122], diazepam [benzodiazepine site] (Positive) (pK<sub>I</sub> 7.8) [285], alprazolam [benzodiazepine site] (Positive) (pEC<sub>50</sub> 7.4) [6], α3IA [benzodiazepine site] (Inverse agonist), α5IA [benzodiazepine site] (Inverse agonist), DMCM [benzodiazepine site] (Inverse agonist), MRK016 [benzodiazepine site] (Inverse agonist), RO4938581 [benzodiazepine site] (Inverse agonist), Ro15-4513 [benzodiazepine site] (Inverse agonist), Ro19-4603 [benzodiazepine site] (Inverse agonist), TP003 [benzodiazepine site] (Antagonist), TPA023 [benzodiazepine site] (Antagonist), bretabenil [benzodiazepine site] (Full agonist), flumazenil [benzodiazepine site] (Partial agonist)

Selective allosteric modulators
zolpidem (Positive) (pK<sub>I</sub> 7.4–7.7) [123, 299], L838417 [benzodiazepine site] (Antagonist), ZK93426 [benzodiazepine site] (Antagonist), indiplon [benzodiazepine site] (Full agonist), oacinaplon [benzodiazepine site] (Full agonist)

Labelled ligands
[<sup>11</sup>C]Flumazenil [benzodiazepine site] (Allosteric modulator, Antagonist), [<sup>18</sup>F]Fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator, Antagonist), [<sup>35</sup>S]TPBS [anion channel] (Channel blocker), [<sup>3</sup>H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [<sup>3</sup>H]Flunitrazepam [benzodiazepine site] (Allosteric modulator, Positive), [<sup>3</sup>H]Gabazine [GABA site] (Antagonist), [<sup>3</sup>H]Muscimol [GABA site] (Agonist)
| Nomenclature | GABA<sub>A</sub> receptor α4 subunit | GABA<sub>A</sub> receptor α5 subunit | GABA<sub>A</sub> receptor α6 subunit |
|-------------|----------------------------------|----------------------------------|----------------------------------|
| HGNC, UniProt | GABRA4, P48169 | GABRA5, P316444 | GABRA6, Q16445 |
| Agonists | gaboxadol [GABA site], isoguvacine [GABA site], muscimol [GABA site], piperidine-4-sulphonic acid [GABA site] (low efficacy) | gaboxadol [GABA site], isoguvacine [GABA site], isonipecotic acid [GABA site], muscimol [GABA site], piperidine-4-sulphonic acid [GABA site] | gaboxadol [GABA site], isoguvacine [GABA site], muscimol [GABA site], piperidine-4-sulphonic acid [GABA site] (low efficacy) |
| Selective agonists | isonipecotic acid [GABA site] (relatively high efficacy) | – | isonipecotic acid [GABA site] (relatively high efficacy) |
| Selective antagonists | bicuculline [GABA site], gabazine [GABA site] | bicuculline [GABA site], gabazine [GABA site] | bicuculline [GABA site], gabazine [GABA site] |
| Channel blockers | TBPS, picrotoxin | TBPS, picrotoxin | TBPS, picrotoxin |
| Endogenous allosteric modulators | 5α-pregnan-3α-ol-20-one (Potentiation), Zn<sup>2+</sup> (Inhibition), tetrahydrodeoxycorticosterone (Potentiation) | flunitrazepam [benzodiazepine site] (Potentiation) (p<sub>K</sub>, 8.3) [122], alprazolam [benzodiazepine site] (Positive) (pEC<sub>50</sub> 8) [6], α5IA [benzodiazepine site] (Inverse agonist), DMCM [benzodiazepine site] (Inverse agonist), Ro15-4513 [benzodiazepine site] (Inverse agonist), Ro19-4603 [benzodiazepine site] (Inverse agonist), TP003 [benzodiazepine site] (Antagonist), TP4023 [benzodiazepine site] (Antagonist), ZK93426 [benzodiazepine site] (Antagonist), bretazenil [benzodiazepine site] (Inverse agonist), flumazenil [benzodiazepine site] (Full agonist), gabazine [benzodiazepine site] (Antagonist), ocicnapon [benzodiazepine site] (Inverse agonist) | 5α-pregnan-3α-ol-20-one (Potentiation), Zn<sup>2+</sup> (Inhibition), tetrahydrodeoxycorticosterone (Potentiation) bretazenil [benzodiazepine site] (Full agonist), flumazenil [benzodiazepine site] (Partial agonist) |
| Allosteric modulators | flumazenil (Partial agonist) | flumazenil (Partial agonist) | flumazenil (Partial agonist) |
| Selective allosteric modulators | Ro15-4513 [benzodiazepine site] (Full agonist), bretazenil [benzodiazepine site] (Full agonist) | α5IA [benzodiazepine site] (Inverse agonist), L655708 [benzodiazepine site] (Inverse agonist), L838417 [benzodiazepine site] (Partial agonist), MRK016 [benzodiazepine site] (Inverse agonist), RO4938581 [benzodiazepine site] (Inverse agonist), ROY24 [benzodiazepine site] (Inverse agonist) | Ro15-4513 [benzodiazepine site] (Full agonist) |
| Labelled ligands | [11C]flumazenil [benzodiazepine site] (Allosteric modulator, Partial agonist), [18F]fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator, Antagonist), [35S]TBPS [anion channel] (Channel blocker), [3H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [3H]Ro154513 [benzodiazepine site] (Allosteric modulator, Full agonist), [3H]muscimol [GABA site] (Antagonist), [3H]muscimol [GABA site] (Agonist), [3H]Ro154513 [benzodiazepine site] (Allosteric modulator, Antagonist), [3H]muscimol [GABA site] (Agonist) | [3H]flumazenil [benzodiazepine site] (Selective Binding) (p<sub>K</sub>, 9.2) [309] – Rat, [11C]flumazenil [benzodiazepine site] (Allosteric modulator, Antagonist), [18F]fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator, Antagonist), [35S]TBPS [anion channel] (Channel blocker), [3H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [3H]L655708 [benzodiazepine site] (Allosteric modulator, Inverse agonist), [3H]flunitrazepam [benzodiazepine site] (Allosteric modulator, Full agonist), [3H]gabazine [GABA site] (Antagonist), [3H]muscimol [GABA site] (Agonist) | [11C]flumazenil [benzodiazepine site] (Allosteric modulator, Partial agonist), [18F]fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator, Antagonist), [35S]TBPS [anion channel] (Channel blocker), [3H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [3H]Ro154513 [benzodiazepine site] (Allosteric modulator, Full agonist), [3H]gabazine [GABA site] (Antagonist), [3H]muscimol [GABA site] (Agonist) |

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Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13350/full

GABA<sub>A</sub> receptors 5879
### Nomenclature

#### GABA<sub>A</sub> receptor α4 subunit
- **GABRA1**, P18505

#### GABA<sub>A</sub> receptor α5 subunit
- **GABRA5**, P47870

#### GABA<sub>A</sub> receptor α6 subunit
- **GABRA6**, P47870

#### Comments
- Diazepam and flunitrazepam are not active at this subunit. Zn<sup>2+</sup> 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 [191]. [3H]Ro154513 selectively labels α4-subunit-containing receptors in the presence of a saturating concentration of a ‘classical’ benzodiazepine (e.g. diazepam)

### Nomenclature

#### GABA<sub>A</sub> receptor β1 subunit
- **GABRB1**, P18505

#### GABA<sub>A</sub> receptor β2 subunit
- **GABRB2**, P47870

#### GABA<sub>A</sub> receptor β3 subunit
- **GABRB3**, P28472

#### GABA<sub>A</sub> receptor γ1 subunit
- **GABRG1**, Q8N1C3

#### GABA<sub>A</sub> receptor γ2 subunit
- **GABRG2**, P18507

#### Comments
- Zn<sup>2+</sup> 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 [191]. [3H]Ro154513 selectively labels α6-subunit-containing receptors in the presence of a saturating concentration of a ‘classical’ benzodiazepine (e.g. diazepam)

