The Concise Guide to PHARMACOLOGY 2025/26: Ion channels

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Abstract

The Concise Guide to Pharmacology 2025/26 marks the seventh edition in this series of biennial publications in the British Journal of Pharmacology. Presented in landscape format, the guide provides a comparative overview of the pharmacology of drug target families. The concise nature of the Concise Guide refers to the style of presentation, being clear, accessible, and well-structured, rather than the scope of the content, which spans approximately 500 pages. The Concise Guide summarises the key pharmacological properties of around 1900 human drug targets, and nearly 7000 interactions, involving around 4400 ligands. While the content is a substantially condensed version of the more detailed information and links available at the www.guidetopharmacology.org website, the printed guide serves as a permanent, citable, point-in-time record, that remains stable despite ongoing updates to the online database. The full contents of this publication can be found at https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bph.70231.

The Concise Guides provide expert-curated recommendations of 'Gold Standard' selective pharmacological tools, available either commercially or as donations, which enable the identification of individual drug targets or families of drug targets. While the Concise Guide offers a more streamlined overview, more comprehensive information, including detailed pharmacological profiles and links to multiple online databases, is available through the Guide to Pharmacology website. The 2025/26 edition of the Concise Guide is based on material current as of mid-2025, and supersedes all previous editions, including the 2023/24 Guide, and earlier Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature and Standards Committee of the International Union of Basic and Clinical Pharmacology (NC-IUPHAR), and as such provides official IUPHAR classification and nomenclature for human drug targets, where applicable.

Ion channels are one of the six major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, nuclear hormone receptors, catalytic receptors, enzymes and transporters. Each section includes nomenclature guidance, concise summaries, information of the best available pharmacological tools, key references, and suggestions for further reading.

Conflict of interest

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

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Introduction: Ion channels are pore-forming proteins that allow the flow of ions across membranes, either plasma membranes, or the membranes of intracellular organelles [545]. Many ion channels (such as most Na, K, Ca and some Cl channels) are gated by voltage but others (such as certain K and Cl channels, TRP channels, ryanodine receptors and IP_3 receptors) are relatively voltage-insensitive and are gated by second messengers and other intracellular and/or extracellular mediators. As such, there is some blurring of the boundaries between "ion channels" and "ligand-gated channels" which are compiled separately in the Guide. Resolution of ion channel structures, beginning with K channels [340] then Cl channels [358] and most recently Na channels [1088] has greatly improved understanding of the structural basis behind ion channel function. Many ion channels (*e.g.*, K, Na, Ca, HCN and TRP channels) share several structural similarities. These channels are thought to have evolved from a common ancestor and have been classified together as the "voltage-gated-like (VGL) ion channel chanome" (see [1583]). Other ion channels, however, such as Cl channels, aquaporins and connexins, have completely different structural properties to the VGL channels, having evolved quite separately.

Currently, ion channels (including ligand-gated ion channels) represent the second largest target for existing drugs after G protein-coupled receptors [1064]. However, the advent of novel, faster screening techniques for compounds acting on ion channels [351] suggests that these proteins represent promising targets for the development of additional, novel therapeutic agents for the near future.

Family structure

S154 Ligand-gated ion channels
S154 5-HT_3 receptors
S156 Acid-sensing (proton-gated) ion channels (ASICs)
S158 Epithelial sodium channel (ENaC)
S161 $GABA_A$ receptors
S167 Glycine receptors
S169 Ionotropic glutamate receptors
S174 IP_3 receptors
S175 Nicotinic acetylcholine receptors (nACh)
S178 P2X receptors
S180 ZAC
S181 Voltage-gated ion channels
S181 CatSper and Two-Pore channels (TPC)
S183 Cyclic nucleotide-regulated channels (CNG)
S185 Potassium channels
S185 Calcium- and sodium-activated potassium channels (K_{Ca}, K_{Na})
S187 Inwardly rectifying potassium channels (K_{IR})
S189 Two-pore domain potassium channels (K_{2P})
S192 Voltage-gated potassium channels (K_v)
S196 Ryanodine receptors (RyR)
S198 Transient Receptor Potential channels (TRP)
S213 Voltage-gated calcium channels (Ca_V)
S215 Voltage-gated proton channel (H_v1)
S216 Voltage-gated sodium channels (Na_V)
S219 Other ion channels
S219 Aquaporins
S221 Chloride channels
S222 ClC family
S224 CFTR
S225 Calcium activated chloride channel (CaCC)
S226 Maxi chloride channel
S227 Volume regulated chloride channels (VRAC)
S228 Connexins and Pannexins
– Mitochondrial calcium uniporter (MCU) complex
S230 Piezo channels
S231 Sodium leak channel, non-selective (NALCN)
– Store-operated ion channels
S232 Orai channels

Ligand-gated ion channels

Ion channels → Ligand-gated ion channels

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 neurone and the subsequent activation of post-synaptically located receptors that mediate a rapid, phasic, electrical signal (the excitatory, or inhibitory, post-synaptic potential). However, in addition to their traditional role in phasic neurotransmission, it is now established that some LGICs mediate a tonic form of neuronal regulation that results from the activation of extra-synaptic receptors by ambient levels of neurotransmitter. The expression of some LGICs by non-excitable cells is suggestive of additional functions.

By convention, the LGICs comprise the excitatory, cation-selective, nicotinic acetylcholine [195, 951], 5-HT_3 [80, 1463], ionotropic glutamate [853, 1404] and P2X receptors [624, 1342] and the inhibitory, anion-selective, $GABA_A$ [104, 1051] and glycine receptors [873, 1573]. The nicotinic acetylcholine, 5-HT_3, $GABA_A$ and glycine receptors (and an additional zinc-activated channel) are pentameric structures and are frequently referred to as the Cys-loop receptors due to the presence of a defining loop of residues formed by a disulphide bond in the extracellular domain of their constituent subunits [955, 1378]. 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 [541]. The ionotropic glutamate and P2X receptors are tetrameric and trimeric structures, respectively. Multiple genes encode the subunits of LGICs and the majority of these receptors are heteromultimers. Such combinational diversity results, within each class of LGIC, in a wide range of receptors with differing pharmacological and biophysical properties and varying patterns of expression within the nervous system and other tissues. The LGICs thus present attractive targets for new therapeutic agents with improved discrimination between receptor isoforms and a reduced propensity for off-target effects. The development of novel, faster screening techniques for compounds acting on LGICs [351] will greatly aid in the development of such agents.

5-HT_3 receptors

Ion channels → Ligand-gated ion channels → 5-HT_3 receptors

Overview: The 5-HT_3 receptor (**nomenclature as agreed by the NC-IUPHARSubcommittee on 5-Hydroxytryptamine (serotonin) receptors** [576]) 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 4 transmembrane (TM) subunits that form an intrinsic cation selective channel [80], but may also form intermediary tetramers in the cell membrane during assembly [600]. Five human 5-HT_3 receptor subunits have been cloned and homo-oligomeric assemblies of 5-HT_3A and hetero-oligomeric assemblies of 5-HT_3A and 5-HT_3B subunits have been characterised in detail. The 5-HT_3C (*HTR3C*, Q8WXA8), 5-HT_3D (*HTR3D*, Q70Z44) and 5-HT_3E (*HTR3E*, A5X5Y0) subunits [678, 1012], like the 5-HT_3B subunit, do not form functional homomers, but are reported to assemble with the 5-HT_3A subunit to influence its functional expression rather than pharmacological profile [559, 1014, 1462]. 5-HT_3A, -C, -D, and -E subunits also interact with the chaperone RIC-3 which predominantly enhances the surface expression of homomeric 5-HT_3A receptor [330, 1462]. The co-expression of 5-HT_3A and 5-HT_3C-E subunits has been demonstrated in human colon [672]. A recombinant hetero-oligomeric 5-HT_3AB receptor has been reported to contain two copies of the 5-HT_3A subunit and three copies of the 5-HT_3B subunit in the order B-B-A-B-A [85], but this is inconsistent with recent reports which show at least one A-A interface [852, 1382]. The 5-HT_3B subunit imparts distinctive biophysical properties upon hetero-oligomeric 5-HT_3AB versus homo-oligomeric 5-HT_3A recombinant receptors [283, 347, 506, 627, 693, 1107, 1310], influences the potency of channel blockers, but generally has only a modest effect upon the apparent affinity of agonists, or the affinity of antagonists ([147], but see [280, 301, 347]) which may be explained by the orthosteric binding site residing at an interface formed between 5-HT_3A subunits [852, 1382]. However, 5-HT_3A and 5-HT_3AB receptors differ in their allosteric regulation by some general anaesthetic agents, small alcohols and indoles [579, 1204, 1301]. The potential diversity of 5-HT_3 receptors is increased by alternative splicing of the genes *HTR3A* and *HTR3E* [159, 565, 1011, 1013, 1014]. In addition, the use of tissue-specific promoters driving expression from different transcriptional start sites has been reported for the *HTR3A*, *HTR3B,HTR3D* and *HTR3E* genes, which could result in 5-HT_3 subunits harbouring different N-termini [627, 1011, 1410]. To date, inclusion of the 5-HT_3A subunit appears imperative for 5-HT_3 receptor function.

Complexes

Nomenclature	5-HT_3AB	5-HT_3A
Subunits	5-HT_3A, 5-HT_3B	5-HT_3A
Agonists	CSTI-300 (Partial agonist) [1179], vortioxetine (Partial agonist) [74, 762]	CSTI-300 (Partial agonist) [1179]
Selective agonists	–	(*S*)-zacopride (Partial agonist) [147, 1006], *meta*-chlorphenylbiguanide [103, 283, 771, 963, 964], 2-methyl-5-HT [103, 283, 771, 963], SR57227A [361] – Rat, 1-phenylbiguanide [103]
Antagonists	–	metoclopramide (pK_i 6–6.4) [147, 566]
Selective antagonists	–	palonosetron (pK_i 10.5) [977], alosetron (pK_i 9.5) [548], granisetron (pK_i~8.6–8.8) [566, 963], tropisetron (pK_i 8.5–8.8) [771, 963], ondansetron (pK_i~7.8–8.3) [147, 566, 963]
Channel blockers	picrotoxinin (pIC_{50} 4.2) [1377], bilobalide (pIC_{50} 2.5) [1377], ginkgolide B (pIC_{50} 2.4) [1377]	picrotoxinin (pIC_{50} 5) [1376], TMB-8 (pIC_{50} 4.9) [1335], diltiazem (pIC_{50} 4.7) [1376], bilobalide (pIC_{50} 3.3) [1376], ginkgolide B (pIC_{50} 3.1) [1376]
Labelled ligands	–	[^{3}H]ramosetron (Antagonist) (pK_d 9.8) [963], [^{3}H]GR65630 (Antagonist) (pK_d 8.6–9.3) [548, 771], [^{3}H]granisetron (Antagonist) (pK_d 8.9) [147, 566], [^{3}H](*S*)-zacopride (Antagonist) (pK_d 8.7) [1078], [^{3}H]LY278584 (Antagonist) (pK_d 8.5) [5]
Functional Characteristics	γ = 0.4-0.8 pS [+ 5-HT_3B, γ = 16 pS]; inwardly rectifying current [+ 5-HT_3B, rectification reduced]; n_H 2-3 [+ 5-HT_3B 1-2]; relative permeability to divalent cations reduced by co-expression of the 5-HT_3B subunit	γ = 0.4-0.8 pS [+ 5-HT_3B, γ = 16 pS]; inwardly rectifying current [+ 5-HT_3B, rectification reduced]; n_H 2-3 [+ 5-HT_3B 1-2]; relative permeability to divalent cations reduced by co-expression of the 5-HT_3B subunit

Subunits

Nomenclature	5-HT_3A	5-HT_3B	5-HT_3C	5-HT_3D	5-HT_3E
HGNC, UniProt	*HTR3A*, P46098	*HTR3B*, O95264	*HTR3C*, Q8WXA8	*HTR3D*, Q70Z44	*HTR3E*, A5X5Y0
Functional Characteristics	γ = 0.4-0.8 pS [+ 5-HT_3B, γ = 16 pS]; inwardly rectifying current [+ 5-HT_3B, rectification reduced]; n_H 2-3 [+ 5-HT_3B 1-2]; relative permeability to divalent cations reduced by co-expression of the 5-HT_3B subunit	γ = 0.4-0.8 pS [+ 5-HT_3B, γ = 16 pS]; inwardly rectifying current [+ 5-HT_3B, rectification reduced]; n_H 2-3 [+ 5-HT_3B 1-2]; relative permeability to divalent cations reduced by co-expression of the 5-HT_3B subunit	–	–	–

Comments: Quantitative data in the table refer to homo-oligomeric assemblies of the human 5-HT_3A subunit, or the receptor native to human tissues. Significant changes introduced by co-expression of the 5-HT_3B subunit are indicated in parenthesis. Although not a selective antagonist, methadone displays multimodal and subunit-dependent antagonism of 5-HT_3 receptors [301]. Similarly, TMB-8, diltiazem, picrotoxin, bilobalide and ginkgolide B are not selective for 5-HT_3 receptors (*e.g.*[1377]). The anti-malarial drugs mefloquine and quinine exert a modestly more potent block of 5-HT_3A versus 5-HT_3AB receptor-mediated responses [1379]. Known better as a partial agonist of nicotinic acetylcholine α4β2 receptors, varenicline is also an agonist of the 5-HT_3A receptor [869]. Human [103, 963], rat [605], mouse [910], guinea-pig [771] ferret [965] and canine [631] orthologues of the 5-HT_3A receptor subunit have been cloned that exhibit intraspecies variations in receptor pharmacology. Notably, most ligands display significantly reduced affinities at the guinea-pig 5-HT_3 receptor in comparison with other species. In addition to the agents listed in the table, native and recombinant 5-HT_3 receptors are subject to allosteric modulation by extracellular divalent cations, alcohols, several general anaesthetics and 5-hydroxy- and halide-substituted indoles (see reviews [32, 33, 1079, 1380, 1381, 1463]). The use of molecular dynamic simulation revealed cryptic binding pockets in cryo-EM structures of 5-HT_3AR, identifying a binding site for the positive allosteric modulator BrAmp, which was validated using site-directed mutagenesis with electrophysiological analysis [148, 503].

Further reading on 5-HT$_3$ receptors

Andrews PL *et al*. (2014) Nausea and the quest for the perfect anti-emetic. *Eur J Pharmacol* **722**: 108-21 [PMID:24157981]

Barnes NM *et al*. (2021) International Union of Basic and Clinical Pharmacology. CX. Classification of Receptors for 5-hydroxytryptamine; Pharmacology and Function. *Pharmacol Rev* **73**: 310-520 [PMID:33370241]

Chang-Halabi Y *et al*. (2023) Crosstalking interactions between P2X4 and 5-HT$_{3A}$ receptors. *Neuropharmacology* **236**: 109574 [PMID:37156336]

Fakhfouri G *et al*. (2015) From Chemotherapy-Induced Emesis to Neuroprotection: Therapeutic Opportunities for 5-HT3 Receptor Antagonists. *Mol Neurobiol* **52**: 1670-1679 [PMID:25377794]

Gibbs E *et al*. (2021) Structure, Function and Physiology of 5-Hydroxytryptamine Receptors Subtype 3. *Subcell Biochem* **96**: 373-408 [PMID:33252737]

Gupta D *et al*. (2016) 5HT3 receptors: Target for new antidepressant drugs. *Neurosci Biobehav Rev* **64**: 311-25 [PMID:26976353]

Lochner M *et al*. (2015) A review of fluorescent ligands for studying 5-HT3 receptors. *Neuropharmacology* **98**: 31-40 [PMID:25892507]

Merecz K *et al*. (2023) An overview of 5-HT$_3$ receptor antagonists as a treatment option for irritable bowel syndrome with diarrhea. *Expert Opin Pharmacother* **24**: 1189-1198 [PMID:37173833]

Rojas C *et al*. (2014) Molecular mechanisms of 5-HT(3) and NK(1) receptor antagonists in prevention of emesis. *Eur J Pharmacol* **722**: 26-37 [PMID:24184669]

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

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

Overview: Acid-sensing ion channels (ASICs, **nomenclature as agreed by NC-IUPHAR** [32, 33, 692]) are members of a Na^+ channel superfamily that includes the epithelial Na^+ channel (ENaC), the FMRF-amide activated channel (FaNaC) of invertebrates, the degenerins (DEG) of *Caenorhabditis elegans*, channels in *Drosophila melanogaster* and the mammalian bile acid-activated ion channel BASIC [1511], previously known as BLINaC [1213] and INaC [1231]. ASIC subunits contain 2 TM domains and a large extracellular part whose shape resembles that of a hand, as shown by high-resolution structures of chicken and human ASIC1a [62, 461, 626, 1334, 1576, 1577]. They assemble as homo- or heterotrimers to form proton-gated, voltage-insensitive, Na^+ permeable, channels that are activated by levels of acidosis occurring in both physiological and pathophysiological conditions with ASIC3 also playing a role in mechanosensation (reviewed in [225, 484, 692, 1187, 1506]). Splice variants of ASIC1 [termed ASIC1a (ASIC, ASICα, BNaC2α) [1455], ASIC1b (ASICβ, BNaC2β) [207] and ASIC1b2 (ASICβ2) [1412]; note that ASIC1a is also permeable to Ca^{2+}], ASIC2 [termed ASIC2a (MDEG1, BNaC1α, BNC1α) [429, 1138, 1457] and ASIC2b (MDEG2, BNaC1β) [832]] differ in the first third of the protein. Unlike ASIC2a (listed in table), heterologous expression of ASIC2b alone does not support H^+-gated currents. A third member, ASIC3 (DRASIC, TNaC1) [1454] is one of the most pH-sensitive isoforms (along with ASIC1a) and has the fastest activation and desensitisation kinetics, however can also carry small sustained currents. ASIC4 (SPASIC) evolved as a proton-sensitive channel but seems to have lost this function in mammals [871]. Mammalian ASIC4 does not support a proton-gated channel in heterologous expression systems but is reported to downregulate the expression of ASIC1a and ASIC3 [19, 228, 335, 483, 828]. ASICs channels are primarily expressed in central (ASIC1a, -2a, 2b and -4) and peripheral neurons including nociceptors (ASIC1-3) where they participate in neuronal sensitivity to acidosis. Humans express, in contrast to rodents, ASIC3 also in the brain [304]. ASICs have also been detected in 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) (ASIC distribution is reviewed in [312, 482, 829]). A neurotransmitter-like function of protons has been suggested, involving postsynaptically located ASICs of the CNS in functions such as learning and fear perception [344, 747, 1633] and of the PNS in mechanoreceptor-neurite transmission [1550, 1551]. ASIC activation also contributes to cell damage in focal ischemia [1171, 1538] and autoimmune inflammation (arthritis and multiple sclerosis) [415, 1549], as well as neuron activation during seizures and pain [134, 313, 314, 327, 1506]. Heterologously expressed heteromultimers form ion channels with differences in kinetics, ion selectivity, pH- sensitivity and sensitivity to blockers that resemble some of the native proton activated currents recorded from neurones [60, 84, 375, 832]. In general, the known small molecule inhibitors of ASICs are non-selective or partially selective, whereas the venom peptide inhibitors have substantially higher selectivity and potency. Several clinically used drugs are known to inhibit ASICs, however they are generally more potent at other targets (*e.g.*amiloride at ENaCs, ibuprofen at COX enzymes) [1060, 1168]. The information in the tables below are for the effects of inhibitors on homomeric channels, for information of known effects on heteromeric channels see the comments below.

Nomenclature	ASIC1	ASIC2
HGNC, UniProt	*ASIC1*, P78348	*ASIC2*, Q16515
Endogenous activators	Extracellular H^+ (ASIC1a) (pEC_{50}~6.2–6.8), Extracellular H^+ (ASIC1b) (pEC_{50}~5.1–6.2)	Extracellular H^+ (pEC_{50}~4.1–5)
Channel blockers	Pi-hexatoxin-Hi1a (ASIC1a) (pIC_{50}~9.3) [158], psalmotoxin 1 (ASIC1a) (pIC_{50} 9) [375], Pi-theraphotoxin-Hm3a (ASIC1a) (pIC_{50}~8.5) [369], Zn^{2+} (ASIC1a) (pIC_{50}~8.2) [234], JNJ-799760 (ASIC1a @pH6.0) (pIC_{50} 7.6) [849], compound 5b (ASIC1a @pH6.7) (pIC_{50} 7.6) [165], JNJ-67869386 (ASIC1a @pH6.0) (pIC_{50} 7.5) [849], mambalgin-1 (ASIC1a) (pIC_{50}~7.3) [327], 6-iodoamiloride (ASIC1a) (pIC_{50} 7.1) [403], ASC06-IgG1 (Inhibition) (pIC_{50}~7.1) [1147], mambalgin-1 (ASIC1b) (pIC_{50}~7) [81], diminazene (ASIC1a & ASIC1b) (pIC_{50}~6.5) [743, 783, 1237], NS383 (ASIC1a @pH6.5) (pIC_{50} 6.4) [982], compound 3b (ASIC1a @pH6.0) (pIC_{50} 6.4) [466], Pb^{2+} (ASIC1b) (pIC_{50}~5.8), A-317567 (ASIC1a) (pIC_{50}~5.7) [346] – Rat, Pb^{2+} (ASIC1a) (pIC_{50}~5.4) [1482], compound 5b (ASIC1a @pH5.0) (pIC_{50} 5.2) [165], amiloride (ASIC1a) (pIC_{50} 5), benzamil (ASIC1a) (pIC_{50} 5) [1455], ethylisopropylamiloride (ASIC1a) (pIC_{50} 5) [1455], nafamostat (ASIC1a) (pIC_{50}~4.9) [1411], amiloride (ASIC1b) (pIC_{50} 4.7) [1455], flurbiprofen (ASIC1a) (pIC_{50} 3.5) [1444] – Rat, ibuprofen (ASIC1a) (pIC_{50}~3.5) [872, 1444]	diminazene (pIC_{50}~6.1) [783], amiloride (pIC_{50} 4.6) [1457], A-317567 (pIC_{50}~4.5) [346], nafamostat (pIC_{50}~4.2) [1411], Cd^{2+} (Partial inhibition) (pIC_{50}~3) [1309]
Labelled ligands	[^{125}I]psalmotoxin 1 (ASIC1a) (pK_d 9.7) [1218]	–
Functional Characteristics	**ASIC1a:** γ =14pS P_{Na}/P_K = 5-13, P_{Na}/P_{Ca} =2.5 rapid activation rate (5.8-13.7 ms), rapid inactivation rate (1.2-4 s) @ pH 6.0, slow recovery (5.3-13s) @ pH 7.4 **ASIC1b:** γ =19 pS P_{Na}/P_K =14.0, $P_{Na} \gg P_{Ca}$ 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	γ=10.4-13.4 pS P_{Na}/P_K =10, P_{Na}/P_{Ca} = 20 rapid activation rate, moderate inactivation rate (3.3-5.5 s) @ pH 5
Comments	ASIC1a and ASIC1b are activated by the heteromeric Texas coral snake toxin MitTx, with pEC_{50} values of ˜8 and ˜7.6 respectively [134]. The inhibition by amiloride and diminazene decreases at more positive voltages. The inhibitory potency of compound 5b, JNJ-67869386, JNJ-799760, ibuprofen and NS383 is decreased at more acidic pH [165, 849, 982].	ASIC2 is also blocked by other diarylamidines [216]. The inhibition by amiloride and diminazene decreases at more positive voltages.

Nomenclature	ASIC3
HGNC, UniProt	*ASIC3*, Q9UHC3
Endogenous activators	Extracellular H^+ (transient component) (pEC_{50}~6.2–6.7), lysophosphatidylcholine (Partial agonist) (pEC_{50} 5.4) [912], Extracellular H^+ (sustained component) (pEC_{50}~3.5–4.3)
Activators	GMQ (largly non-desensitizing; at pH 7.4) (pEC_{50}~3) [1590], arcaine (at pH 7.4) (pEC_{50}~2.9) [813], agmatine (at pH 7.4) (pEC_{50}~2) [813]
Channel blockers	APETx2 (transient component only) (pIC_{50} 7.2) [326], diminazene (pIC_{50}~6.5) [783], A-317567 (pIC_{50} 6) [755], NS383 (@ pH6.5; inhibition of rat but not human ASIC3) (pIC_{50} 5.7) [982] – Rat, nafamostat (transient component) (pIC_{50}~5.6) [1411], Ugr 9-1 (transient component) (pIC_{50} 5) [1061], amiloride (transient component only - sustained component enhanced by 200µM amiloride at pH 4) (pIC_{50} 4.2–4.8) [1454], Gd^{3+} (pIC_{50} 4.4) [60], Zn^{2+} (pIC_{50} 4.2) [637], aspirin (sustained component) (pIC_{50} 4) [1444], diclofenac (sustained component) (pIC_{50} 4) [1444], salicylic acid (sustained component) (pIC_{50} 3.6) [1444]
Functional Characteristics	γ=13-15 pS; biphasic 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
Comments	ASIC3 is activated by Mit-Toxin (pEC_{50} ˜6.1) [134]. The inhibition by amiloride and diminazene decreases at more positive voltages. The inhibitory potency of NS383 is decreased at more acidic pH [982].

Comments: Psalmotoxin 1 (PcTx1) inhibits ASIC1a by increasing the affinity to H+ and promoting channel desensitization [214, 375]. PcTx1 has little effect on ASIC2a, ASIC3 or ASIC1a expressed as a heteromultimer with ASIC3 or ASIC2 if the holding pH between acidic stimulations is 7.4 [375, 644]. PcTx1 and π-Hm3a potentiate ASIC1b currents [215, 369]. ASIC1-containing homo- and heteromers are inhibited by Mambalgins, toxins contained in the black mamba venom, which induce in ASIC1a an acidic shift of the pH dependence of activation [327]. π-Hi1a is selective for ASIC1a with mild potentiating activity at ASIC1b. It inhibits channel activation and is very slowly reversible [198]. APETx2 most potently blocks homomeric ASIC3 channels, but also ASIC2b+ASIC3, ASIC1b+ASIC3, and ASIC1a+ASIC3 heteromeric channels with IC_{50} values of 117 nM, 900 nM and 2 μM, respectively. APETx2 has no effect on ASIC1a or ASIC2a+ASIC3, however, it does potentiate ASIC1b and ASIC2a homomers in the low micromolar range (1-10 μM) [326, 328, 783]. APETx2 however also inhibits voltage-gated Na^+ channels [125, 1097]. The antibody ASC06-IgG1 binds to the structurally intact channel in the upper part of the extracellular domain with substantial contact on the finger domain and is highly selective for ASIC1a over other subtypes [1147]. IC_{50} value for A-317567 was determined using high throughput electrophysiology on human ASIC3 expressed in HEK293 cells [755]. For some of the newer small molecule inhibitors it is not known whether they inhibit ion channels in addition to ASICs [165, 849, 982]. The pEC_{50} values for proton activation of ASIC channels are influenced by numerous factors including extracellular di- and poly-valent ions, Zn^{2+}, protein kinase C and serine proteases (reviewed in [692, 1506]). Rapid acidification is required for activation of ASIC1 and ASIC3 due to fast inactivation/desensitization. pEC_{50} values for H^+-activation of either transient, or sustained, currents mediated by ASIC3 vary in the literature and may reflect species and/or methodological differences [61, 290, 1454]. The transient ASIC current component is Na^+-selective (P_{Na}/P_K of about 10) [1454, 1561] whereas the sustained current component that is observed with ASIC3 and some ASIC heteromers is non-selective between Na^+ and K^+ [290]. The reducing agents dithiothreitol (DTT) and glutathione (GSH) increase ASIC1a currents expressed in CHO cells and ASIC-like currents in sensory ganglia and central neurons [45, 233] whereas oxidation, through the formation of intersubunit disulphide bonds, reduces currents mediated by ASIC1a [1601]. ASIC1a is also irreversibly modulated by extracellular serine proteases, such as trypsin, through proteolytic cleavage [1449]. Non-steroidal anti-inflammatory drugs (NSAIDs) are direct inhibitors of ASIC currents (reviewed in [82]). Extracellular Zn^{2+} potentiates proton activation of homomeric and heteromeric channels incorporating ASIC2a, but not homomeric ASIC1a or ASIC3 channels [83]. However, removal of contaminating Zn^{2+} by chelation reveals a high affinity block of homomeric ASIC1a and heteromeric ASIC1a+ASIC2 channels by Zn^{2+} indicating complex biphasic actions of the divalent [234]. Nitric oxide potentiates submaximal currents activated by H^+ mediated by ASIC1a, ASIC1b, ASIC2a and ASIC3 [168]. 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 [469, 1433]. Inflammatory conditions and particular pro-inflammatory mediators such as arachidonic acid induce overexpression of ASIC-encoding genes and enhance ASIC currents [314, 907, 1289]. The sustained current component mediated by ASIC3 is potentiated by hypertonic solutions in a manner that is synergistic with the effect of arachidonic acid [314]. ASIC3 is partially activated by the lipids lysophosphatidylcholine (LPC) and arachidonic acid [912]. MitToxin, which is contained in the venom of the Texas coral snake, activates several ASIC subtypes [134]. Selective activation of ASIC3 by GMQ, likely by binding to the central vestibule, is potentiated by mild acidosis and reduced extracellular Ca^{2+} [1590].