### Nomenclature

#### GABA<sub>A</sub> receptor γ3 subunit
- **GABRG3**, Q99928

#### GABA<sub>A</sub> receptor δ subunit
- **GABRD**, O14764

#### GABA<sub>A</sub> receptor ε subunit
- **GABRE**, P78334

#### GABA<sub>A</sub> receptor θ subunit
- **GABRQ**, Q9UN88

#### GABA<sub>A</sub> receptor π subunit
- **GABRP**, O00591

#### Comments
- Zn<sup>2+</sup> 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 [191].

### Allosteric modulators

- **etazolate** (Binding) (pIC<sub>50</sub> 5.5) [378]

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- Full Contents of ConciseGuide: [http://onlinelibrary.wiley.com/doi/10.1111/bph.13350/full](http://onlinelibrary.wiley.com/doi/10.1111/bph.13350/full)
The presence of the low efficacy agonist [3H]azetomidate is proposed to occur at a distinct locus. Many intravenous anaesthetics and alcohols also exert a regulatory influence upon GABA_A receptor activity. Specific amino acid residues within constituent GABA_A receptor subunits influence allosteric regulation by anesthetic and non-anesthetic compounds have been identified. Photoaffinity labeling of distinct amino acid residues within purified GABA_A receptors by the etomidate derivative, [3H]azetomidate, has also been demonstrated and this binding subject to positive allosteric regulation by anesthetic steroids. An array of natural products including flavonoid and terpenoid compounds exert varied actions at GABA_A receptors (reviewed in detail).

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]; fragment dioxane derivatives [positive allosteric modulators selective for β1- versus β2-, or β3-subunit-containing receptors]; loreclezole, etomidate, tracazolate, mefenamic acid, etifoxine, stiripentol, valerenic acid amide [positive allosteric modulators with selectivity for β2/β3- over β1-subunit-containing receptors]; [99, 192-194]; tracazolate [intrinsic efficacy, i.e., potentiation, or inhibition, is dependent upon the identity of the β1-, β2-, or β3-subunit co-assembled with α1- and β1-subunits]; amiloride [selective blockade of receptors containing an α6-subunit]; furosemide [selective blockade of receptors containing an α6-subunit co-assembled with β2/β3-, but not β1-subunit]; La^{3+} [potentiates responses mediated by α1β3/β2 receptors, weakly inhibits α6β3/β2 receptors, and strongly blocks α6β3 and α4β3 receptors]; ethanol [selectively potentiates responses mediated by α4β3 and α6β3 receptors versus receptors in which β2 replaces β3, or γ replaces δ]; D1 and D2 [selectively potentiate responses mediated by δ-subunit-containing receptors]. It should be noted that the apparent selectivity of some positive allosteric modulators (e.g., neurosteroids such as 3α-pregnan-3α-ol-20-one [3α-pregnan-3α-ol-20-one for δ-subunit-containing receptors (e.g., α1β3) may be a consequence of the unusually low efficacy of GABA at this receptor isoform].
Glycine receptors

Ligand-gated ion channels → Glycine receptors

Overview: The inhibitory glycine receptor (nomenclature as agreed by the NC-IUPHAR Subcommittee 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-HT_3 receptors [215]. The receptor is expressed either as a homo-pentamer of α subunits, or a complex now thought to harbour 2α and 3β subunits [28, 118], 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 (α1INS and α1del), α2 (α2A and α2B), α3 (α3S and α3L) and β (βΔ7) subunits and by mRNA editing of the α2 and α3 subunit [91, 230, 261]. Both α2 splicing and α3 mRNA editing can produce subunits (i.e., α2B and α3P18SL) 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 subynaptic proteins involved in cytoskeletal structure and thus clusters and anchors hetero-oligomeric receptors to the synapse [185, 188, 247]. G-protein βγ subunits enhance the open state probability of native and recombinant glycine receptors by association with domains within the large intracellular loop [371, 372]. Intracellular chloride concentration modulations the kinetics of native and recombinant glycine receptors [280]. Intracellular Ca^{2+} appears to increase native and recombinant glycine receptor affinity, prolonging channel open events, by a mechanism that does not involve phosphorylation [105].

| Nomenclature       | glycine receptor α1 subunit | glycine receptor α2 subunit |
|--------------------|----------------------------|----------------------------|
| HGNC, UniProt      | GLRA1, P23415              | GLRA2, P23416              |
| Selective agonists | glycine > β-alanine > taurine | glycine > β-alanine > taurine |
| (potency order)    | γ = 86 pS (main state); (+ β = 44 pS) | γ = 111 pS (main state); (+ β = 54 pS) |
| Functional         |                            |                            |
| Characteristics    |                            |                            |
| Selective antagonists |                    | HU-210 (pEC_{50} 7), WIN55212-2 (pEC_{50} 6.7), HU-308 (pEC_{50} 6), ginkgolide X (pEC_{50} 5.6), pregnenolone sulphate (pK_i 5.3), bilobalide (pEC_{50} 4.7), tropisetron (pK_i 4.1), colchicine (pEC_{50} 3.5), HU-308 (weak inhibition), PMBA, strychnine |
| Channel blockers   |                            |                            |
| ginkgolide X (pEC_{50} 6.1), pregnenolone sulphate (pK_i 5.7), nifedipine (pEC_{50} 5.5), bilobalide (pEC_{50} 4.7), tropisetron (pK_i 4.1), colchicine (pEC_{50} 3.5), HU-308 (weak inhibition), PMBA, strychnine | ginkgolide B (pEC_{50} 5.1–6.2), cyanoatriphenylborate (pEC_{50} 5.9) [292], picrotixin (pEC_{50} 5.3), picrotixin (pEC_{50} 5.2) |
| Endogenous         |                            |                            |
| allosteric modulators |                        |                            |
| Zn^{2+} (Potentiation) (pEC_{50} 7.4), Cu^{2+} (Inhibition) (pEC_{50} 4.8–5.4), Zn^{2+} (Inhibition) (pEC_{50} 4.8), Extracellular H^{+} (Inhibition) (pEC_{50} 4.8) | Zn^{2+} (Potentiation) (pEC_{50} 6.3), Cu^{2+} (Inhibition) (pEC_{50} 4.8), Zn^{2+} (Inhibition) (pEC_{50} 4.8) |
| Selective allosteric modulators |                          |                            |
| anandamide (Potentiation) (pEC_{50} 7.4), HU-210 (Potentiation) (pEC_{50} 6.6), α,β9-tetrahydrocannabinol (Potentiation) (pEC_{50} ~5.5) | α,β9-tetrahydrocannabinol (Potentiation) (pEC_{50} ~6) |
| Labelled ligands   | [³H]strychnine (Antagonist) | [³H]strychnine (Antagonist) |
| Nomenclature | glycine receptor α3 subunit | glycine receptor α4 subunit (pseudogene in humans) | glycine receptor β subunit |
|--------------|-----------------------------|------------------------------------------------|---------------------------|
| HGNC, UniProt | GLRA3, Q75311               | GLRA4, Q5JXX5                                  | GLRB, P48167               |
| Selective agonists (potency order) | glycine > β-alanine > taurine | –                                          | –                          |
| Functiona characteristics | –                                        | –                                          | –                          |
| Selective antagonists | HU-210 (pIC<sub>50</sub> 7.3), HU-308 (pIC<sub>50</sub> 7), WIN55212-2 (pIC<sub>50</sub> 7), (1E,20Z,18S)-8-hydroxyxvariabilin (pIC<sub>50</sub> 5.2), nifedipine (pIC<sub>50</sub> 4.5), strychnine | –                                          | –                          |
| Channel blockers | picrotoxin (pIC<sub>50</sub> 6.4), ginkgolide B (pIC<sub>50</sub> 5.7), picrotin (pIC<sub>50</sub> 5.2), picROTOXIN (block is weaker when β subunit is co-expressed) | –                                          | –                          |
| Endogenous allosteric modulators | Cu<sup>2+</sup> (Inhibition) (pIC<sub>50</sub> 5), Zn<sup>2+</sup> (Inhibition) (pIC<sub>50</sub> 3.8) | –                                          | –                          |
| Selective allosteric modulators | Δ<sup>9</sup>-tetrahydrocannabinol (Potentiation) (pEC<sub>50</sub> ~ 5.3) | –                                          | –                          |
| Labelled ligands | [3H]<sub>strychnine</sub> (Antagonist) | –                                          | –                          |
| Comments | –                                          | –                                          | Ligand interaction data for hetero-oligomer receptors containing the β subunit are also listed under the α subunit |