Additional notes on the channels: Until recently they were thought to be vertebrate specific channels, however are now known to have evolved over 600 million years ago and appear to be conserved throughout the superphylum of animals known as deuterostomes (which includes vertebrates, tunicates, starfish, sea urchins, sea cucumbers and acorn worms) [871]. Recently an ion-conducting-independent signaling mechanism has been revealed for ASIC1a whereby the acidosis-activated channel recruits RIPK1 to its C-terminus resulting in RIPK1 phosphorylation and activation of necroptosis. This pathways is suggested to be the primary cause of ASIC-mediated neuronal cell death in ischemic stroke [1475, 1491].

Further reading on Acid-sensing (proton-gated) ion channels (ASICs)

Gründer S *et al*. (2024) Acid-sensing ion channels and downstream signalling in cancer cells: is there a mechanistic link? *Pflugers Arch* **476**: 659-672 [PMID:38175291]

Gründer S. (2020) *In The Oxford Handbook of Neuronal Ion Channels* Oxford University Press:

Kellenberger S *et al*. (2015) International Union of Basic and Clinical Pharmacology. XCI. structure, function, and pharmacology of acid-sensing ion channels and the epithelial Na+ channel. *Pharmacol Rev* **67**: 1-35 [PMID:25287517]

Rook ML *et al*. (2021) Coupling structure with function in acid-sensing ion channels: challenges in pursuit of proton sensors. *J Physiol* **599**: 417-430 [PMID:32306405]

Verkest C *et al*. (2022) Mechanisms of Action of the Peptide Toxins Targeting Human and Rodent Acid-Sensing Ion Channels and Relevance to Their In Vivo Analgesic Effects. *Toxins (Basel)* **14**: [PMID:36287977]

Epithelial sodium channel (ENaC)

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

Overview

Epithelial sodium channels (ENaC) are located on the apical membrane of epithelial cells in the kidney tubules, lungs, respiratory tract, male and female reproductive tracts, sweat and salivary glands, placenta, colon, and several other organs [171, 348, 512, 513, 1260]. In these epithelia, Na^+ ions enter epithelial cells from the extracellular fluid *via* ENaC and are subsequently pumped out into the interstitial fluid by the Na^+/K^+-ATPase on the basolateral membrane [1123]. Because sodium is a major electrolyte in the extracellular fluid (ECF), the osmotic changes caused by sodium

flux are accompanied by parallel water movement [143]. Thus, ENaC plays a central role in regulating ECF volume and blood pressure, primarily through its function in the kidney [1190]. The expression of ENaC subunits- and therefore its activity- is controlled by the renin-angiotensin-aldosterone system and other factors involved in electrolyte homeostasis [722, 1190].
Genetic studies of systemic pseudohypoaldosteronism type I revealed that ENaC activity depends on three essential subunits encoded by three separate genes encoding homologous proteins [194, 513]. Within the wider protein superfamily that includes ENaC, the first crystal structure determined was that of ASIC, which revealed a trimeric structure with a large extracellular domain anchored in the membrane by a bundle of six transmembrane helices (two per subunit) [62, 626]. The first 3D structure of human ENaC was determined using single-particle cryo-electron microscopy at 3.7Å resolution [1031], later improved to 3.0Å [1032]. These structures confirmed that ENaC has a quaternary structure similar to ASIC. ENaC assembles as a heterotrimer, with α-, γ-, and β-subunits arranged in clockwise order when viewed from above [252]. In contrast to ASIC1, which can form a functional homotrimer, ENaC is only fully functional as a heterotrimer composed of either αβγ or δβγ [692]. Recently, Houser and Baconguis co-expressed human δ, β, and γ and determined the structures of complexes using single-particle cryoelectron microscopy. The structures showed that β and γ positions are conserved among the different complexes while the α position in the αβγ trimer is occupied by either δ or another β [573].
In the respiratory and female reproductive tracts, large regions of the epithelium consist of multiciliated cells with a microtubule-based cytoskeleton. In these cells, ENaC is distributed along the entire length of the cilia [368]. This localization substantially increases ENaC density on the cell surface and enables precise regulation of periciliary fluid osmolarity throughout its depth [368]. In the *vas deferens* of the male reproductive tract, the luminal surface is covered with microvilli and stereocilia supported by actin bundles [1260]. In these cells, both ENaC and the aquaporin AQP9 are localized to the projections as well as to the basal and smooth muscle layers [1260]. In contrast, CFTR- the chloride channel defective in cystic fibrosis- is confined to the apical cell surface but is absent from cilia and microvilli [368, 1260]. Collectively, ENaC function regulates epithelial fluid volume, which is essential for mucociliary clearance in the respiratory tract, gamete transport, fertilization, implantation, and cell migration [368, 513, 919].

Genes and Phylogeny

The human genome contains four homologous genes (*SCNN1A, SCNN1B, SCNN1G*, and *SCNN1D*) encoding the α-, β-, γ-, and δ-ENaC subunits, respectively [172, 833, 1229, 1456]. These subunits share 23-34% sequence identity and <20% identity with ASIC subunits [513]. Genes encoding all four ENaC subunits are present in bony vertebrates, except in ray-finned fishes, which have lost them entirely. The mouse genome has also lost *SCNN1D*, the gene for δ-ENaC [457, 513]. The α-, β-, and γ-ENaC genes are present in jawless vertebrates (*e.g.*, lampreys) and cartilaginous fishes (*e.g.*, sharks) [513].
Methylation analysis of the 5′-flanking regions of *SCNN1A, SCNN1B*, and *SCNN1G* in human cells revealed an inverse correlation between gene expression and DNA methylation, suggesting epigenetic transcriptional control of ENaC genes [1115].

Channel biogenesis, assembly and function

ENaC subunit expression is regulated primarily by aldosterone and by numerous other extracellular and intracellular factors [719, 1069, 1190]. Most studies indicate that expression of the three subunits is not tightly coordinated [166]. However, transport of the subunits to the membrane requires all three intact subunits, and even a single missense mutation can reduce the number of assembled channels on the cell surface [359].
ENaC is constitutively active, meaning Na^+ flow does not require an activating factor. Thus, heterologous cells expressing ENaC (*e.g.*, human cRNAs in *Xenopus* oocytes) must be maintained in amiloride-containing solutions to block channel activity. ENaC activity is then measured by replacing the bath with amiloride-free solution. The channel alternates between two states: 1) open and 2) closed. The probability of ENaC being open is referred to as open probability (P_o). ENaC regulation involves two key parameters: (1) membrane channel density and (2) open probability [680, 692].
Open probability is markedly reduced by extracellular Na^+ in a process known as sodium self-inhibition [123, 568, 1265].
A key regulatory feature is that the α- and γ-subunits contain conserved extracellular serine protease cleavage sites [513]. Proteolytic cleavage by enzymes such as furin and plasmin activates ENaC [37, 718, 1191].

Diseases associated with ENaC mutations

Mutations in *SCNN1A*, *SCNN1B*, or *SCNN1G* can cause partial or complete loss of ENaC activity [194, 510]. Such loss-of-function mutations are associated with systemic or multi-system autosomal recessive pseudohypoaldosteronism type I (OMIM abbreviation: PHA1B) [194, 368, 509, 513, 1228, 1599]. No PHA-causing mutations have been identified in SCNN1D. Patients with PHA experience severe salt wasting in all aldosterone target organs expressing ENaC, including kidney, sweat glands, salivary glands, and respiratory tract. In infancy and early childhood, the resulting electrolyte disturbances, dehydration, and acidosis often require recurrent hospitalization. The frequency and severity of salt-wasting episodes generally improve with age [511]. PHA1B also affects female reproductive system function [132, 368].
The ENaC carboxy-terminal region contains a short consensus sequence called the PY motif. Mutations in this motif in *SCNN1B* and *SCNN1G* are associated with Liddle syndrome, a disorder marked by early-onset hypertension [131, 1270]. The PY motif is recognized by Nedd4-2, a ubiquitin ligase. Mutations that disrupt this recognition reduce ENaC ubiquitylation, leading to channel accumulation at the membrane and increased ENaC activity [1192].

ENaC expression in tumors

Intracellular sodium concentrations are often elevated in cancer cells compared with normal cells, leading to the hypothesis that ENaC overexpression may contribute to metastasis [799]. However, RNA-seq analysis of ENaC genes and clinical data of cervical cancer patients from The Cancer Genome Atlas (TCGA) revealed a negative correlation with histologic grades of tumor [1302]. Similarly, in breast cancer cells, overexpression or siRNA-mediated knockdown of α-ENaC showed that higher α-ENaC levels suppress cell proliferation [1493]. In contrast, TCGA data showed that elevated *SCNN1A* expression correlates with poor prognosis in ovarian cancer [858]. Thus, the role of ENaC in tumorigenesis appears to be tissue-specific.

COVID-19

SARS-CoV-2 virions, the cause of COVID-19, are covered with glycosylated spike (S) proteins. These proteins bind to membrane-bound ACE2 as the first step of viral entry. Entry depends on S-protein cleavage (at Arg-667/Ser-668) by a serine protease. Anand *et al*. identified a sequence motif at this cleavage site homologous to the furin cleavage site in ENaCα [38]. A comprehensive review of COVID-19 pathophysiology suggests a role for ENaC in the early stages of infection in respiratory epithelia [441].

ENaC Inhibitors for Cystic Fibrosis

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disorder among Caucasians. CF is caused by mutations in the gene that codes for CFTR (Cystic Fibrosis Transmembrane Conductance Regulator). CFTR is a chloride and bicarbonate channel located on the apical membrane [262]. CFTR-mediated movement of Cl^- and HCO_3^- ions into the lumen also drives water flow into the lumen by osmosis. CFTR is expressed in many tissues but the most severe effect of mutated CFTR is observed in the respiratory tract in the form of airway surface liquid (ASL) depletion which leads to mucus accumulation, inflammation and bacterial infections that lead to mortality.

Normal CFTR activity inhibits ENaC by causing a reduction in surface expression of ENaC as well as its P_o [1169]. In many epithelia, ENaC and CFTR are not co-localized on the apical membrane indicating that the two channels do not directly interact [368, 1258, 1260]. In the absence of a functional CFTR, ENaC activity increases (also named as "hyperactivated ENaC"), leading to increased Na^+ and water absorption and consequently ASL depletion. These observations have led to the development of inhibitors targeting ENaC in the airways to ameliorate ASL dehydration [794, 903, 1261]. Most of the ENaC inhibitors in development are designed for application by inhalation and improved lung retention to avoid damaging the vital activity of ENaC in other tissues [277, 749]. Despite the development of many ENaC inhibitors for CF [275], nearly all drug candidates were discontinued at Preclinical, Phase 1 or Phase 2 stage of clinical trials [277, 794, 903]. However, there is one candidate, EDT001, that is still under Phase 2 clinical trial [277]. The persistence of the scientists and the drug companies and the versatility of their approaches provide hope that an appropriate useful treatment will emerge to help CF patients.

Thus, insights into the physiological and pathological roles of ENaC across diverse tissues continue to guide the development of targeted inhibitors, with cystic fibrosis representing a prominent example where modulation of ENaC activity may translate fundamental biology into therapeutic benefit.

Complexes

Nomenclature	ENaCαβγ
Subunits	ENaC α, ENaC β, ENaC γ
Activators	S3969 (pEC_{50} 5.9) [864]
Inhibitors	BI1265162 (pIC_{50} 8.5) [525] – Mouse, EDT001 (pIC_{50} 7.2) [275]
Channel blockers	P552-02 (pIC_{50} 8.1), benzamil (pIC_{50}~8), amiloride (pIC_{50} 6.7–7), triamterene (pIC_{50}~5.3) [172, 691]

Subunits

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

Further reading on Epithelial sodium channel (ENaC)

Hanukoglu I. (2017) ASIC and ENaC type sodium channels: conformational states and the structures of the ion selectivity filters. *FEBS J* **284**: 525-545 [PMID:27580245]

Houser A *et al*. (2025) Structural insights into subunit-dependent functional regulation in epithelial sodium channels. *Structure* **33**: 349-362.e4 [PMID:39667931]

Kellenberger S *et al*. (2015) International Union of Basic and Clinical Pharmacology. XCI. structure, function, and pharmacology of acid-sensing ion channels and the epithelial Na+ channel. *Pharmacol Rev* **67**: 1-35 [PMID:25287517]

Kleyman TR *et al*. (2020) Regulating ENaC's gate. *Am J Physiol Cell Physiol* **318**: C150-C162 [PMID:31721612]

Rossier BC *et al*. (2015) Epithelial sodium transport and its control by aldosterone: the story of our internal environment revisited. *Physiol Rev* **95**: 297-340 [PMID:25540145]

Sharma S *et al*. (2020) High-resolution imaging of the actin cytoskeleton and epithelial sodium channel, CFTR, and aquaporin-9 localization in the vas deferens. *Mol Reprod Dev* **87**: 305-319 [PMID:31950584]

$GABA_A$ receptors

Ion channels → Ligand-gated ion channels → $GABA_A$ receptors

Overview: The $GABA_A$ receptor is a ligand-gated ion channel of the Cys-loop family that includes the nicotinic acetylcholine, 5-HT_3 and strychnine-sensitive glycine receptors. $GABA_A$ receptor-mediated inhibition within the CNS occurs by fast synaptic transmission, sustained tonic inhibition and temporally intermediate events that have been termed '$GABA_{A}$, slow' [179]. $GABA_A$ receptors exist as pentamers of 4TM subunits that form an intrinsic anion selective channel. Sequences of six α, three β, three γ, one δ, three ρ, one ϵ, one π and one θ $GABA_A$ receptor subunits have been reported in mammals [1051, 1052, 1274, 1278]. 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 [279]. The three ρ-subunits, (ρ1-3) function as either homo- or hetero-oligomeric assemblies [205, 1602]. Receptors formed from ρ-subunits, because of their distinctive pharmacology that includes insensitivity to bicuculline, benzodiazepines and barbiturates, have sometimes been termed $GABA_C$ receptors [1602], **but they are classified as $GABA_A$ receptors by NC-IUPHAR on the basis of structural and functional criteria** [79, 1051, 1052].

Many $GABA_A$ receptor subtypes contain α-, β- and γ-subunits with the likely stoichiometry 2α.2β.1γ [733, 1051]. It is thought that the majority of $GABA_A$ receptors harbour a single type of α- and β -subunit variant. The α1β2γ2 hetero-oligomer constitutes the largest population of $GABA_A$ receptors in the CNS, followed by the α2β3γ2 and α3β3γ2 isoforms. Receptors that incorporate the α4- α5-or α6-subunit, or the β1-, γ1-, γ3-, δ-, ϵ- and θ-subunits, are less numerous, but they may nonetheless serve important functions. For example, extrasynaptically located receptors that contain α6- and δ-subunits in cerebellar granule cells, or an α4- and δ-subunit in dentate gyrus granule cells and thalamic neurones, mediate a tonic current that is important for neuronal excitability in response to ambient concentrations of GABA [104, 388, 966, 1251, 1295]. GABA binding occurs at the β+/α- subunit interface and the homologous γ+/α- subunits interface creates the benzodiazepine site. A second site for benzodiazepine binding has recently been postulated to occur at the α+/β- interface ([1161]; reviewed by [1277]). 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 [1578]). The trafficking, cell surface expression, internalisation and function of $GABA_A$ receptors and their subunits are discussed in detail in several recent reviews [222, 613, 870, 1438] 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 [32, 33, 79, 1051] class the $GABA_A$ receptors according to their subunit structure, pharmacology and receptor function. Currently, eleven native $GABA_A$ receptors are classed as conclusively identified (*i.e.*, α1β2γ2, α2βγ2, α3βγ2, α4βγ2, α4β2δ, α4β3δ, α5βγ2, α6βγ2, α6β2δ, α6β3δ and ρ) with further receptor isoforms occurring with high probability, or only tentatively [1051, 1052]. It is beyond the scope of this Guide to discuss the pharmacology of individual $GABA_A$ receptor isoforms in detail; such information can be gleaned in the reviews [54, 55, 79, 417, 647, 733, 750, 967, 1051, 1052, 1274, 1276]. 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 [205, 648, 1008, 1602].

Several high-resolution cryo-electron microscopy structures have been described in which the full-length human α1β3γ2L $GABA_A$ receptor in lipid nanodiscs is bound to the channel-blocker picrotoxin, the competitive antagonist bicuculline, the agonist GABA (γ-aminobutyric acid), and the classical benzodiazepines alprazolam and diazepam [918].

Nomenclature	$GABA_A$ receptor α1 subunit	$GABA_A$ receptor α2 subunit
HGNC, UniProt	*GABRA1*, P14867	*GABRA2*, P47869
Agonists	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], isonipecotic acid [GABA site], muscimol [GABA site], piperidine-4-sulphonic acid [GABA site]
Antagonists	bicuculline [GABA site], gabazine [GABA site]	bicuculline [GABA site], gabazine [GABA site]
Channel blockers	TBPS, picrotoxin	TBPS, picrotoxin
Allosteric modulators	flumazenil [benzodiazepine site] (Antagonist) (pK_i 9.1) [1276], α3IA [benzodiazepine site] (Inverse agonist) [1276], α5IA [benzodiazepine site] (Inverse agonist) [1276], DMCM [benzodiazepine site] (Inverse agonist) [1160]	flumazenil [benzodiazepine site] (Antagonist at α1 receptors, but allosteric modulator at other subtypes.) (pK_i 9.1) [1276], α3IA [benzodiazepine site] (Inverse agonist) [1276], α5IA [benzodiazepine site] (Inverse agonist) [1276], DMCM [benzodiazepine site] (Inverse agonist) [1160]
Endogenous allosteric modulators	5α-pregnan-3α-ol-20-one (Potentiation), Zn^{2+} (Inhibition), tetrahydrodeoxycorticosterone (Potentiation)	5α-pregnan-3α-ol-20-one (Potentiation), Zn^{2+} (Inhibition), tetrahydrodeoxycorticosterone (Potentiation)
Allosteric modulators (Positive)	clonazepam [benzodiazepine site] (pK_i 8.9) [1139], flunitrazepam [benzodiazepine site] (pK_i 8.3) [497], diazepam [benzodiazepine site] (pK_i 7.8) [1139], alprazolam [benzodiazepine site] (pEC_{50} 7.4) [27]	clonazepam [benzodiazepine site] (pK_i 8.8) [1139], flunitrazepam [benzodiazepine site] (pK_i 8.3) [497], alprazolam [benzodiazepine site] (pEC_{50} 7.9) [27], diazepam [benzodiazepine site] (pK_i 7.8) [1139]
Selective allosteric modulators	zolpidem (Positive) (pK_i 7.4–7.7) [498, 1240, 1276], L838417 [benzodiazepine site] (Antagonist) [1276]	L838417 [benzodiazepine site] (Partial agonist) [1276], TPA023 [benzodiazepine site] (Partial agonist) [1276]
Labelled ligands	[^{11}C]flumazenil [benzodiazepine site] (Allosteric modulator, Antagonist), [^{18}F]fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator), [^{35}S]TBPS [anion channel] (Channel blocker), [^{3}H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [^{3}H]flunitrazepam [benzodiazepine site] (Allosteric modulator), [^{3}H]gabazine [GABA site] (Antagonist), [^{3}H]muscimol [GABA site] (Agonist), [^{3}H]zolpidem [benzodiazepine site] (Allosteric modulator)	[^{11}C]flumazenil [benzodiazepine site] (Allosteric modulator), [^{18}F]fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator), [^{35}S]TBPS [anion channel] (Channel blocker), [^{3}H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [^{3}H]flunitrazepam [benzodiazepine site] (Allosteric modulator, Full agonist), [^{3}H]gabazine [GABA site] (Antagonist), [^{3}H]muscimol [GABA site] (Agonist)
Comments	Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [748]	Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [748]

Nomenclature	$GABA_A$ receptor α3 subunit	$GABA_A$ receptor α4 subunit
HGNC, UniProt	*GABRA3*, P34903	*GABRA4*, P48169
Agonists	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, partially selective)
Antagonists	bicuculline [GABA site], gabazine [GABA site]	bicuculline [GABA site], gabazine [GABA site]
Channel blockers	TBPS, picrotoxin	TBPS, picrotoxin
Allosteric modulators	flumazenil [benzodiazepine site] (Antagonist at α1 receptors, but allosteric modulator at other subtypes.) (pK_i 9) [1160, 1276], α5IA [benzodiazepine site] (Inverse agonist) [1276], DMCM [benzodiazepine site] (Inverse agonist) [1160]	bretazenil [benzodiazepine site] (Full agonist) [1160]
Endogenous allosteric modulators	5α-pregnan-3α-ol-20-one (Potentiation), Zn^{2+} (Inhibition), tetrahydrodeoxycorticosterone (Potentiation)	5α-pregnan-3α-ol-20-one (Potentiation), Zn^{2+} (Inhibition), tetrahydrodeoxycorticosterone (Potentiation)
Allosteric modulators (Positive)	clonazepam [benzodiazepine site] (pK_i 8.7) [1139], flunitrazepam [benzodiazepine site] (pK_i 7.8) [497], diazepam [benzodiazepine site] (pK_i 7.8) [1139], alprazolam [benzodiazepine site] (pEC_{50} 7.2) [27]	–
Selective allosteric modulators	α3IA [benzodiazepine site] (higher affinity, partially selective) [1276], L838417 [benzodiazepine site] (Partial agonist) [1276], Ro19-4603 [benzodiazepine site] (Inverse agonist), TP003 [benzodiazepine site] (Partial agonist) [1276], TPA023 [benzodiazepine site] (Partial agonist) [1276]	Ro15-4513 [benzodiazepine site] (Full agonist)
Labelled ligands	[^{11}C]flumazenil [benzodiazepine site] (Allosteric modulator), [^{18}F]fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator), [^{35}S]TBPS [anion channel] (Channel blocker), [^{3}H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [^{3}H]flunitrazepam [benzodiazepine site] (Allosteric modulator, Full agonist), [^{3}H]gabazine [GABA site] (Antagonist), [^{3}H]muscimol [GABA site] (Agonist)	[^{11}C]flumazenil [benzodiazepine site] (Allosteric modulator, Partial agonist), [^{18}F]fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator), [^{35}S]TBPS [anion channel] (Channel blocker), [^{3}H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [^{3}H]Ro154513 [benzodiazepine site] (Allosteric modulator, Full agonist), [^{3}H]gabazine [GABA site] (Antagonist), [^{3}H]muscimol [GABA site] (Agonist)
Comments	Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [748]	Diazepam and flunitrazepam are not active at this subunit. Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [748]. [^{3}H]Ro154513 labels α4βγ2 and α6βγ2 receptors in the presence of a saturating concentration of a 'classical' benzodiazepine (*e.g.*diazepam).

Nomenclature	$GABA_A$ receptor α5 subunit	$GABA_A$ receptor α6 subunit
HGNC, UniProt	*GABRA5*, P31644	*GABRA6*, Q16445
Agonists	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, relatively selective)
Antagonists	bicuculline [GABA site], gabazine [GABA site]	bicuculline [GABA site], gabazine [GABA site]
Channel blockers	TBPS, picrotoxin	TBPS, picrotoxin
Allosteric modulators	flumazenil [benzodiazepine site] (Antagonist at α1 receptors, but allosteric modulator at other subtypes.) (pK_i 9.2) [1276], α3IA [benzodiazepine site] (Inverse agonist) [1276], DMCM [benzodiazepine site] (Inverse agonist) [1160]	flumazenil [benzodiazepine site] (Partial agonist) (pK_i 6.8) [1276], bretazenil [benzodiazepine site] (Full agonist) [1160]
Endogenous allosteric modulators	5α-pregnan-3α-ol-20-one (Potentiation), Zn^{2+} (Inhibition), tetrahydrodeoxycorticosterone (Potentiation)	5α-pregnan-3α-ol-20-one (Potentiation), Zn^{2+} (Inhibition), tetrahydrodeoxycorticosterone (Potentiation)
Allosteric modulators (Positive)	flunitrazepam [benzodiazepine site] (pK_i 8.3) [497], alprazolam [benzodiazepine site] (pEC_{50} 8) [27]	–
Selective allosteric modulators	α5IA [benzodiazepine site] (Inverse agonist) [1276], L655708 [benzodiazepine site] (Inverse agonist) [1160], L838417 [benzodiazepine site] (Partial agonist) [1276], MRK016 [benzodiazepine site] (Inverse agonist) [1276], RO4938581 [benzodiazepine site] (Inverse agonist) [1276], RY024 [benzodiazepine site] (Inverse agonist) [1276]	LAU159 (Full agonist) [1275, 1276], LAU463 (Full agonist) [1275, 1276], PZ-II-029 (Full agonist) [1275, 1276], Ro15-4513 [benzodiazepine site] (Full agonist), amiloride (Antagonist) [1276], furosemide (Antagonist) [1276]
Labelled ligands	[^{3}H]RY80 [benzodiazepine site] (Selective Binding) (pK_d 9.2) [1284] – Rat, [^{11}C]flumazenil [benzodiazepine site] (Allosteric modulator), [^{18}F]fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator), [^{35}S]TBPS [anion channel] (Channel blocker), [^{3}H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [^{3}H]L655708 [benzodiazepine site] (Allosteric modulator, Inverse agonist), [^{3}H]flunitrazepam [benzodiazepine site] (Allosteric modulator, Full agonist), [^{3}H]gabazine [GABA site] (Antagonist), [^{3}H]muscimol [GABA site] (Agonist)	[^{11}C]flumazenil [benzodiazepine site] (Allosteric modulator, Partial agonist), [^{18}F]fluoroethylflumazenil [benzodiazepine site] (Allosteric modulator), [^{35}S]TBPS [anion channel] (Channel blocker), [^{3}H]CGS8216 [benzodiazepine site] (Allosteric modulator, Mixed), [^{3}H]Ro154513 [benzodiazepine site] (Allosteric modulator, Full agonist), [^{3}H]gabazine [GABA site] (Antagonist), [^{3}H]muscimol [GABA site] (Agonist)
Comments	Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [748]	Diazepam and flunitrazepam are not active at channels containing this subunit. Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [748]. [^{3}H]Ro154513 selectively labels α6-subunit and α4-subunit-containing receptors in the presence of a saturating concentration of a 'classical' benzodiazepine (*e.g.*diazepam). Sieghart *et al.* (2022) provides a review of the pharmacology of α6-containing $GABA_A$ receptors.

Nomenclature	$GABA_A$ receptor β1 subunit	$GABA_A$ receptor β2 subunit	$GABA_A$ receptor β3 subunit
HGNC, UniProt	*GABRB1*, P18505	*GABRB2*, P47870	*GABRB3*, P28472
Channel blockers	TBPS, picrotoxin	TBPS, picrotoxin	TBPS, picrotoxin
Allosteric modulators	–	–	etazolate (Binding) (pIC_{50} 5.5) [1600]
Comments	Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [748]		

Nomenclature	$GABA_A$ receptor γ1 subunit	$GABA_A$ receptor γ2 subunit	$GABA_A$ receptor γ3 subunit
HGNC, UniProt	*GABRG1*, Q8N1C3	*GABRG2*, P18507	*GABRG3*, Q99928
Channel blockers	TBPS, picrotoxin	TBPS, picrotoxin	TBPS, picrotoxin
Comments	Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [748], So far, the only publication investigating the pharmacology of more than three or four ligands at γ1 receptors was Khom *et al*. (2006) [700].	Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively [748]	

Nomenclature	$GABA_A$ receptor δ subunit	$GABA_A$ receptor ϵ subunit	$GABA_A$ receptor θ subunit
HGNC, UniProt	*GABRD*, O14764	*GABRE*, P78334	*GABRQ*, Q9UN88
Selective agonists	DS2 [1276], gaboxadol [GABA site], tracazolate [1276]	–	–
Channel blockers	TBPS, picrotoxin	TBPS, picrotoxin	TBPS, picrotoxin
Comments	Zn^{2+} is an endogenous allosteric regulator and causes potent inhibition of receptors formed from binary combinations of α and β subunits, incorporation of a δ or γ subunit causes a modest, or pronounced, reduction in inhibitory potency, respectively	–	–

Nomenclature	$GABA_A$ receptor π subunit	$GABA_A$ receptor ρ1 subunit	$GABA_A$ receptor ρ2 subunit	$GABA_A$ receptor ρ3 subunit
HGNC, UniProt	*GABRP*, O00591	*GABRR1*, P24046	*GABRR2*, P28476	*GABRR3*, A8MPY1
Agonists	–	isoguvacine [GABA site] (Partial agonist), muscimol [GABA site] (Partial agonist)	isoguvacine [GABA site] (Partial agonist), muscimol [GABA site] (Partial agonist)	isoguvacine [GABA site] (Partial agonist), muscimol [GABA site] (Partial agonist)
Selective agonists	–	(±)-*cis*-2-CAMP [GABA site], 5-Me-IAA [GABA site]	(±)-*cis*-2-CAMP [GABA site], 5-Me-IAA [GABA site]	(±)-*cis*-2-CAMP [GABA site], 5-Me-IAA [GABA site]
Antagonists	–	gaboxadol [GABA site] [744], isonipecotic acid [GABA site], piperidine-4-sulphonic acid [GABA site]	gaboxadol [GABA site] [744], isonipecotic acid [GABA site], piperidine-4-sulphonic acid [GABA site]	gaboxadol [GABA site] [744], isonipecotic acid [GABA site], piperidine-4-sulphonic acid [GABA site]
Selective antagonists	–	*cis*-3-ACPBPA [GABA site], *trans*-3-ACPBPA [GABA site], TPMPA [GABA site], aza-THIP [GABA site]	*cis*-3-ACPBPA [GABA site], *trans*-3-ACPBPA [GABA site], TPMPA [GABA site], aza-THIP [GABA site]	*cis*-3-ACPBPA [GABA site], *trans*-3-ACPBPA [GABA site], TPMPA [GABA site], aza-THIP [GABA site]
Channel blockers	TBPS, picrotoxin	TBPS, picrotoxin	TBPS, picrotoxin	TBPS, picrotoxin
Comments	–	Bicuculline is not active at this subunit	Bicuculline is not active at this subunit	Bicuculline is not active at this subunit