**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 isomers 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. RUS135 demonstrates comparable potency, but additionally blocks GABA<sub>A</sub> receptors. There are conflicting reports concerning the ability of cannabinoids to inhibit [210], or potentiate and at high concentrations activate [4, 73, 128, 363, 368] glycine receptors. Nonetheless, cannabinoid analogues may hold promise in distinguishing between glycine receptor subtypes [368]. 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 [363]. Several analogues of muscimol and piperidine act as agonists and antagonists of both glycine and GABA<sub>A</sub> receptors. PicROTOXIN acts as an allosteric inhibitor that appears to bind within the pore, and shows strong selectivity towards homomeric receptors. While its components, picROTOXIN 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 [369]. Binding of picROTOXIN within the...
pore has been demonstrated in the crystal structure of the related C. elegans GluCl Cys-loop receptor [132]. In addition to the compounds listed in the table, numerous agents act as allosteric regulators of glycine receptors (comprehensively reviewed in [197, 216, 354, 373]). Zn²⁺ 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 [237]. The effect of Zn²⁺ is somewhat mimicked by Ni²⁺. Endogenous Zn²⁺ is essential for normal glycinergic neurotransmission mediated by α₁ subunit-containing receptors [135]. Elevation of intracellular Ca²⁺ 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 [225], or through βγ subunits [370] is debated. Recent crystal structures of the bacterial homologue, GLIC, have identified transmembrane binding pockets for both anaesthetics [259] and alcohols [144]. 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-HT₃ 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 [220]. Additional tropeines, including atropine, modulate glycine receptor activity.

Further Reading

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Ionotropic glutamate receptors

Ligand-gated ion channels → Ionotropic glutamate receptors

Overview: The ionotropic glutamate receptors comprise members of the NMRA (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 [76, 208, 338]. 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) [168, 193, 226, 250, 338]. The X-ray structure of a homeric ionotropic glutamate receptor (GluA2 - see below) has recently been solved at 3.6Å resolution [313] and although providing the most complete structural information currently available may not representative of the subunit arrangement of, for example, the heteromic NMRA receptors [171]. 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 [55, 65, 76, 93, 155, 156, 179, 265, 266, 267, 338, 362]. 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 recently been re-addressed by NC-IUPHAR [62]. The scheme developed recommends a revised nomenclature for ionotropic glutamate receptor subunits that is adopted here.

NMRA receptors

NMRA 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 NMRA 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 [56, 92]. The minimal requirement for efficient functional expression of NMRA 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 [106, 171, 226]. 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 NMRA receptor channel commonly has a high relative permeability to Ca2+ and is blocked, in a voltage-dependent manner, by Mg2+ such that at resting potentials the response is substantially inhibited.

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 [95, 152, 239, 336]). 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; [199, 276, 279]). Two additional kainate receptor subunit, 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 [156, 276, 279]). Kainate receptors may also exhibit ‘metabotropic’ functions [199, 288]. As found for AMPA receptors, kainate receptors are modulated by auxiliary subunits (Neto proteins, [200, 276]). An important functional difference between AMPA and kainate receptors is that the latter require extracellular Na+ and Cl- for their activation [35, 282]. 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 Ca2+; (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 [150, 300]. GluK1 and GluK2, but not other kainate receptor subunits, are similarly edited and similarly broadly similar functional characteristics apply to kainate receptors lacking either an RNA edited GluK1, or GluK2, subunit [199, 276]. Native AMPA and kainate receptors displaying differential channel conductances, Ca2+ permeabilities and sensitivity to block by intracellular polyamines have been identified [64, 150, 206]. 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 non-desensitized state. TARPs also stabilise the non-desensitized conformation of AMPA receptors and facilitate the action of cyclothiazide [239]. Splice variants of GluK1-3 also exist which affects their trafficking [199, 276].
| Nomenclature          | GluA1 | GluA2 | GluA3 | GluA4 |
|-----------------------|-------|-------|-------|-------|
| HGNC, UniProt         | GRIA1, P42261 | GRIA2, P42262 | GRIA3, P42263 | GRIA4, P48058 |
| Agonists              | (S)-5-fluorowillardiine, AMPA | (S)-5-fluorowillardiine, AMPA | (S)-5-fluorowillardiine, AMPA | (S)-5-fluorowillardiine, AMPA |
| Selective antagonists | ATPO, GYKIS3655, GYKIS3784 (active isomer, non-competitive), NBQX, tezampanel | ATPO, GYKIS3655, GYKIS3784 (active isomer, non-competitive), NBQX, tezampanel | ATPO, GYKIS3655, GYKIS3784 (active isomer, non-competitive), NBQX, tezampanel | ATPO, GYKIS3655, GYKIS3784 (active isomer, non-competitive), NBQX, tezampanel |
| Channel blockers      | extracellular argiotoxin, extracellular joro toxin (selective for channels lacking GluA2) | extracellular argiotoxin | extracellular argiotoxin, extracellular joro toxin (selective for channels lacking GluA2) | extracellular argiotoxin, extracellular joro toxin (selective for channels lacking GluA2) |
| Allosteric modulators | LY392098 (Positive) (pEC\textsubscript{50} 5.8) [240], LY404187 (Positive) (pEC\textsubscript{50} 5.2) [240], cyclothiazide (Positive) (pEC\textsubscript{50} 4.7) [240], CX516 (Positive), CX546 (Positive), IDRA-21 (Positive), LY503430 (Positive), S18986 (Positive), aniracetam (Positive), piracetam (Positive) | | | |
| Labelled ligands      | [\textsuperscript{3}H]AMPA (Agonist), [\textsuperscript{3}H]CNQX (Antagonist) | [\textsuperscript{3}H]AMPA (Agonist), [\textsuperscript{3}H]CNQX (Antagonist) | [\textsuperscript{3}H]AMPA, [\textsuperscript{3}H]CNQX (Antagonist) | [\textsuperscript{3}H]AMPA (Agonist), [\textsuperscript{3}H]CNQX (Antagonist) |
| Comments              | 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. | | | |

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| Nomenclature | GluD1 | GluD2 | GluK1 | GluK2 | GluK3 | GluK4 | GluK5 |
|--------------|--------|--------|--------|--------|--------|--------|--------|
| Agonists     | GRID1, Q9ULK0 | GRID2, O43424 | GRIK1, P39086 | GRIK2, Q13002 | GRIK3, Q13003 | GRIK4, Q16099 | GRIK5, Q16478 |
| (S)-4-AHCP, (S)-5-iodowillardiine, 8-deoxy-neodysherbaine, ATPA, LY339434, SYM2081, domoic acid, dysherbaine, kainate | SYM2081, domoic acid, dysherbaine, kainate (low potency) | SYM2081, domoic acid, dysherbaine, kainate | SYM2081, domoic acid, dysherbaine, kainate |
| Selective antagonists | – | – | 2,4-epi-neodysherbaine | – | – | – |
| Allosteric modulators | – | – | concanavalin A (Positive) | concanavalin A (Positive) | – | – |
| Labelled ligands | – | – | \[^3\text{H}]\text{UBP310}\text{ (Agonist) } (pK_d 7.7) [13], \[^3\text{H}](2S,4R)-4-methylglutamate (Agonist), \[^3\text{H}]\text{kainate} (Agonist) | \[^3\text{H}]\text{UBP310}\text{ (Agonist) } (pK_d 6.3) [13], \[^3\text{H}](2S,4R)-4-methylglutamate (Agonist), \[^3\text{H}]\text{kainate} (Agonist) | \[^3\text{H}](2S,4R)-4-methylglutamate (Agonist), \[^3\text{H}]\text{kainate} (Agonist) | \[^3\text{H}](2S,4R)-4-methylglutamate (Agonist), \[^3\text{H}]\text{kainate} (Agonist) |
| Comments | – | – | Intracellular polyamines are subtype selective channel blockers (GluK3 \(\gg\) GluK2) | | | |