Comments: The potency and efficacy of many GABA agonists vary between $GABA_A$ receptor isoforms [417, 677, 750]. For example, gaboxadol is a partial agonist at receptors with the subunit composition α4β3γ2, but elicits currents in excess of those evoked by GABA at the α4β3δ receptor where GABA itself is a low efficacy agonist [118, 156]. The antagonists bicuculline and gabazine differ in their ability to suppress spontaneous openings of the $GABA_A$ receptor, the former being more effective [1385]. The presence of the γ subunit within the heterotrimeric complex reduces the potency and efficacy of agonists [1320]. The $GABA_A$ receptor contains multiple allosteric binding sites. Most drugs modulating $GABA_A$ receptors can bind to several different sites [383]. Distinct allosteric sites bind barbiturates and endogenous (*e.g.*, 5α-pregnan-3α-ol-20-one) and synthetic (*e.g.*, alphaxalone) neuroactive steroids in a diastereo- or enantio-selective manner [105, 533, 569, 1424]. Picrotoxinin and TBPS act at an allosteric site within the chloride channel pore to negatively regulate channel activity; negative allosteric regulation by γ-butyrolactone derivatives also involves the picrotoxinin site, whereas positive allosteric regulation by such compounds is proposed to occur at a distinct locus. Many intravenous (*e.g.*, etomidate, propofol) and inhalational (*e.g.*, halothane, isoflurane) anaesthetics and alcohols also exert a regulatory influence upon $GABA_A$ receptor activity [138, 1050]. Specific amino acid residues within $GABA_A$ receptor α- and β-subunits that influence allosteric regulation by anaesthetic and non-anaesthetic compounds have been identified [530, 569]. Photoaffinity labelling of distinct amino acid residues within purified $GABA_A$ receptors by the etomidate derivative, [^{3}H]azietomidate, has also been demonstrated [805], and this binding is subject to positive allosteric regulation by neurosteroids [804]. An array of natural products including flavonoid and terpenoid compounds exert varied actions at $GABA_A$ receptors (reviewed in detail in [647]).

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 [1386]); fragrant dioxane derivatives (positive allosteric modulators selective for β1- versus β2-, or β3-subunit-containing receptors [1254]); loreclezole, etomidate, tracazolate, mefenamic acid, etifoxine, stiripentol, valerenic acid amide (positive allosteric modulators with selectivity for β2/β3- over β1-subunit-containing receptors [405, 701, 733]); tracazolate (intrinsic efficacy, *i.e.*, potentiation, or inhibition, is dependent upon the identity of the γ1-3-, δ-, or ϵ-subunit co-assembled with α1- and β1-subunits [1384]); amiloride (selective blockade of receptors containing an α6-subunit [406]); furosemide (selective blockade of receptors containing an α6-subunit co-assembled with β2/β3-, but not β1-subunit [733]); La^{3+} (potentiates responses mediated by α1β3γ2L receptors, weakly inhibits α6β3γ2L receptors, and strongly blocks α6β3δ and α4β3δ receptors [156, 1230]); ethanol (selectively potentiates responses mediated by α4β3δ and α6β3δ receptors versus receptors in which β2 replaces β3, or γ replaces δ [1460], but see also [732]); DS1 and DS2 (selectively potentiate responses mediated by δ-subunit-containing receptors [1451]). It should be noted that the apparent selectivity of some positive allosteric modulators (*e.g.*, neurosteroids such as 5α-pregnan-3α-ol-20-one for δ-subunit-containing receptors (*e.g.*, α1β3δ) may be a consequence of the unusually low efficacy of GABA at this receptor isoform [104, 118].

Further reading on $GABA_A$ receptors

Atack JR. (2008) GABA(A) receptor subtype-selective efficacy: TPA023, an alpha2/alpha3 selective non-sedating anxiolytic and alpha5IA, an alpha5 selective cognition enhancer. *CNS Neurosci Ther* **14**: 25-35 [PMID:18482097]

Braat S *et al*. (2015) The GABAA Receptor as a Therapeutic Target for Neurodevelopmental Disorders. *Neuron* **86**: 1119-30 [PMID:26050032]

Calvo DJ *et al*. (2016) Dynamic Regulation of the GABAA Receptor Function by Redox Mechanisms. *Mol Pharmacol* **90**: 326-33 [PMID:27439531]

Masiulis S *et al*. (2019) $GABA_A$ receptor signalling mechanisms revealed by structural pharmacology. *Nature* **565**: 454-459 [PMID:30602790]

Mele M *et al*. (2016) Role of $GABA_A$ R trafficking in the plasticity of inhibitory synapses. *J Neurochem* **139**: 997-1018 [PMID:27424566]

Sieghart W *et al*. (2018) International Union of Basic and Clinical Pharmacology. CVI: $GABA_A$ Receptor Subtype- and Function-selective Ligands: Key Issues in Translation to Humans. *Pharmacol Rev* **70**: 836-878 [PMID:30275042]

Glycine receptors

Ion channels → 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 $GABA_A$, nicotinic acetylcholine and 5-HT_3 receptors and Zn^{2+}- activated channels. The glycine receptor is expressed either as a homo-pentamer of α subunits, or a complex of 4α and 1β subunits [1630], that contains 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 ($α1^{INS}$ and $α1^{del}$), α2 (α2A and α2B), α3 (α3S and α3L) and β (βΔ7) subunits and by mRNA editing of the α2 and α3 subunit [364, 936, 1041]. Both α2 splicing and α3 mRNA editing can produce subunits (*i.e.*, α2B and α3P185L) with enhanced agonist sensitivity. Predominantly, the adult form of the receptor contains α1 (or α3) and β subunits whereas the immature form is mostly composed of only α2 subunits [905]. The α4 subunit is a pseudogene in humans [775]. High resolution molecular structures are available for α1 homomeric, α3 homomeric, and αβ hteromeric receptors in a variety of ligand-induced conformations [343, 343, 584, 585, 586, 1584]. As in other Cys-loop receptors, the orthosteric binding site for agonists and the competitive antagonist strychnine is formed at the interfaces between the subunits' extracellular domains. 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. This a cytoskeletal attachment protein that binds to a number of subsynaptic proteins involved in cytoskeletal structure and thus clusters and anchors hetero-oligomeric receptors to the synapse [708, 975]. G protein βγ subunits enhance the open state probability of native and recombinant glycine receptors by association with domains within the large intracellular loop [1571, 1572]. Intracellular chloride concentration modulates the kinetics of native and recombinant glycine receptors [1124]. Intracellular Ca^{2+} appears to increase native and recombinant glycine receptor affinity, prolonging channel open events, by a mechanism that does not involve phosphorylation [418]. Extracellular Zn^{2+} potentiates GlyR function at nanomolar concentrations [954]. and causes inhibition at higher micromolar concentrations (17).

Nomenclature	glycine receptor α1 subunit	glycine receptor α2 subunit
HGNC, UniProt	*GLRA1*, P23415	*GLRA2*, P23416
Selective agonists (potency order)	glycine > β-alanine > taurine	glycine > β-alanine > taurine
Selective antagonists	ginkgolide X (pIC_{50} 6.1), pregnenolone sulphate (pK_i 5.7), nifedipine (pIC_{50} 5.5), bilobalide (pIC_{50} 4.7), tropisetron (pK_i 4.1), colchicine (pIC_{50} 3.5), PMBA, onternabez (weak inhibition), strychnine	HU-210 (pIC_{50} 7), WIN55212-2 (pIC_{50} 6.7), onternabez (pIC_{50} 6), ginkgolide X (pIC_{50} 5.6), pregnenolone sulphate (pK_i 5.3), bilobalide (pIC_{50} 5.1), tropisetron (pK_i 4.9), colchicine (pIC_{50} 4.2), 5,7-dichlorokynurenic acid (pIC_{50} 3.7), PMBA, strychnine
Channel blockers	ginkgolide B (pIC_{50} 5.1–6.2), cyanotriphenylborate (pIC_{50} 5.9) [1201], picrotin (pIC_{50} 5.3), picrotoxinin (pIC_{50} 5.3), picrotoxin (pIC_{50} 5.2)	picrotoxinin (pIC_{50} 6.4), picrotoxin (pIC_{50} 5.6), ginkgolide B (pIC_{50} 4.9–5.4), picrotin (pIC_{50} 4.9), cyanotriphenylborate (pIC_{50}>4.7) [1201]
Endogenous allosteric modulators	Zn^{2+} (Potentiation) (pEC_{50} 7.4), Cu^{2+} (Inhibition) (pIC_{50} 4.8–5.4), Zn^{2+} (Inhibition) (pIC_{50} 4.8), Extracellular H^+ (Inhibition)	Zn^{2+} (Potentiation) (pEC_{50} 6.3), Cu^{2+} (Inhibition) (pIC_{50} 4.8), Zn^{2+} (Inhibition) (pIC_{50} 3.4)
Selective allosteric modulators	anandamide (Potentiation) (pEC_{50} 7.4), HU-210 (Potentiation) (pEC_{50} 6.6), $Δ^9$-tetrahydrocannabinol (Potentiation) (pEC_{50}~5.5)	$Δ^9$-tetrahydrocannabinol (Potentiation) (pEC_{50}~6)
Labelled ligands	[^{3}H]strychnine (Antagonist)	[^{3}H]strychnine (Antagonist)
Functional Characteristics	γ = 86 pS (main state); (+ β = 44 pS)	γ = 111 pS (main state); (+ β = 54 pS)

Nomenclature	glycine receptor α3 subunit	glycine receptor α4 subunit *(pseudogene in humans)*	glycine receptor β subunit
HGNC, UniProt	*GLRA3*, O75311	*GLRA4*, Q5JXX5	*GLRB*, P48167
Selective agonists (potency order)	glycine > β-alanine > taurine	–	–
Selective antagonists	HU-210 (pIC_{50} 7.3), WIN55212-2 (pIC_{50} 7), onternabez (pIC_{50} 7), (12E,20Z,18S)-8-hydroxyvariabilin (pIC_{50} 5.2), nifedipine (pIC_{50} 4.5), strychnine	–	nifedipine (when co-expressed with the α1 subunit) (pIC_{50} 5.9), pregnenolone sulphate (when co-expressed with the α1 subunit) (pK_i 5.6), tropisetron (when co-expressed with the α2 subunit) (pK_i 5.3), pregnenolone sulphate (when co-expressed with the α2 subunit) (pK_i 5), nifedipine (when co-expressed with the α3 subunit) (pIC_{50} 4.9), bilobalide (when co-expressed with the α2 subunit) (pIC_{50} 4.3), bilobalide (when co-expressed with the α1 subunit) (pIC_{50} 3.7), ginkgolide X (when co-expressed with the α1 subunit) (pIC_{50}>3.5), ginkgolide X (when co-expressed with the α2 subunit) (pIC_{50}>3.5)
Channel blockers	picrotoxinin (pIC_{50} 6.4), ginkgolide B (pIC_{50} 5.7), picrotin (pIC_{50} 5.2), picrotoxin (block is weaker when β subunit is co-expressed)	–	ginkgolide B (when co-expressed with the α2 subunit) (pIC_{50} 6.1–6.9), ginkgolide B (when co-expressed with the α1 subunit) (pIC_{50} 5.6–6.7), ginkgolide B (when co-expressed with the α3 subunit) (pIC_{50} 6.3), cyanotriphenylborate (when co-expressed with the human α1 subunit) (pIC_{50} 5.6) [1201] – Rat, cyanotriphenylborate (when co-expressed with the human α2 subunit) (pIC_{50} 5.1) [1201] – Rat, picrotoxinin (when co-expressed with the α3 subunit) (pIC_{50} 5.1), picrotin (when co-expressed with the α1 subunit) (pIC_{50} 4.6), picrotin (when co-expressed with the α3 subunit) (pIC_{50} 4.6), picrotoxinin (when co-expressed with the α1 subunit) (pIC_{50} 4.6), picrotoxin (when co-expressed with the α2 subunit) (pIC_{50} 4.5), picrotoxin (when co-expressed with the α1 subunit) (pIC_{50} 3.7)
Endogenous allosteric modulators	Cu^{2+} (Inhibition) (pIC_{50} 5), Zn^{2+} (Inhibition) (pIC_{50} 3.8)	–	Zn^{2+} (Inhibition) (pIC_{50} 4.9), Zn^{2+} (Inhibition) (pIC_{50} 3.7)
Selective allosteric modulators	Δ^9-tetrahydrocannabinol (Potentiation) (pEC_{50}~5.3)	–	–
Labelled ligands	[^{3}H]strychnine (Antagonist)	–	–
Functional Characteristics	γ = 105 pS (main state); (+ β = 48 pS)	–	–
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 isoforms are indicated (see detailed view pages for each subunit: α1, α2, α3, α4, β). Pregnenolone sulphate, tropisetron and colchicine, for example, although not selective antagonists of glycine receptors, are included for this purpose. Strychnine is a potent and selective competitive glycine receptor antagonist with affinities in the range 5-15 nM. RU5135 demonstrates comparable potency, but additionally blocks $GABA_A$ receptors. There are conflicting reports concerning the ability of cannabinoids to inhibit [860], or potentiate and at high concentrations activate [15, 310, 527, 1537, 1563] glycine receptors. Nonetheless, cannabinoid analogues may hold promise in distinguishing between glycine receptor subtypes [1563]. 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 [1537]. Several analogues of muscimol and piperidine act as agonists and antagonists of both glycine and $GABA_A$ receptors. Picrotoxin acts as an allosteric inhibitor that appears to bind within the pore, and shows strong selectivity towards homomeric receptors. While its components, picrotoxinin and picrotin, have equal potencies at α1 receptors, their potencies at α2 and α3 receptors differ modestly and may allow some distinction between different receptor types [1564]. Binding of picrotoxin within the pore has been demonstrated in the crystal structure of the related *C. elegans*

GluCl Cys-loop receptor [538]. In addition to the compounds listed in the table, numerous agents act as allosteric regulators of glycine receptors (comprehensively reviewed in [773, 874, 1501, 1573]). Zn^{2+} acts through distinct binding sites of high- and low-affinity to allosterically enhance channel function at low (<10 µM) concentrations and inhibits responses at higher concentrations in a subunit selective manner [953]. The effect of Zn^{2+} is somewhat mimicked by Ni^{2+}. Endogenous Zn^{2+} is essential for normal glycinergic neurotransmission mediated by α1 subunit-containing receptors [549]. Elevation of intracellular Ca^{2+} produces fast potentiation of glycine receptor-mediated responses. Dideoxyforskolin (4 µM) and tamoxifen (0.2-5 µM) both potentiate responses to low glycine concentrations (15 µM), but act as inhibitors at higher glycine concentrations (100 µM). Additional modulatory agents that enhance glycine receptor function include inhalational, and several intravenous general anaesthetics (*e.g.* minaxolone, propofol and pentobarbitone) and certain neurosteroids. Ethanol and higher order n-alcohols also enhance glycine receptor function although whether this occurs by a direct allosteric action at the receptor [917], or through βγ subunits [1570] is debated. Recent crystal structures of the bacterial homologue, GLIC, have identified transmembrane binding pockets for both anaesthetics [1036] and alcohols [575]. Solvents inhaled as drugs of abuse (*e.g.* toluene, 1-1-1-trichloroethane) may act at sites that overlap with those recognising alcohols and volatile anaesthetics to produce potentiation of glycine receptor function. The function of glycine receptors formed as homomeric complexes of α1 or α2 subunits, or hetero-oligomers of α1/β or α2/β subunits, is differentially affected by the $5\text{-}HT_3$ receptor antagonist tropisetron (ICS 205-930) which may evoke potentiation (which may occur within the femtomolar range at the homomeric glycine α1 receptor), or inhibition, depending upon the subunit composition of the receptor and the concentrations of the modulator and glycine employed. Potentiation and inhibition by tropeines involves different binding modes [899]. Additional tropeines, including atropine, modulate glycine receptor activity.