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| Nomenclature                        | GluN1                      | GluN2A                      | GluN2B                      | GluN2C                      | GluN2D                      |
|------------------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| HGNC, UniProt                      | D-aspartic acid [glutamate site], D-serine [glycine site], L-aspartic acid [glutamate site], glycine [glycine site] | D-aspartic acid [glutamate site] (GluN2D = GluN2C = GluN2B > GluN2A), D-serine [glycine site] (GluN2D > GluN2C = GluN2B > GluN2A), L-aspartic acid [glutamate site] (GluN2D = GluN2B > GluN2C = GluN2A), glycine [glycine site] (GluN2D > GluN2C > GluN2B > GluN2A) | D-aspartic acid [glutamate site] (GluN2D = GluN2C = GluN2B > GluN2A), D-serine [glycine site] (GluN2D > GluN2C = GluN2B > GluN2A), L-aspartic acid [glutamate site] (GluN2D = GluN2B > GluN2C = GluN2A), glycine [glycine site] (GluN2D > GluN2C > GluN2B > GluN2A) | D-aspartic acid [glutamate site] (GluN2D = GluN2C = GluN2B > GluN2A), D-serine [glycine site] (GluN2D > GluN2C = GluN2B > GluN2A), L-aspartic acid [glutamate site] (GluN2D = GluN2B > GluN2C = GluN2A), glycine [glycine site] (GluN2D > GluN2C > GluN2B > GluN2A) |
| Endogenous agonists                | (-)-HA966 [glycine site] (Partial agonist), (RS)-[tetrzol-5-y]glutamate [glutamate site], NMDSA [glutamate site], homoquinolinic acid [glutamate site] (Partial agonist) | (-)-HA966 [glycine site] (Partial agonist), (RS)-[tetrzol-5-y]glutamate [glutamate site] (GluN2D = GluN2C = GluN2B > GluN2A), NMDSA [glutamate site] (GluN2D > GluN2C > GluN2B > GluN2A), homoquinolinic acid [glutamate site] (GluN2B = GluN2A > GluN2D > GluN2C, partial agonist at GluN2A and GluN2C) | (-)-HA966 [glycine site] (Partial agonist), (RS)-[tetrzol-5-y]glutamate [glutamate site] (GluN2D = GluN2C = GluN2B > GluN2A), NMDSA [glutamate site] (GluN2D > GluN2C > GluN2B > GluN2A), homoquinolinic acid [glutamate site] (GluN2B = GluN2A > GluN2D > GluN2C, partial agonist at GluN2A and GluN2C) | (-)-HA966 [glycine site] (Partial agonist), (RS)-[tetrzol-5-y]glutamate [glutamate site] (GluN2D = GluN2C = GluN2B > GluN2A), NMDSA [glutamate site] (GluN2D > GluN2C > GluN2B > GluN2A), homoquinolinic acid [glutamate site] (GluN2B = GluN2A > GluN2D > GluN2C, partial agonist at GluN2A and GluN2C) |
| Selective antagonists               | 5,7-dichlorokynurenic acid [glycine site], GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site] | 5,7-dichlorokynurenic acid [glycine site], CCP37849 [glutamate site], GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], NVP-AAM077 [glutamate site] (GluN2A > GluN2B) [14, 97, 103, 252], UB141 [glutamate site] (GluN2D = GluN2C > GluN2A > GluN2B) [243], conantokin-G [glutamate site] (GluN2B = GluN2D = GluN2C = GluN2A), d-AP5 [glutamate site], d-CCPene [glutamate site], selfotel [glutamate site] | 5,7-dichlorokynurenic acid [glycine site], CCP37849 [glutamate site], GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], NVP-AAM077 [glutamate site] (GluN2A > GluN2B) [14, 97, 103, 252], UB141 [glutamate site] (GluN2D = GluN2C > GluN2A > GluN2B) [243], conantokin-G [glutamate site] (GluN2B = GluN2D = GluN2C = GluN2A), d-AP5 [glutamate site], d-CCPene [glutamate site], selfotel [glutamate site] | 5,7-dichlorokynurenic acid [glycine site], CCP37849 [glutamate site], GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], UBP141 [glutamate site] (GluN2D = GluN2C > GluN2A > GluN2B) [243], conantokin-G [glutamate site] (GluN2B = GluN2D = GluN2C = GluN2A), d-AP5 [glutamate site], d-CCPene [glutamate site], selfotel [glutamate site] | 5,7-dichlorokynurenic acid [glycine site], CCP37849 [glutamate site], GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], UBP141 [glutamate site] (GluN2D = GluN2C > GluN2A > GluN2B) [243], conantokin-G [glutamate site] (GluN2B = GluN2D = GluN2C = GluN2A), d-AP5 [glutamate site], d-CCPene [glutamate site], selfotel [glutamate site] |
(continued)

| Nomenclature | GluN1 | GluN2A | GluN2B | GluN2C | GluN2D |
|--------------|-------|-------|-------|-------|-------|
| Channel blockers | – | Mg²⁺ (GluN2A = GluN2B > GluN2C = GluN2D), N¹-dansyl-spermine (GluN2A = GluN2B >> GluN2C = GluN2D), amantidine (GluN2C = GluN2D > GluN2B >> GluN2A), dizocilpine, ketamine, phencyclidine | Mg²⁺ (GluN2A = GluN2B > GluN2C = GluN2D), N¹-dansyl-spermine (GluN2A = GluN2B >> GluN2C = GluN2D), amantidine (GluN2C = GluN2D > GluN2B ≥ GluN2A), dizocilpine, ketamine, phencyclidine | Mg²⁺ (GluN2A = GluN2B > GluN2C = GluN2D), N¹-dansyl-spermine (GluN2A = GluN2B >> GluN2C = GluN2D), amantidine (GluN2C = GluN2D > GluN2B ≥ GluN2A), dizocilpine, ketamine, phencyclidine | Mg²⁺ (GluN2A = GluN2B > GluN2C = GluN2D), N¹-dansyl-spermine (GluN2A = GluN2B >> GluN2C = GluN2D), amantidine (GluN2C = GluN2D > GluN2B ≥ GluN2A), dizocilpine, ketamine, phencyclidine |
| Labelled ligands | [³H]CGP39653 [glutamate site] (Antagonist), [³H]CGP61594 [glycine site] (Antagonist), [³H]CGS19755 [glutamate site] (Antagonist), [³H]CPP [glutamate site] (Antagonist), [³H]MDL105519 [glycine site] (Antagonist), [³H]dizocilpine [cation channel] (Antagonist), [³H]glycine [glycine site] (Agonist) | [³H]CGP39653 [glutamate site] (Antagonist), [³H]CGP61594 [glycine site] (Antagonist), [³H]CGS19755 [glutamate site] (Antagonist), [³H]CPP [glutamate site] (Antagonist), [³H]MDL105519 [glycine site] (Antagonist), [³H]dizocilpine [cation channel] (Channel blocker), [³H]glycine [glycine site] (Agonist) | [³H]CGP39653 [glutamate site] (Antagonist), [³H]CGP61594 [glycine site] (Antagonist), [³H]CGS19755 [glutamate site] (Antagonist), [³H]CPP [glutamate site] (Antagonist), [³H]MDL105519 [glycine site] (Antagonist), [³H]dizocilpine [cation channel] (Channel blocker), [³H]glycine [glycine site] (Agonist) | [³H]CGP39653 [glutamate site] (Antagonist), [³H]CGP61594 [glycine site] (Antagonist), [³H]CGS19755 [glutamate site] (Antagonist), [³H]CPP [glutamate site] (Antagonist), [³H]MDL105519 [glycine site] (Antagonist), [³H]dizocilpine [cation channel] (Channel blocker), [³H]glycine [glycine site] (Agonist) | [³H]CGP39653 [glutamate site] (Antagonist), [³H]CGP61594 [glycine site] (Antagonist), [³H]CGS19755 [glutamate site] (Antagonist), [³H]CPP [glutamate site] (Antagonist), [³H]MDL105519 [glycine site] (Antagonist), [³H]dizocilpine [cation channel] (Channel blocker), [³H]glycine [glycine site] (Agonist) |

**Nomenclature**

GluN3A

**HGNc, UniProt**

GluN3A, GRIN3A, Q8TCU5

**Comments**

See the main comments section below for information on the pharmacology of GluN3A and GluN3B subunits.

**Comments: NMDA receptors**

Potency orders unreferenced in the table are from [55, 84, 93, 194, 267, 338]. In addition to the glutamate and glycine binding sites documented in the table, physiologically important inhibitory modulatory sites exist for Mg²⁺, Zn²⁺, and protons [65, 76, 338]. Voltage-independent inhibition by Zn²⁺ binding with high affinity within the ATD is highly subunit selective (GluN2A >> GluN2B >> GluN2C = GluN2D; [267, 338]). The receptor is also allosterically modulated, in both positive and negative directions, by endogenous neuroactive steroids in a subunit dependent manner [141, 221]. 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 traxoprodil increase the fraction of receptors blocked by protons at ambient concentration. Inclusion of exon 5 also abolishes potentiation by polyamines and inhibition by Zn²⁺ that occurs through binding in the ATD [337]. Ifenprodil, traxoprodil, haloperidol, felbamate and Ro 8-4304 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 [171]. LY233536 is a competitive antagonist that also displays selectivity for GluN2B over GluN2A subunit-containing receptors.

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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 [27, 89, 125, 229]. 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 Mg2+, single-channel conductance and maximal open probability and channel deactivation time [65, 92, 112]. Incorporation of the GluN3A subunit into tri-heteromers containing GluN1 and GluN2 subunits is associated with decreased single-channel conductance, reduced permeability to Ca2+ and decreased susceptibility to block by Mg2+ [46, 130]. Reduced permeability to Ca2+ has also been observed following the inclusion of GluN3B in tri-heteromers. The expression of GluN3A, or GluN3B, with GluN1 alone forms, in X. laevis oocytes, a cation channel with unique properties that include activation by glycine (but not NMDA), lack of permeation by Ca2+ and resistance to blockade by Mg2+ and NMDA receptor antagonists [50]. The function of heteromers composed of GluN1 and GluN3A is enhanced by Zn2+, or glycine site antagonists, binding to the GluN1 subunit [218]. Zn2+ 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 [312].

**AMPA and Kainate receptors**

All AMPA receptors are additionally activated by kainate (and domoic acid) with relatively low potency, (EC50 100 μM). Inclusion of TARPs within the receptor complex increases the potency and maximal effect of kainate [152, 239]. AMPA is weak partial agonist at GluK1 and at heteromeric assemblies of GluK1/GluK2, GluK1/GluK5 and GluK2/GluK5 [156]. Quinoxalinediones such as CNQX and NBQX show limited selectivity between AMPA and kainate receptors. Tezampanel also has kainate (GluK1) receptor activity as has CIYK53655 (GluK3 and GluK2/GluK3) [156]. 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 [13, 275]. (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 (2S,4R)-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 and GluD2 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 [377]. 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 [251].
## IP₃ receptor

**Ligand-gated ion channels → IP₃ receptor**

### Overview:
The inositol 1,4,5-trisphosphate receptors (IP₃R) are ligand-gated Ca²⁺ release channels on intracellular Ca²⁺ store sites (such as the endoplasmic reticulum). They are responsible for the mobilization of intracellular Ca²⁺ stores and play an important role in intracellular Ca²⁺ signalling in a wide variety of cell types. Three different gene products (types I-III) have been isolated, which assemble as large tetrameric structures. IP₃Rs are closely associated with certain proteins: calmodulin (CALM1, CALM2, CALM3, P62158) and FKBP (and calcineurin via FKBP). They are phosphorylated by PKA, PKC, PKG and CaMKII.

| Nomenclature | IP₃R1 | IP₃R2 | IP₃R3 |
|--------------|-------|-------|-------|
| HGNC, UniProt | ITPR1, Q14643 | ITPR2, Q14571 | ITPR3, Q14573 |
| Functional Characteristics | Ca²⁺: (P BA/P K) 70 pS (50 mM Ca²⁺) | Ca²⁺: single-channel conductance 70 pS (50 mM Ca²⁺) | Ca²⁺: single-channel conductance 88 pS (55 mM Ba²⁺) |
| Endogenous activators | cytosolic ATP (< mM range), cytosolic Ca²⁺ | cytosolic Ca²⁺ (nM range), IP₃ (endogenous; nM - μM range) | cytosolic Ca²⁺ (nM range), IP₃ (endogenous; nM - μM range) |
| Activators | adenophosphin A (pharmacological; nM range), inositol 2,4,5-trisphosphate (pharmacological; also activated by other InsP₃ analogues) | adenophosphin A (pharmacological; nM range), inositol 2,4,5-trisphosphate (pharmacological; also activated by other InsP₃ analogues) | – |
| Antagonists | PIP₂ (μM range), caffeine (mM range), decavanadate (μM range), xestospongin C (μM range) | decavanadate (μM range) | decavanadate (μM range) |
| Comments | IP₃ R1 is also antagonised by calmodulin at high cytosolic Ca²⁺ concentrations | – | – |

**Comments:** The absence of a modulator of a particular isoform of receptor indicates that the action of that modulator has not been determined, not that it is without effect.

### Further Reading

- Barker CJ et al. (2013) New horizons in cellular regulation by inositol polyphosphates: insights from the pancreatic β-cell. *Pharmacol. Rev.* 65: 641-69 [PMID:23429059]
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Nicotinic acetylcholine receptors