Further reading on Glycine receptors

Burgos CF *et al.* (2016) Structure and Pharmacologic Modulation of Inhibitory Glycine Receptors. *Mol Pharmacol* **90**: 318-25 [PMID:27401877]

Dutertre S *et al.* (2012) Inhibitory glycine receptors: an update. *J Biol Chem* **287**: 40216-23 [PMID:23038260]

Lynch JW. (2004) Molecular structure and function of the glycine receptor chloride channel. *Physiol Rev* **84**: 1051-95 [PMID:15383648]

Perkins DI *et al.* (2010) Molecular targets and mechanisms for ethanol action in glycine receptors. *Pharmacol Ther* **127**: 53-65 [PMID:20399807]

Yevenes GE *et al.* (2011) Allosteric modulation of glycine receptors. *Br J Pharmacol* **164**: 224-36 [PMID:21557733]

Ionotropic glutamate receptors

Ion channels → Ligand-gated ion channels → Ionotropic glutamate receptors

Overview: The ionotropic glutamate receptors comprise members of the NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid) and kainate receptor classes, named originally according to their preferred, synthetic, agonist [508, 853, 1404]. 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), 3 TM domains (M1, M3 and M4), a channel lining re-entrant 'p-loop' (M2) located between M1 and M3 and an intracellular carboxy- terminal domain (CTD) [659, 757, 925, 993, 1404]. The X-ray structure of a homomeric ionotropic glutamate receptor (GluA2- see below) has been solved at 3.6Å resolution [1298] and although providing detailed structural information, may not be representative of the subunit arrangement of, for example, the heteromeric NMDA receptors [674]. 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 [210, 266, 371, 508, 620, 621, 696, 1071, 1072, 1073, 1404, 1533]. Agents that discriminate between subunit isoforms are, where appropriate, noted in the tables and additional compounds that distinguish between receptor isoforms are indicated in the text below.
The classification of glutamate receptor subunits has been re-addressed by NC-IUPHAR [253]. The scheme developed recommends a nomenclature for ionotropic glutamate receptor subunits that is adopted here.

NMDA receptors

NMDA receptors assemble as obligate heteromers that may be drawn from GluN1, GluN2A, GluN2B, GluN2C, GluN2D, GluN3A and GluN3B subunits. Alternative splicing can generate eight isoforms of GluN1 with differing pharmacological properties. Various splice variants of GluN2B, 2C, 2D and GluN3A have also been reported. Activation of NMDA receptors containing GluN1 and GluN2 subunits requires the binding of two agonists, glutamate to the S1 and S2 regions of the GluN2 subunit and glycine to S1 and S2 regions of the GluN1 subunit [211, 370]. The minimal requirement for efficient functional expression of NMDA receptors *in vitro* is a di-heteromeric assembly of GluN1 and at least one GluN2 subunit variant, as a dimer of heterodimers arrangement in the extracellular domain [420, 674, 925]. However, more complex tri-heteromeric assemblies, incorporating multiple subtypes of GluN2 subunit, or GluN3 subunits, can be generated *in vitro* and occur *in vivo*. The NMDA receptor channel commonly has a high relative permeability to Ca^{2+} and is blocked, in a voltage-dependent manner, by Mg^{2+} such that at resting potentials the response is substantially inhibited.

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 [376, 612, 956, 1395]). 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; [796, 1104, 1119]). Two additional kainate receptor subunits, GluK4 and GluK5, when expressed individually, form high affinity binding sites for kainate, but lack function, but can form heteromers when expressed with GluK1-3 subunits (*e.g.* GluK2/K5; reviewed in [620, 1104, 1119]). Kainate receptors may also exhibit 'metabotropic' functions [796, 1183]. As found for AMPA receptors, kainate receptors are modulated by auxiliary subunits (Neto proteins, [797, 1104]). An important function difference between AMPA and kainate receptors is that the latter require extracellular Na^+ and Cl^- for their activation [145, 1132]. RNA encoding the GluA2 subunit undergoes extensive RNA editing in which the codon encoding a p-loop glutamine residue (Q) is converted to one encoding arginine (R). This Q/R site strongly influences the biophysical properties of the receptor. Recombinant AMPA receptors lacking RNA edited GluA2 subunits are: (1) permeable to Ca^{2+}; (2) blocked by intracellular polyamines at depolarized potentials causing inward rectification (the latter being reduced by TARPs); (3) blocked by extracellular argiotoxin and joro spider toxins and (4) demonstrate higher channel conductances than receptors containing the edited form of GluA2 [603, 1248]. GluK1 and GluK2, but not other kainate receptor subunits, are similarly edited and broadly similar functional characteristics apply to kainate receptors lacking either an RNA edited GluK1, or GluK2, subunit [796, 1104]. Native AMPA and kainate receptors displaying differential channel conductances, Ca^{2+} permeabilities and sensitivity to block by intracellular polyamines have been identified [265, 603, 846]. GluA1-4 can exist as two variants generated by alternative splicing (termed 'flip' and 'flop') that differ in their desensitization kinetics and their desensitization in the presence of cyclothiazide which stabilises the nondesensitized state. TARPs also stabilise the non-desensitized conformation of AMPA receptors and facilitate the action of cyclothiazide [956]. Splice variants of GluK1-3 also exist which affects their trafficking [796, 1104].

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, GYKI53655, GYKI53784 (active isomer, non-competitive), NBQX, tezampanel	ATPO, GYKI53655, GYKI53784 (active isomer, non-competitive), NBQX, tezampanel	ATPO, GYKI53655, GYKI53784 (active isomer, non-competitive), NBQX, tezampanel	ATPO, GYKI53655, GYKI53784 (active isomer, non-competitive), NBQX, tezampanel
Channel blockers	extracellular argiotoxin, extracellular joro spider toxin (selective for channels lacking GluA2)	extracellular argiotoxin	extracellular argiotoxin, extracellular joro spider toxin (selective for channels lacking GluA2)	extracellular argiotoxin, extracellular joro spider toxin (selective for channels lacking GluA2)
Allosteric modulators (Positive)	LY392098 (pEC_{50} 5.8) [962], LY404187 (pEC_{50} 5.2) [962], cyclothiazide (pEC_{50} 4.7) [962], CX516, CX546, IDRA-21, LY503430, S18986, aniracetam, piracetam	LY404187 (pEC_{50} 6.8) [962], LY392098 (pEC_{50} 6.7) [962], cyclothiazide (pEC_{50} 5.7) [962], CX516, CX546, IDRA-21, LY503430, S18986, aniracetam, piracetam	LY404187 (pEC_{50} 5.8) [962], LY392098 (pEC_{50} 5.7) [962], cyclothiazide (pEC_{50} 4.9) [962], CX516, CX546, IDRA-21, LY503430, S18986, aniracetam, piracetam	LY392098 (pEC_{50} 6.7) [962], LY404187 (pEC_{50} 6.7) [962], cyclothiazide (pEC_{50} 5.4) [962], CX516, CX546, IDRA-21, LY503430, S18986, aniracetam, piracetam
Labelled ligands	[^{3}H]AMPA (Agonist), [^{3}H]CNQX (Antagonist)	[^{3}H]AMPA (Agonist), [^{3}H]CNQX (Antagonist)	[^{3}H]AMPA, [^{3}H]CNQX	[^{3}H]AMPA (Agonist), [^{3}H]CNQX
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.	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.	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	Piracetam and aniracetam are examples of pyrrolidinones. Cyclothiazide, S18986, and IDRA-21 are examples of benzothiadiazides. CX516 and CX546 are examples of benzylpiperidines. LY392098, LY404187 and LY503430 are examples of biarylpropylsulfonamides. Also blocked by intracellular polyamines

Nomenclature	GluD1	GluD2
HGNC, UniProt	*GRID1*, Q9ULK0	*GRID2*, O43424

Nomenclature	GluK1	GluK2	GluK3	GluK4	GluK5
HGNC, UniProt	*GRIK1*, P39086	*GRIK2*, Q13002	*GRIK3*, Q13003	*GRIK4*, Q16099	*GRIK5*, Q16478
Agonists	dysiherbaine [1214] – Rat, SYM2081 [1095], kainate [1286], (*S*)-4-AHCP, (*S*)-5-iodowillardiine, 8-deoxy-neodysiherbaine, ATPA, domoic acid	dysiherbaine [1214] – Rat, domoic acid [176], SYM2081 [1625] – Rat, kainate [176, 1286]	SYM2081 [1211] – Rat, kainate (low potency) [1211] – Rat, dysiherbaine	SYM2081, domoic acid, dysiherbaine, kainate	SYM2081, domoic acid, dysiherbaine, kainate
Selective agonists	LY339434 [1286]	–	–	–	–
Selective antagonists	2,4-epi-neodysiherbaine, ACET, LY382884, LY466195, MSVIII-19, NS3763 (non-competitive), UBP302, UBP310	2,4-epi-neodysiherbaine	–	–	–
Allosteric modulators (Positive)	concanavalin A	concanavalin A	–	–	–
Labelled ligands	[^{3}H]UBP310 (Antagonist) (pK_d 7.7) [56], [^{3}H]SYM2081 (Agonist), [^{3}H]kainate (Agonist)	[^{3}H]kainate (Agonist) [1625] – Rat, [^{3}H]SYM2081 (Agonist)	[^{3}H]UBP310 (Antagonist) (pK_d 6.3) [56], [^{3}H]SYM2081 (Agonist), [^{3}H]kainate (Agonist)	[^{3}H]SYM2081 (Agonist), [^{3}H] kainate (Agonist)	[^{3}H]SYM2081 (Agonist), [^{3}H] kainate (Agonist)
Comments	–	Intracellular polyamines are subtype selective channel blockers (GluK3 ≫ GluK2). GluK2 mediates cold sensing in mice [169].	Domoic acid and concanavalin A are inactive at the GluK3 subunit. Intracellular polyamines are subtype selective channel blockers (GluK3 ≫ GluK2)	–	–

Nomenclature	GluN1
HGNC, UniProt	*GRIN1*, Q05586
Endogenous agonists	D-aspartic acid [glutamate site], D-serine [glycine site], L-aspartic acid [glutamate site], glycine [glycine site]
Agonists	(+)-HA966 [glycine site] (Partial agonist), (*RS*)-(tetrazol-5-yl)glycine [glutamate site], NMDA [glutamate site], homoquinolinic acid [glutamate site] (Partial agonist)
Selective antagonists	L701324 [glycine site] (pIC$_{50}$ 8.7) [756] – Rat, GV196771A [glycine site] (pK_i 8.1–8.4) [231] – Rat, L689560 [glycine site] (pIC$_{50}$ 8.1) [789] – Rat, 5,7-dichlorokynurenic acid [glycine site]
Labelled ligands	[^{3}H]MDL105519 [glycine site] (Antagonist) (pK_d~8.5) [204] – Rat, [^{3}H]CGP39653 [glutamate site] (Selective Antagonist), [^{3}H]CGP61594 [glycine site] (Antagonist), [^{3}H] CGS19755 [glutamate site] (Antagonist), [^{3}H]CPP [glutamate site] (Selective Antagonist), [^{3}H]L689560 [glycine site] (Antagonist), [^{3}H]dizocilpine [cation channel] (Antagonist), [^{3}H]glycine [glycine site] (Agonist)