Ligand-gated ion channels → 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-HT\(_3\) receptors [7, 236, 308, 324, 361]. All nicotinic receptors are pentamers in which each of the five subunits contains four \(\alpha\)-helical transmembrane domains. Genes encoding a total of 17 subunits (\(\alpha_1-10\), \(\beta_1-4\), \(\gamma\), \(\delta\) and \(\epsilon\)) have been identified [169]. All subunits with the exception of \(\alpha 8\) (present in avian species) have been identified in mammals. All \(\alpha\) subunits possess two tandem cysteine residues near to the site involved in acetylcholine binding, and subunits not named \(\alpha\) lack these residues [236]. The orthosteric ligand binding site is formed by residues within at least three peptide domains on the \(\alpha\) 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 [113, 375]; see also [132]). The high resolution crystal structure of the mulluscian acetylcholine binding protein, a structural homologue of the extracellular domain of a \(\alpha\) subunit bound to \(\alpha\)-bungarotoxin at 1.94 \(\AA\) resolution [72], has revealed the orthosteric binding site in detail (reviewed in [49, 169, 291, 308]). Nicotinic receptors at the somatic neuromuscular junction of adult animals have the stoichiometry (\(\alpha 1\)\(_2\)\(\beta\)\(_1\)\(_\epsilon\), whereas an extrajunctional (\(\alpha 1\)\(_2\)\(\beta\)\(_1\)\(_\gamma\) \(\epsilon\) receptor predominates in embryonic and denervated skeletal muscle and other pathological states. Other nicotinic receptors are assembled as combinations of \(\alpha 2\) and \(\beta\) (2-6) and \(\beta\) (2-4) subunits. For \(\alpha 2\), \(\alpha 3\), \(\alpha 4\) and \(\beta 2\) and \(\beta 4\) subunits, pairwise combinations of \(\alpha\) and \(\beta\) (e.g. \(\alpha 3\)\(_4\beta\)\(_2\) and \(\alpha 4\)\(_2\beta\)\(_2\)\(_\epsilon\)) are sufficient to form a functional receptor in vitro, but far more complex isomers may exist in vivo (reviewed in [116, 117, 236]). There is strong evidence that the pairwise assembly of some \(\alpha\) and \(\beta\) subunits can occur with variable stoichiometry [e.g. \(\alpha 2\)\(_4\)\(\beta\)\(_2\) \(\alpha 4\)\(_2\)\(\beta\)\(_2\)\(_\epsilon\)] which influences the biochemical and pharmacological properties of the receptor [236]. \(\alpha 5\) and \(\beta 3\) 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 \(\alpha\) and \(\beta\) pair [e.g. \(\alpha 4\)\(_2\)\(\beta\)\(_2\)\(_\epsilon\), \(\alpha 4\)\(_4\beta\)\(_2\)\(_\epsilon\), \(\alpha 5\)\(_6\)\(_\beta\)\(_2\), see [236] for further examples]. The \(\alpha\) subunit can form a functional receptor when co-expressed with \(\beta 4\) in vitro, but more efficient expression ensues from incorporation of a third partner, such as \(\beta 3\) [366]. The \(\alpha 7\), \(\alpha 8\), and \(\alpha 9\) subunits form functional homo-oligomers, but can also combine with a second subunit to constitute a hetero-oligomeric assembly (e.g. \(\alpha 7\)\(_2\beta 2\) and \(\alpha 9\alpha 10\)). For functional expression of the \(\alpha 10\) subunit, co-assembly with \(\alpha 9\) is necessary. The latter, along with the \(\alpha 10\) 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 [236]. 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 [10, 167, 235]). 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 [212]. Headings for this table reflect abbreviations designating nACh receptor subtypes based on the predominant \(\alpha\) subunit contained in that receptor subtype. An asterisk following the indicated \(\alpha\) subunit denotes that other subunits are known to, or may, assemble with the indicated \(\alpha\) 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 [62]).

| Nomenclature | Nicotinic acetylcholine receptor \(\alpha 1\) subunit | Nicotinic acetylcholine receptor \(\alpha 2\) subunit | Nicotinic acetylcholine receptor \(\alpha 3\) subunit | Nicotinic acetylcholine receptor \(\alpha 4\) subunit |
|--------------|-----------------|-----------------|-----------------|-----------------|
| HGNC, UniProt | CHRNA1, P02708 | CHRNA2, Q1S822 | CHRNA3, P32297 | CHRNA4, P43681 |
| Commonly used antagonists | \((\alpha 1)\_2\beta 1\_\delta\) and \((\alpha 1)\_2\beta 1\_\epsilon\): \(\alpha\)-bungarotoxin \(\sim\) pancuronium \(\sim\) vecuronium \(\sim\) rocuronium \(\sim\) tubocurarine (IC\(_{50}\) = 43 - 82 nM) | \(\alpha 2\)\(_\beta\)\(_2\): DH\(_{JE}\) (\(K_p = 0.9 \mu M\), tubocurarine (\(K_p = 1.4 \mu M\)), \(\alpha 2\)\(_4\): DH\(_{JE}\) (\(K_p = 3.6 \mu M\), tubocurarine (\(K_p = 4.2 \mu M\)) | \(\alpha 3\)\(_2\): DH\(_{JE}\) (\(K_p = 1.6 \mu M\), \(\delta\)_C\(_{50}\) = 2.0 \(\mu M\), tubocurarine (\(K_p = 2.4 \mu M\)), \(\alpha 3\)\(_4\): DH\(_{JE}\) (\(K_p = 19 \mu M\), \(\delta\)_C\(_{50}\) = 26 \(\mu M\), tubocurarine (\(K_p = 2.2 \mu M\)) | \(\alpha 4\)\(_2\): DH\(_{JE}\) (\(K_p = 0.1 \mu M\), \(\delta\)_C\(_{50}\) = 0.2 \(\mu M\), tubocurarine (\(K_p = 0.8 \sim 0.9 \mu M\)), \(\alpha 4\)\(_4\): DH\(_{JE}\) (\(K_p = 0.01 \mu M\), \(\delta\)_C\(_{50}\) = 0.19 \(\mu M\), \(\delta\)_C\(_{50}\) = 0.19 \(\mu M\), tubocurarine (\(K_p = 0.2 \mu M\), \(\delta\)_C\(_{50}\) = 50 \(\mu M\) |
| Functional characteristics | \((\alpha 1)\_2\beta 1\_\delta\): \(P_{CA}\_P_{Na} = 0.16 - 0.2\), \(P_N = 0.65 - 1.38\), \(P_{CA}\_P_{Na} = 2.1 - 2.9\%\), \((\alpha 1)\_2\beta 1\_\epsilon\): \(P_{CA}\_P_{Na} = 0.65 - 1.38\), \(P_{CA}\_P_{Na} = 2.1 - 2.9\%\), \(P_N = 0.65 - 1.38\)| \(\alpha 2\)\(_\beta\)\(_2\): \(P_{CA}\_P_{Na} = 1.5\)| \(\alpha 3\)\(_2\): \(P_{CA}\_P_{Na} = 1.5\), \(P_N = 2.6 - 2.9\%\), \(\alpha 3\)\(_4\): \(P_{CA}\_P_{Na} = 0.78 - 1.1\), \(P_{CA}\_P_{Na} = 2.7 - 4.6\%\)| \(\alpha 4\)\(_2\): \(P_{CA}\_P_{Na} = 1.65\), \(P_N = 2.6 - 2.9\%\), \(\alpha 4\)\(_4\): \(P_{CA}\_P_{Na} = 1.5 - 3.0\%\) |
| Selective agonists | succinylcholine (selective for \((\alpha 1)\_2\beta 1\_\delta\)) | - | - | varenicline (\(P_{N} = 6.6\)) [61], TC-2559 [57], rivacline (\(P_{N} = 57\)) [270] |
| Nomenclature                      | Nicotinic acetylcholine receptor α1 subunit | Nicotinic acetylcholine receptor α2 subunit | Nicotinic acetylcholine receptor α3 subunit | Nicotinic acetylcholine receptor α4 subunit |
|----------------------------------|--------------------------------------------|--------------------------------------------|--------------------------------------------|--------------------------------------------|
| Selective antagonists            | α-bungarotoxin, α-conotoxin GI, α-conotoxin MI, panchuronium, waglerin-1 (selective for (α1)β1Δε) | –                                             | α-conotoxin Aulβ (α3)Δ4, α-conotoxin MIβ (α3)β2, α-conotoxin PnIA (α3)β2, α-conotoxin TxA (α3)β2, α-conotoxin GI-C (α3)β2 | –                                             |
| Channel blockers                 | gallamine ([(α1)2β]β6 and (α1)ββΔε) (pIC<sub>50</sub> ~ 6), mecamylamine ([(α1)2β]β6Δε) (pIC<sub>50</sub> ~ 5.8) | hexamethonium, mecamylamine                 | mecamylamine (α3)β4 (pIC<sub>50</sub> 6.4), mecamylamine (α3)β2 (pIC<sub>50</sub> 5.1), A-867744 (α3)β4 [222], NS1738 (α3)β4 [335], hexamethonium (α3)β4, hexamethonium (α3)β2 | mecamylamine (α4)β2 (pIC<sub>50</sub> 5.4–5.5), mecamylamine (α4)β4 (pIC<sub>50</sub> 6.5–5.3), hexamethonium (α4)β2 (pIC<sub>50</sub> 5.2–4.5), hexamethonium (α4)β4 (pIC<sub>50</sub> 4), A-867744 (α4)β2 [222], NS1738 (α4)β2 [335] |
| Allosteric modulators            | –                                             | LY2087101 (Positive) [37]                   | –                                             | LY2087101 (Positive) [37]                   |
| Selective allosteric modulators  | –                                             | –                                             | –                                             | NS9283 (Positive) [198]                     |
| Labelled ligands                 | [125]Iα-bungarotoxin (Selective Antagonist), [3]Hα-bungarotoxin (Selective Antagonist) | [125]Jepibatidine (Agonist) (p<sub>Kd</sub> 11–10.7) – Rat, [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 11–10.7) – Rat, [125]Jepibatidine (Agonist) (p<sub>Kd</sub> 10.4), [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 10.4), [125]Jepibatidine (Agonist) (p<sub>Kd</sub> 10.1–10.1) – Rat, [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 10.1–10.1) – Rat, [3]HJcytisine (Agonist) | [125]Jepibatidine (Agonist) (p<sub>Kd</sub> 11.1), [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 11.1), [125]Jepibatidine (Agonist) (p<sub>Kd</sub> 10.9–10.5) – Rat, [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 10.9–10.5) – Rat, [125]Jepibatidine (Agonist) (p<sub>Kd</sub> 9.6), [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 9.6), [125]Jepibatidine (Agonist) (p<sub>Kd</sub> 9.5–9.5) – Rat, [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 9.5–9.5) – Rat, [3]HJcytisine (Agonist) | [125]Jepibatidine (Agonist) (p<sub>Kd</sub> 11–10.5), [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 11–10.5), [3]HJcytisine (Agonist) (p<sub>Kd</sub> 10), [125]Jepibatidine (Agonist) (p<sub>Kd</sub> 10) – Rat, [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 9.7), [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 9.7), [3]HJcytisine (Agonist) (p<sub>Kd</sub> 9.4) – R, [125]Jepibatidine (Agonist) (p<sub>Kd</sub> 9.5–9.3) – Rat, [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 9.5–9.3) – Rat, [3]HJcytisine (Agonist) (p<sub>Kd</sub> 9.4–9.2), [125]Jepibatidine (Agonist) (p<sub>Kd</sub> 9.1–9) – Rat, [3]HJepibatidine (Agonist) (p<sub>Kd</sub> 9.1–9) – Rat, [3]HJcytisine (Agonist) (p<sub>Kd</sub> 9.1–9) – Rat |
| Nomenclature | nicotinic acetylcholine receptor α5 subunit | nicotinic acetylcholine receptor α6 subunit | nicotinic acetylcholine receptor α7 subunit |
|--------------|------------------------------------------|------------------------------------------|------------------------------------------|
| HGNC, UniProt | CHRNA5, P30532                           | CHRNA6, Q15825                           | CHRNA7, P36544                           |
| Commonly used antagonists | – | α6/α3[β]β3 chimera: DHβE (IC₅₀ = 1.1 μM) | (α7)₅: DHβE (IC₅₀ = 8 - 20 μM); (α7)₅: tubocurarine (IC₅₀ = 3.1 μM) |
| Functional Characteristics | – | – | Pₐₕ/ₚₐₙ = 6.6-20, Pₜ = 8.8 - 11.4% |
| Selective agonists | – | – | enceneline (Partial agonist) (pKᵦ: 8.4) [1, 227], AQW051 ([125I]α-bungarotoxin binding assay) (pKᵦ: 7.6) [149], 4BP-TQS (allosteric) [113], A-582941 ((α7)₅) [30], PHA-543613 ((α7)₅) [359], PHA-709829 ((α7)₅) [3], PNU-282987 ((α7)₅) [32], bradanicline ((α7)₅) [127] |
| Selective antagonists | α-conotoxin MII, α-conotoxin PnIA, α-conotoxin TxIA, α-conotoxin-GIC | α-conotoxin MII (α6[β]2³), α-conotoxin MII [H9A, L15A] (α6[β]2³), α-conotoxin PIA (α6/α3[β]β3 chimera) | α-bungarotoxin ((α7)₅), α-conotoxin ArIB ((α7)₅), α-conotoxin Iml ((α7)₅), methyllycaconitine ((α7)₅) |
| Channel blockers | – | mecamylamine (α6/α3[β]β3 chimera) (pIC₅₀ 5) | mecamylamine ((α7)₅) (pIC₅₀ 4.8) |
| Allosteric modulators | – | hexamethonium (α6/α3[β]β3 chimera) (pIC₅₀ 4) | A-867744 (Positive) [222], LY2087101 (Positive) [37], NS1738 (Positive) [335] |
| Selective allosteric modulators | – | – | JNJ1930942 (Positive) [77], PNU-120596 (Positive) [148] |
| Labelled ligands | – | [³H]epibatidine (Agonist) (pKₐ: 10.5) – Chicken, [¹²⁵I]α-conotoxin MII (Antagonist) | [³H]epibatidine (Agonist) (pKₐ: 12.2), [³H]AZ11637326 (Agonist) (pKₐ: 9.6) [115], [³H]methyllycaconitine (Antagonist) (pKₐ: 8.7) – Rat, [¹²⁵I]α-bungarotoxin (Selective Antagonist) (pKₐ: 9.1–8.3), [³H]α-bungarotoxin (Selective Antagonist) (pKₐ: 9.1–8.3) |
### Nomenclature

| CHRN4, UniProt | CHRNB1, P11230 | CHRNB2, P17787 | CHRNB3, Q05901 | CHRNB4, P30926 | CHRNG, P07510 | CHRND, Q07001 | CHRNE, Q04844 |
|----------------|----------------|----------------|----------------|----------------|---------------|---------------|---------------|
| Nicotinic acetylcholine receptor α8 subunit (avian) | Nicotinic acetylcholine receptor α9 subunit | Nicotinic acetylcholine receptor β3 subunit | Nicotinic acetylcholine receptor β4 subunit | Nicotinic acetylcholine receptor γ subunit | Nicotinic acetylcholine receptor δ subunit | Nicotinic acetylcholine receptor ε subunit | Nicotinic acetylcholine receptors |

### Functional Characteristics

\[ (\alpha_9)_5: P_{Ca}/P_{Na} = 9; \alpha_9 \alpha_{10}: P_{Ca}/P_{Na} = 9, P_f = 22\% \]

### Labelled ligands

- \[^{[3]}H]epibatidine (pK\textsubscript{d} 9.7), \[^{[125]}I]\alpha\text{-bungarotoxin} (native α8*) (pK\textsubscript{d} 8.3), \[^{[3]}H]\alpha\text{-bungarotoxin} (native α8*) (pK\textsubscript{d} 8.3)
- \[^{[3]}H]methyllycaconitine (Antagonist) (pK\textsubscript{d} 8.1), \[^{[125]}I]\alpha\text{-bungarotoxin} (Antagonist), \[^{[3]}H]\alpha\text{-bungarotoxin} (Antagonist)
- \[^{[3]}H]methyllycaconitine (Antagonist) (pK\textsubscript{d} 8.1)

### 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 [117] and quantitative data across numerous assay systems are summarized in [161]. Quantitative data presented in the table for commonly used antagonists and channel blockers for human receptors studied under voltage-clamp are from [41, 52, 268, 269, 273, 360]. 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 [358]).
P2X receptors

Ligand-gated ion channels → P2X receptors

Overview: P2X receptors (nomenclature as agreed by the NC-IUPHAR Subcommittee on P2X Receptors [62, 180]) have a trimeric topology [163, 175, 254] with two putative TM domains, gating primarily Na⁺, K⁺ and Ca²⁺, 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, [195]). P2X2, P2X4 and P2X7 receptors have been shown to form functional homopolymers which, in turn, activate pores permeable to low molecular weight solutes [321]. The hemi-channel pannexin-1 has been implicated in the pore formation induced by P2X7 [274], but not P2X2 [51], receptor activation.