Nomenclature	GluN2A	GluN2B	GluN2C	GluN2D
HGNC, UniProt	*GRIN2A*, Q12879	*GRIN2B*, Q13224	*GRIN2C*, Q14957	*GRIN2D*, O15399
Endogenous agonists	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)	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)
Agonists	(+)-HA966 [glycine site] (Partial agonist), (*RS*)-(tetrazol-5-yl)glycine [glutamate site] (GluN2D > GluN2C = GluN2B > GluN2A), NMDA [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*)-(tetrazol-5-yl)glycine [glutamate site] (GluN2D > GluN2C = GluN2B > GluN2A), NMDA [glutamate site] (GluN2D > GluN2C > GluN2B > GluN2A), homoquinolinic acid [glutamate site] (GluN2B ≥ GluN2A ≥ GluN2D > GluN2C; partial agonist at GluN2A and GluN2C)	(*RS*)-(tetrazol-5-yl)glycine [glutamate site] (GluN2D > GluN2C = GluN2B > GluN2A), NMDA [glutamate site] (GluN2D > GluN2C > GluN2B > GluN2A), homoquinolinic acid [glutamate site] (GluN2B ≥ GluN2A ≥ GluN2D > GluN2C; partial agonist at GluN2A and GluN2C)	(*RS*)-(tetrazol-5-yl)glycine [glutamate site] (GluN2D > GluN2C = GluN2B > GluN2A), NMDA [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], CGP37849 [glutamate site], GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], NVP-AAM077 [glutamate site] (GluN2A > GluN2B (human), but weakly selective for rat GluN2A versus GluN2B) [58, 393, 416, 1007], UBP141 [glutamate site] (GluN2D ≥ GluN2C > GluN2A ≥ GluN2B) [974], conantokin-G [glutamate site] (GluN2B > GluN2D = GluN2C = GluN2A), d-AP5 [glutamate site], d-CCPene [glutamate site] (GluN2A = GluN2B > GluN2C = GluN2D), selfotel [glutamate site]	5,7-dichlorokynurenic acid [glycine site], CGP37849 [glutamate site], GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], NVP-AAM077 [glutamate site] (GluN2A > GluN2B (human), but weakly selective for rat GluN2A versus GluN2B) [58, 393, 416, 1007], UBP141 [glutamate site] (GluN2D ≥ GluN2C > GluN2A ≥ GluN2B) [974], conantokin-G [glutamate site] (GluN2B > GluN2D = GluN2C = GluN2A), d-AP5 [glutamate site], d-CCPene [glutamate site] (GluN2A = GluN2B > GluN2C = GluN2D), selfotel [glutamate site]	5,7-dichlorokynurenic acid [glycine site], CGP37849 [glutamate site], GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], UBP141 [glutamate site] (GluN2D ≥ GluN2C > GluN2A ≥ GluN2B) [974], conantokin-G [glutamate site] (GluN2B > GluN2D = GluN2C = GluN2A), d-AP5 [glutamate site], d-CCPene [glutamate site] (GluN2A = GluN2B > GluN2C = GluN2D), selfotel [glutamate site]	5,7-dichlorokynurenic acid [glycine site], CGP37849 [glutamate site], GV196771A [glycine site], L689560 [glycine site], L701324 [glycine site], LY233053 [glutamate site], UBP141 [glutamate site] (GluN2D ≥ GluN2C > GluN2A ≥ GluN2B) [974], conantokin-G [glutamate site] (GluN2B > GluN2D = GluN2C = GluN2A), d-AP5 [glutamate site], d-CCPene [glutamate site] (GluN2A = GluN2B > GluN2C = GluN2D), selfotel [glutamate site]
Channel blockers	Mg^{2+} (GluN2A = GluN2B > GluN2C = GluN2D), N^1-dansyl-spermine (GluN2A = GluN2B ≫ GluN2C = GluN2D), amantadine (GluN2C = GluN2D ≥ GluN2B ≥ GluN2A), dizocilpine, ketamine, phencyclidine	Mg^{2+} (GluN2A = GluN2B > GluN2C = GluN2D), N^1-dansyl-spermine (GluN2A = GluN2B ≫ GluN2C = GluN2D), amantadine (GluN2C = GluN2D ≥ GluN2B ≥ GluN2A), dizocilpine, ketamine, phencyclidine	phencyclidine (pIC_{50} 7.1) [341], ketamine (pIC_{50} 6.2) [341], amantadine (GluN2C = GluN2D ≥ GluN2B ≥ GluN2A) (pIC_{50} 4.7) [341], Mg^{2+} (GluN2A = GluN2B > GluN2C = GluN2D), N^1-dansyl-spermine (GluN2A = GluN2B ≫ GluN2C = GluN2D), dizocilpine	Mg^{2+} (GluN2A = GluN2B > GluN2C = GluN2D), N^1-dansyl-spermine (GluN2A = GluN2B ≫ GluN2C = GluN2D), amantadine (GluN2C = GluN2D ≥ GluN2B ≥ GluN2A), dizocilpine, ketamine, phencyclidine

Labelled ligands	[^{3}H]CGP39653 [glutamate site] (Antagonist), [^{3}H]CGP61594 [glycine site] (Antagonist), [^{3}H]CGS19755 [glutamate site] (Antagonist), [^{3}H]CPP [glutamate site] (Antagonist), [^{3}H]L689560 [glycine site] (Antagonist), [^{3}H]MDL105519 [glycine site] (Antagonist), [^{3}H]dizocilpine [cation channel] (Channel blocker), [^{3}H]glycine [glycine site] (Agonist)	[^{3}H]CGP39653 [glutamate site] (Antagonist), [^{3}H]CGP61594 [glycine site] (Antagonist), [^{3}H]CGS19755 [glutamate site] (Antagonist), [^{3}H]CPP [glutamate site] (Antagonist), [^{3}H]L689560 [glycine site] (Antagonist), [^{3}H]MDL105519 [glycine site] (Antagonist), [^{3}H]dizocilpine [cation channel] (Channel blocker), [^{3}H]glycine [glycine site] (Agonist)	[^{3}H]CGP39653 [glutamate site] (Antagonist), [^{3}H]CGP61594 [glycine site] (Antagonist), [^{3}H]CGS19755 [glutamate site] (Antagonist), [^{3}H]CPP [glutamate site] (Antagonist), [^{3}H]L689560 [glycine site] (Antagonist), [^{3}H]MDL105519 [glycine site] (Antagonist), [^{3}H]dizocilpine [cation channel] (Channel blocker), [^{3}H]glycine [glycine site] (Agonist)	[^{3}H]CGP39653 [glutamate site] (Antagonist), [^{3}H]CGP61594 [glycine site] (Antagonist), [^{3}H]CGS19755 [glutamate site] (Antagonist), [^{3}H]CPP [glutamate site] (Antagonist), [^{3}H]L689560 [glycine site] (Selective Antagonist), [^{3}H]MDL105519 [glycine site] (Antagonist), [^{3}H]dizocilpine [cation channel] (Channel blocker), [^{3}H]glycine [glycine site] (Agonist)

Nomenclature	GluN3A	GluN3B
HGNC, UniProt	*GRIN3A*, Q8TCU5	*GRIN3B*, O60391
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 [210, 341, 371, 758, 1073, 1404]. In addition to the glutamate and glycine binding sites documented in the table, physiologically important inhibitory modulatory sites exist for Mg^{2+}, Zn^{2+}, and protons [266, 508, 1404]. Voltage-independent inhibition by Zn^{2+} binding with high affinity within the ATD is highly subunit selective (GluN2A ≫ GluN2B > GluN2C ≥ GluN2D; [1073, 1404]). The receptor is also allosterically modulated, in both positive and negative directions, by endogenous neuroactive steroids in a subunit dependent manner [567, 900]. 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 Zn^{2+} that occurs through binding in the ATD [1403]. 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 [674]. LY233536 is a competitive antagonist that also displays selectivity for GluN2B over GluN2A subunit-containing receptors. Similarly, CGP61594 is a photoaffinity label that interacts selectively with receptors incorporating GluN2B versus GluN2A, GluN2D and, to a lesser extent, GluN2C subunits. TCN-201 and TCN-213 have been shown to block GluN2A NMDA receptors selectively by a mechanism that involves allosteric inhibition of glycine binding to the GluN1 site [112, 360, 507, 931]. In addition to influencing the pharmacological profile of the NMDA receptor, the identity of the GluN2 subunit co-assembled with GluN1 is an important determinant of biophysical properties that include sensitivity to block by Mg^{2+}, single-channel conductance and maximal open probability and channel deactivation time [266, 370, 454]. Incorporation of the GluN3A subunit into tri-heteromers containing GluN1 and GluN2 subunits is associated with decreased single-channel conductance, reduced permeability to Ca^{2+} and decreased susceptibility to block by Mg^{2+} [189, 532]. Reduced permeability to Ca^{2+} has also been observed following the inclusion of GluN3B in tri-heteromers. The expression of GluN3A, or GluN3B, with GluN1 alone forms, in *Xenopus laevis* oocytes, a cation channel with unique properties that include activation by glycine (but not NMDA), lack of permeation by Ca^{2+} and resistance to blockade by Mg^{2+} and NMDA receptor antagonists [199]. The function of heteromers composed of GluN1 and GluN3A is enhanced by Zn^{2+}, or glycine site antagonists, binding to the GluN1 subunit [887]. Zn^{2+} also directly activates such complexes. The co-expression of GluN1, GluN3A and GluN3B appears to be required to form glycine-activated receptors in mammalian cell hosts [1296].

AMPA and Kainate receptors

All AMPA receptors are additionally activated by kainate (and domoic acid) with relatively low potency, (EC_{50} ~ 100 μM). Inclusion of TARPs within the receptor complex increases the potency and maximal effect of kainate [612, 956]. AMPA is weak partial agonist at GluK1 and at heteromeric assemblies of GluK1/GluK2, GluK1/GluK5 and GluK2/GluK5 [620]. Quinoxalinediones such as CNQX and NBQX show limited selectivity between AMPA and kainate receptors. Tezampanel also has kainate (GluK1) receptor activity as has GYKI53655 (GluK3 and GluK2/GluK3) [620]. 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 [56, 1103]. (2S,4R)-4-methylglutamate (SYM2081) is equipotent in activating (and desensitising) GluK1 and GluK2 receptor isoforms and, *via* the induction of desensitisation at low concentrations, has been used as a functional antagonist of kainate receptors. Both (2*S*,4*R*)-4-methylglutamate and LY339434 have agonist activity at NMDA receptors. (2S,4R)-4-methylglutamate is also an inhibitor of the glutamate transporters EAAT1 and EAAT2.

Delta subunits

GluD1 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 [1593]. 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 [998]. Their physiological role is uncertain. It may be structural, contributing as trans-synaptic organizers [508].

Further reading on Ionotropic glutamate receptors

Filippini A *et al.* (2017) The Good and the Bad of Glutamate Receptor RNA Editing. *Mol Neurobiol* **54**: 6795-6805 [PMID:27766534]

Gangwar SP *et al.* (2024) Kainate receptor channel opening and gating mechanism. *Nature* **630**: 762-768 [PMID:38778115]

Greger IH *et al.* (2017) Structural and Functional Architecture of AMPA-Type Glutamate Receptors and Their Auxiliary Proteins. *Neuron* **94**: 713-730 [PMID:28521126]

Hackos DH *et al.* (2017) Diverse modes of NMDA receptor positive allosteric modulation: Mechanisms and consequences. *Neuropharmacology* **112**: 34-45 [PMID:27484578]

Huettner JE. (2015) Glutamate receptor pores. *J Physiol (Lond.)* **593**: 49-59 [PMID:25556787]

Iacobucci GJ *et al.* (2017) NMDA receptors: linking physiological output to biophysical operation. *Nat Rev Neurosci* **18**: 236-249 [PMID:28303017]

Krieger J *et al.* (2015) Structure, Dynamics, and Allosteric Potential of Ionotropic Glutamate Receptor N-Terminal Domains. *Biophys J* **109**: 1136-48 [PMID:26255587]

Lussier MP *et al.* (2015) Dynamic Regulation of N-Methyl-d-aspartate (NMDA) and α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid (AMPA) Receptors by Posttranslational Modifications. *J Biol Chem* **290**: 28596-603 [PMID:26453298]

Møllerud S *et al.* (2017) Lessons from crystal structures of kainate receptors. *Neuropharmacology* **112**: 16-28 [PMID:27236079]

Segura-Covarrubias G *et al.* (2025) Structural basis of GluK2 kainate receptor activation by a partial agonist. *Nat Struct Mol Biol* **32**: 1456-1469 [PMID:40442317]

Yuzaki M *et al.* (2017) A GluD Coming-Of-Age Story. *Trends Neurosci* **40**: 138-150 [PMID:28110935]

Zhou HX *et al.* (2017) Advancing NMDA Receptor Physiology by Integrating Multiple Approaches. *Trends Neurosci* **40**: 129-137 [PMID:28187950]

Zhuo M. (2017) Ionotropic glutamate receptors contribute to pain transmission and chronic pain. *Neuropharmacology* **112**: 228-234 [PMID:27543416]

IP_3 receptors

Ion channels → Ligand-gated ion channels → IP_3 receptors

Overview: The inositol 1,4,5-trisphosphate receptors (IP_3R) are ligand-gated Ca^{2+}-release channels on intracellular Ca^{2+} store sites (such as the endoplasmic reticulum). They are responsible for the mobilization of intracellular Ca^{2+} stores and play an important role in intracellular Ca^{2+} signalling in a wide variety of cell types. Three different gene products (types I-III) have been isolated, which assemble as large tetrameric structures. IP_3Rs are closely associated with certain proteins: calmodulin (*CALM1*CALM2CALM3, P62158) and FKBP (and calcineurin *via* FKBP). They are phosphorylated by PKA, PKC, PKG and CaMKII.

Nomenclature	IP_3R1	IP_3R2	IP_3R3
HGNC, UniProt	*ITPR1*, Q14643	*ITPR2*, Q14571	*ITPR3*, Q14573
Endogenous activators	cytosolic ATP (< mM range), cytosolic Ca^{2+} Concentration range: $<7.5 \times 10^{-4}$M, IP_3 (endogenous; nM - μM range)	cytosolic Ca^{2+} (nM range), IP_3 (endogenous; nM - μM range)	cytosolic Ca^{2+} (nM range), IP_3 (endogenous; nM - μM range)
Activators	adenophostin A (pharmacological; nM range), inositol 2,4,5-trisphosphate (pharmacological; also activated by other $InsP_3$ analogues)	adenophostin A (pharmacological; nM range), inositol 2,4,5-trisphosphate (pharmacological; also activated by other $InsP_3$ analogues)	–
Antagonists	PIP_2 (μM range), caffeine (mM range), decavanadate (μM range), xestospongin C (μM range)	decavanadate (μM range)	decavanadate (μM range)
Functional Characteristics	Ca^{2+}: (P_{Ba}/P_K ~6) single-channel conductance ~70 pS (50 mM Ca^{2+})	Ca^{2+}: single-channel conductance ~70 pS (50 mM Ca^{2+}) ~390 pS (220 mM Cs^+)	Ca^{2+}: single-channel conductance ~88 pS (55 mM Ba^{2+})
Comments	IP_3 R1 is also antagonised by calmodulin at high cytosolic Ca^{2+} 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 on IP_3 receptors

Berridge MJ. (2016) The Inositol Trisphosphate/Calcium Signaling Pathway in Health and Disease. *Physiol Rev* **96**: 1261-96 [PMID:27512009]

Gambardella J *et al*. (2020) Inositol 1,4,5-Trisphosphate Receptors in Human Disease: A Comprehensive Update. *J Clin Med* **9**: 1096 [PMID:32290556]

Garcia MI *et al*. (2017) Cardiac inositol 1,4,5-trisphosphate receptors. *Biochim Biophys Acta* **1864**: 907-914 [PMID:27884701]

Mak DO *et al*. (2015) Inositol 1,4,5-trisphosphate receptors in the endoplasmic reticulum: A single-channel point of view. *Cell Calcium* **58**: 67-78 [PMID:25555684]

Prole DL *et al*. (2019) Structure and Function of IP_3 Receptors. *Cold Spring Harb Perspect Biol* **11**: [PMID:30745293]

Rossi AM *et al*. (2018) IP_3 receptors - lessons from analyses *ex cellula*. *J Cell Sci* **132**: [PMID:30552138]

Seo MD *et al*. (2015) Structural insights into endoplasmic reticulum stored calcium regulation by inositol 1,4,5-trisphosphate and ryanodine receptors. *Biochim Biophys Acta* **1853**: 1980-91 [PMID:25461839]

Thillaiappan NB *et al*. (2019) IP_3 receptors and Ca^{2+} entry. *Biochim Biophys Acta Mol Cell Res* **1866**: 1092-1100 [PMID:30448464]