| Nomenclature | P2X1 | P2X2 | P2X3 | P2X4 |
|--------------|------|------|------|------|
| HGNC, UniProt | P2RX1, P51575 | P2RX2, P9UBL9 | P2RX3, P6373 | P2RX4, Q99571 |
| Agonists | αβ-meATP, BzATP, L-βγ-meATP | – | αβ-meATP, BzATP | – |
| Antagonists | TNP-ATP (pIC₅₀ ~8.9) [342], Ip5I (pIC₅₀ ~8.5), NF023 (pIC₅₀ ~6.7), NF449 (pIC₅₀ ~6.3) [174] | – | TNP-ATP (pIC₅₀ ~8.9) [342], AF353 (pIC₅₀ ~8) [111], A317491 (pIC₅₀ ~7.5) [157], RO3 (pIC₅₀ ~7.5) [100] | – |
| Selective allosteric modulators | MRS 2219 (Positive) [154] | – | – | ivermectin (Positive) [181] – Rat |

| Nomenclature | P2X5 | P2X6 | P2X7 |
|--------------|------|------|------|
| HGNC, UniProt | P2RX5, Q93086 | P2RX6, O15547 | P2RX7, Q99572 |
| Antagonists | – | – | A804598 (pIC₅₀ ~8), Brilliant blue G (pIC₅₀ ~8) [164], A839977 (pIC₅₀ ~7.7) [81, 83, 137], A740003 (pIC₅₀ 7.4) [138], Decavanadate (pA₂ ~ 7.4) (pA₂ 7.4) [234], A438079 (pIC₅₀ ~6.9) [81] |
| Selective allosteric modulators | – | – | Chelerythrine (Negative) (pIC₅₀ 5.2) [303], AZ11645373 (Negative) [232, 318], KN62 (Negative) [110, 303], ivermectin (Positive) [260] |
| Comments | – | – | Effects of the allosteric regulators at P2X7 receptors are species-dependent. |

Comments: A317491 and RO3 also block the P2X2:P2X3 heterotrimer [100, 157]. NF449, A317491 and RO3 are more than 10-fold selective for P2X2 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 [81, 83, 137]. Several P2X receptors (particularly P2X1 and P2X3) may be inhibited by desensitisation using stable agonists (e.g. αβ-meATP); suramin and PRAD5 are non-selective antagonists at rat and human P2X1-3, 5 and hP2X4, but not rP2X4,6,7 [40], and can also inhibit ATPase activity [63]. Ip5I is inactive at rP2X2, an antagonist at rP2X3 (pIC₅₀ 5.6) and enhances agonist responses at rP2X4 [183]. Antagonist potency of NF023 at recombinant P2X2, P2X3 and P2X5 is two orders of magnitude lower than that at P2X1 receptors [315]. The P2X7

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Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13350/full
The receptor may be inhibited in a non-competitive manner by the protein kinase inhibitors KN62 and chelerythrine [303], while the p38 MAP kinase inhibitor GTPγS and the cyclic imide AZ11645373 show a species-dependent non-competitive action [82, 232, 233, 318]. The pH-sensitive dye used in culture media, phenol red, is also reported to inhibit P2X1 and P2X3 containing channels [184]. Some recombinant P2X receptors expressed to high density bind [35S]ATPγS and [3H]αβ-meATP, although the latter can also bind to 5′-nucleotidase [231]. [3H]A317491 and [3H]A804598 have been used as high affinity antagonist radioligands for P2X3 (and P2X2/3) and P2X7 receptors, respectively [83].

Further Reading

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Coddou C et al. (2011) Activation and regulation of purinergic P2X receptor channels. Pharmacol. Rev. 63: 641-83 [PMID:21737531]
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Khakh BS et al. (2001) International union of pharmacology. XXIV. Current status of the nomenclature and properties of P2X receptors and their subunits. Pharmacol. Rev. 53: 107-18 [PMID:11171941]
Khakh BS et al. (2012) Neuromodulation by extracellular ATP and P2X receptors in the CNS. Neuron 76: 51-69 [PMID:23040806]
North RA et al. (2013) P2X receptors as drug targets. Mol. Pharmacol. 83: 759-69 [PMID:23253448]
Overview: The ryanodine receptors (RyRs) are found on intracellular Ca\textsuperscript{2+} storage/release organelles. The family of RyR genes encodes three highly related Ca\textsuperscript{2+} release channels: RyR1, RyR2 and RyR3, which assemble as large tetrameric structures. These RyR channels are ubiquitously expressed in many types of cells and participate in a variety of important Ca\textsuperscript{2+} signaling phenomena (neurotransmission, secretion, etc.). In addition to the three mammalian isoforms described below, various nonmammalian isoforms of the ryanodine receptor have been identified [323]. The function of the ryanodine receptor channels may also be influenced by closely associated proteins such as the tacrolimus (FK506)-binding protein, calmodulin [365], triadin, calsequestrin, junctin and sorcin, and by protein kinases and phosphatases.

| Nomenclature | RyR1 | RyR2 | RyR3 |
|--------------|------|------|------|
| HGNC, UniProt | RYR1, P21817 | RYR2, Q92736 | RYR3, Q15413 |

Functional Characteristics
- \( Ca^{2+}: (P_{Ca}/P_{K}) \) single-channel conductance:
  - RyR1: 90 pS (50 mM Ca\textsuperscript{2+}), 770 pS (200 mM K\textsuperscript{+})
  - RyR2: 90 pS (50 mM Ca\textsuperscript{2+}), 720 pS (210 mM K\textsuperscript{+})
  - RyR3: 140 pS (50 mM Ca\textsuperscript{2+}), 777 pS (250 mM K\textsuperscript{+})

Endogenous activators
- Cytosolic ATP (endogenous; mM range), cytosolic Ca\textsuperscript{2+} (endogenous; \( \mu \)M range), luminal Ca\textsuperscript{2+} (endogenous)

Activators
- Caffeine (pharmacological; mM range), ryanodine (pharmacological; mM \(-\) \( \mu \)M range), suramin (pharmacological; \( \mu \)M range)

Endogenous antagonists
- Cytosolic Ca\textsuperscript{2+} Concentration range: \( >1\times10^{-4} \)M, cytosolic Mg\textsuperscript{2+} (mM range)

Antagonists
- Dantrolene

Channel blockers
- Procaine, ruthenium red, ryanodine Concentration range: \( >1\times10^{-4} \)M

Comments
- RyR1 is also activated by depolarisation via DHP receptor, calmodulin at low cytosolic Ca\textsuperscript{2+} concentrations, CaM kinase and PKA; antagonised by calmodulin at high cytosolic Ca\textsuperscript{2+} concentrations
- RyR2 is also activated by CaM kinase and PKA; antagonised by calmodulin at high cytosolic Ca\textsuperscript{2+} concentrations
- RyR3 is also activated by calmodulin at low cytosolic Ca\textsuperscript{2+} concentrations; antagonised by calmodulin at high cytosolic Ca\textsuperscript{2+} concentrations

Comments: The modulators of channel function included in this table are those most commonly used to identify ryanodine-sensitive Ca\textsuperscript{2+} release pathways. Numerous other modulators of ryanodine receptor/channel function can be found in the reviews listed below. The absence of a modulator of a particular isoform of receptor indicates that the action of that modulator has not been determined, not that it is without effect. The potential role of cyclic ADP ribose as an endogenous regulator of ryanodine receptor channels is controversial. A region of RyR likely to be involved in ion translocation and selection has been identified [107, 381].

Searchable database: http://www.guidetopharmacology.org/index.jsp
Full Contents of ConciseGuide: http://onlinelibrary.wiley.com/doi/10.1111/bph.13350/full
Further Reading

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**ZAC**

Ligand-gated ion channels → 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-HT3, GABA_A and strychnine-sensitive glycine receptors [69, 143]. 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 [69, 143].

| Nomenclature | ZAC   |
|--------------|-------|
| HGNC, UniProt| ZACN, Q401N2 |

**Functional Characteristics**

Outwardly rectifying current (both constitutive and evoked by Zn^2+).  
Zn^{2+} (Selective) (pEC_{50} 3.3) [69]  
tubocurarine (pIC_{50} 5.2) [69]

**Comments**

Although tabulated as an antagonist, it is possible that tubocurarine acts as a channel blocker.

Searchable database: [http://www.guidetopharmacology.org/index.jsp](http://www.guidetopharmacology.org/index.jsp)

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