Nicotinic acetylcholine receptors (nACh)

Ion channels → Ligand-gated ion channels → Nicotinic acetylcholine receptors (nACh)

Overview: Nicotinic acetylcholine (ACh) 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 [28, 951, 1281, 1360, 1528]. All nicotinic receptors are pentamers in which each of the five subunits contains 4 TM domains. Genes encoding a total of 17 subunits (α1-10, β1-4, γ, δ and ϵ) have been identified [662]. All subunits with the exception of α8 (present in avian species) have been identified in mammals. All α subunits possess two tandem cysteine residues near to the site involved in acetylcholine binding, and subunits not named α lack these residues [951]. The orthosteric ligand binding site is formed by residues within at least three peptide domains on the α subunit (principal component), and three on the adjacent subunit (complementary component). Nicotinic ACh receptors 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 4 TM domains [456, 1579]; see also [538]). The high resolution crystal structure of the molluscan ACh binding protein, a structural homologue of the extracellular binding domain of a nicotinic receptor pentamer, in complex with several nicotinic receptor ligands (*e.g.*[191]) and the crystal structure of the extracellular domain of the α1 subunit bound to α-bungarotoxin at 1.94Â resolution [305], has revealed the orthosteric binding site in detail (reviewed in [196, 662, 1199, 1281]). Nicotinic receptors at the somatic neuromuscular junction of adult animals have the stoichiometry $(\alpha1)_2\beta1\delta\epsilon$, whereas an extrajunctional $(\alpha1)_2\beta1\gamma\delta$ receptor predominates in embryonic and denervated skeletal muscle and other pathological states. Other nicotinic receptors are assembled as combinations of α(2-6) and β(2-4) subunits. For α2, α3, α4 and β2 and β4 subunits, pairwise combinations of α and β (*e.g.*α3β4 and α4β2) are sufficient to form a functional receptor *in vitro*, but far more complex isoforms may exist *in vivo* (reviewed in [467, 468, 951]). There is strong evidence that the pairwise assembly of some α and β subunits can occur with variable stoichiometry [*e.g.* $(\alpha4)_2(\beta2)_2$ or $(\alpha4)_3(\beta2)_2$] which influences the biophysical and pharmacological properties of the receptor [951]. α5 and β3 subunits lack function when expressed alone, or pairwise, but participate in the formation of functional hetero-oligomeric receptors when expressed as a third subunit with another α and β pair [e.g. α4α5αβ2, α4αβ2β3, α5α6β2, see [951] for further examples]. The α6 subunit can form a functional receptor when co-expressed with β4 *in vitro*, but more efficient expression ensues from incorporation of a third partner, such as β3 [1560]. The α7, α8, and α9 subunits form functional homo-oligomers, but can also combine with a second subunit to constitute a hetero-oligomeric assembly (*e.g.*α7β2 and α9α10). For functional expression of the α10 subunit, co-assembly with α9 is necessary. The latter, along with the α10 subunit, appears to be largely confined to cochlear and vestibular hair cells. Comprehensive listings of nicotinic receptor subunit combinations identified from recombinant expression systems, or *in vivo*, are given in [951]. 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 [48, 650, 950]).

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 [868]. Headings for this table reflect abbreviations designating nACh receptor subtypes based on the predominant α subunit contained in that receptor subtype. An asterisk following the indicated α subunit denotes that other subunits are known to, or may, assemble with the indicated α subunit to form the designated nACh receptor subtype(s). Where subunit stoichiometries within a specific nACh receptor subtype are known, numbers of a particular subunit larger than 1 are indicated by a subscript following the subunit (enclosed in parentheses- see also [253]).

Nomenclature	nicotinic acetylcholine receptor α1 subunit	nicotinic acetylcholine receptor α2 subunit	nicotinic acetylcholine receptor α3 subunit	nicotinic acetylcholine receptor α4 subunit
HGNC, UniProt	*CHRNA1*, P02708	*CHRNA2*, Q15822	*CHRNA3*, P32297	*CHRNA4*, P43681
Commonly used antagonists	$(\alpha1)_2\beta1\gamma\delta$ and $(\alpha1)_2\beta1\delta\epsilon$: α-bungarotoxin > pancuronium > vecuronium > rocuronium > tubocurarine (IC_{50} = 43 - 82 nM)	α2β2: DHβE (K_B = 0.9 μM), tubocurarine (K_B = 1.4 μM); α2β4: DHβE (K_B = 3.6 μM), tubocurarine (K_B = 4.2 μM)	α3β2: DHβE (K_B = 1.6 μM, IC_{50} = 2.0 μM), tubocurarine (K_B = 2.4 μM); α3β4: DHβE (K_B = 19 μM, IC_{50} = 26 μM), tubocurarine (K_B = 2.2 μM)	α4β2: DHβE (K_B = 0.1 μM; IC_{50} = 0.08 - 0.9 μM), tubocurarine (K_B = 3.2 μM, IC_{50} = 34 μM); α4β4: DHβE (K_B = 0.01 μM, IC_{50} = 0.19 - 1.2 μM), tubocurarine (K_B = 0.2 μM, IC_{50} = 50 μM)
Selective agonists	succinylcholine (selective for $(\alpha1)_2\beta1\gamma\delta$)	–	–	varenicline [248], rivanicline [332], TC-2559 (α4β2) [219]
Selective antagonists	α-bungarotoxin, α-conotoxin GI, α-conotoxin MI, pancuronium, waglerin-1 (selective for $(\alpha1)_2\beta1\delta\epsilon$)	–	α-conotoxin AuIB (α3β4), α-conotoxin MII (α3β2), α-conotoxin PnIA (α3β2), α-conotoxin TxIA (α3β2), α-conotoxin-GIC (α3β2)	–
Channel blockers	gallamine ($(\alpha1)_2\beta1\gamma\delta$ and $(\alpha1)_2\beta1\delta\epsilon$) ($pIC_{50}$~6), mecamylamine ($(\alpha1)_2\beta1\delta\epsilon$) ($pIC_{50}$~5.8)	hexamethonium, mecamylamine	mecamylamine (α3β4) (pIC_{50} 6.4), mecamylamine (α3β2) (pIC_{50} 5.1), A-867744 (α3β4) [906], NS1738 (α3β4) [1389], hexamethonium (α3β4), hexamethonium (α3β2)	mecamylamine (α4β4) (pIC_{50} 5.3–6.5), mecamylamine (α4β2) (pIC_{50} 5.4–5.4), hexamethonium (α4β2) (pIC_{50} 4.5–5.2), hexamethonium (α4β4) (pIC_{50} 4), A-867744 (α4β2) [906], NS1738 (α4β2) [1389]
Allosteric modulators (Positive)	–	LY2087101 [151]	–	LY2087101 (potentiates α4β2 and α4β4) [151]
Selective allosteric modulators	–	–	–	NS9283 (Positive) [780]
Labelled ligands	[^{125}I]α-bungarotoxin (Selective Antagonist), [^{3}H]α-bungarotoxin (Selective Antagonist)	[^{125}I]epibatidine (Agonist), [^{3}H]epibatidine (Agonist), [^{3}H]cytisine (Agonist)	[^{125}I]epibatidine (Agonist), [^{3}H]epibatidine (Agonist), [^{125}I]epibatidine (Agonist), [^{3}H]epibatidine (Agonist), [^{3}H]cytisine (Agonist)	[^{125}I]epibatidine (Agonist), [^{3}H]epibatidine (Agonist), [^{3}H]cytisine (Agonist), [^{125}I]epibatidine (Agonist), [^{3}H]epibatidine (Agonist), [^{3}H]epibatidine (Agonist) – Rat, [^{3}H]cytisine (Agonist)
Functional Characteristics	$(\alpha1)_2\beta\gamma\delta$: P_{Ca}/P_{Na} = 0.16 - 0.2, P_f = 2.1 - 2.9%; $(\alpha1)_2\beta\delta\epsilon$: P_{Ca}/P_{Na} = 0.65 - 1.38, P_f = 4.1 - 7.2%	α2β2: P_{Ca}/P_{Na} ˜ 1.5	α3β2: P_{Ca}/P_{Na} = 1.5; α3β4: P_{Ca}/P_{Na} = 0.78 - 1.1, P_f = 2.7 - 4.6%	α4β2: P_{Ca}/P_{Na} = 1.65, P_f = 2.6 - 2.9%; α4β4: P_f = 1.5 - 3.0 %

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/α3β2β3 chimera: DHβE (IC_{50} = 1.1 μM)	$(α7)_5$: DHβE (IC_{50} = 8 - 20 μM); $(α7)_5$: tubocurarine (IC_{50} = 3.1 μM)
Selective agonists	–	–	encenicline (Partial agonist) [926, 1028], AQW051 ([125I]α- bungarotoxin binding assay) [594], 4BP-TQS (allosteric) [456], A-582941 ($(α7)_5$) [121], PHA-543613 ($(α7)_5$) [1517], PHA-709829 ($(α7)_5$) [11], PNU-282987 ($(α7)_5$) [129], bradanicline ($(α7)_5$) [521]
Selective antagonists	α-conotoxin MII, α-conotoxin PnIA, α-conotoxin TxIA, α-conotoxin-GIC	α-conotoxin MII (α6β2*), α-conotoxin MII [H9A, L15A] (α6β2β3), α-conotoxin PIA (α6/α3β2β3 chimera)	α-bungarotoxin ($(α7)_5$), α-conotoxin ArIB ($(α7)_5$), α-conotoxin ImI ($(α7)_5$), methyllycaconitine ($(α7)_5$)
Channel blockers	–	mecamylamine (α6/α3β2β3 chimera) (pIC_{50} 5), hexamethonium (α6/α3β2β3 chimera) (pIC_{50} 4)	mecamylamine ($(α7)_5$) (pIC_{50} 4.8)
Allosteric modulators (Positive)	–	–	A-867744 ($(α7)_5$:Type 2; also blocks α3β4 and α4β2) [906], LY2087101 ($(α7)_5$:Type 1) [151], NS1738 ($(α7)_5$:-Type 1; also blocks α3β4 and α4β2) [1389]
Selective allosteric modulators	–	–	BNC375 (Positive) (pEC_{50} 5.6) [1483], JNJ1930942 (Positive) [325], PNU-120596 (Positive) [593]
Labelled ligands	–	[^{3}H]epibatidine (Agonist) – Chicken, [^{125}I]α-conotoxin MII (Antagonist)	[^{3}H]epibatidine (Agonist), [^{3}H]A-585539 (Agonist) [39], [^{3}H]AZ11637326 (Agonist) [465], [^{125}I] α-bungarotoxin (Selective Antagonist) (pK_d 8.3–9.1), [^{3}H]α-bungarotoxin (Selective Antagonist) (pK_d 8.3–9.1), [^{3}H]methyllycaconitine (Antagonist) (pK_d 8.7) – Rat
Functional Characteristics	–	–	P_{Ca}/P_{Na} = 6.6-20, P_f = 8.8 - 11.4%

Nomenclature	nicotinic acetylcholine receptor α8 subunit (avian)	nicotinic acetylcholine receptor α9 subunit	nicotinic acetylcholine receptor α10 subunit
HGNC, UniProt	–	*CHRNA9*, Q9UGM1	*CHRNA10*, Q9GZZ6
Commonly used antagonists	$(α8)_5$: α-bungarotoxin > atropine≥tubocurarine≥strychnine	$(α9)_5$: α-bungarotoxin > methyllycaconitine > strychnine ˜ tropisetron > tubocurarine; α9α10: α-bungarotoxin > tropisetron = strychnine > tubocurarine	α9α10: α-bungarotoxin > tropisetron = strychnine > tubocurarine
Selective antagonists	–	α-bungarotoxin (α9α10), α-bungarotoxin ($(α9)_5$), α-conotoxin RgIA (α9α10), muscarine (α9α10), muscarine ($(α9)_5$), nicotine (α9α10), nicotine ($(α9)_5$), strychnine ($(α9)_5$), strychnine (α9α10)	α-bungarotoxin (α9α10), α-conotoxin RgIA (α9α10), muscarine (α9α10), nicotine (α9α10), strychnine (α9α10)
Labelled ligands	[^{3}H]epibatidine ($(α8)_5$) (pK_d 9.7), [^{125}I]α-bungarotoxin (native α8*) (pK_d 8.3), [^{3}H]α-bungarotoxin (native α8*) (pK_d 8.3)	[^{3}H]methyllycaconitine (Antagonist) (pK_d 8.1), [^{125}I] α-bungarotoxin (Antagonist), [^{3}H]α-bungarotoxin (Antagonist)	[^{3}H]methyllycaconitine (Antagonist) (pK_d 8.1)
Functional Characteristics	–	$(α9)_5$: P_{Ca}/P_{Na} = 9; α9α10: P_{Ca}/P_{Na} = 9, P_f = 22%	α9α10: P_{Ca}/P_{Na} = 9, P_f = 22%

Nomenclature	nicotinic acetylcholine receptor β1 subunit	nicotinic acetylcholine receptor β2 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
HGNC, UniProt	*CHRNB1*, P11230	*CHRNB2*, P17787	*CHRNB3*, Q05901	*CHRNB4*, P30926	*CHRNG*, P07510	*CHRND*, Q07001	*CHRNE*, Q04844
Antagonists	–	–	–	–	–	PhTX-11 (pIC_{50} 6.2–6.3) [1328]	–
Comments	Ligand interaction data for hetero-oligomeric receptors containing the β1 subunit are listed under the α1 subunits	Ligand interaction data for hetero-oligomeric receptors containing the β2 subunit are listed under the α subunits	Ligand interaction data for hetero-oligomeric receptors containing the β3 subunit are listed under the α subunits	Ligand interaction data for hetero-oligomeric receptors containing the β4 subunit are listed under the α subunits	Ligand interaction data for hetero-oligomeric receptors containing the γ subunit are listed under the α1 subunits	Ligand interaction data for hetero-oligomeric receptors containing the δ subunit are listed under the α1 subunits	Ligand interaction data for hetero-oligomeric receptors containing the ϵ subunit are listed under the α1 subunits

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, ACh. A summary of their profile across differing receptors is provided in [468] and quantitative data across numerous assay systems are summarized in [628]. Quantitative data presented in the table for commonly used antagonists and channel blockers for human receptors studied under voltage-clamp are from [164, 203, 1075, 1076, 1086, 1527]. 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 [1513]).

Further reading on Nicotinic acetylcholine receptors (nACh)

Auerbach A. (2015) Agonist activation of a nicotinic acetylcholine receptor. *Neuropharmacology* **96**: 150-6 [PMID:25446670]
Bertrand D *et al*. (2015) Therapeutic Potential of α7 Nicotinic Acetylcholine Receptors. *Pharmacol Rev* **67**: 1025-73 [PMID:26419447]
Bouzat C *et al*. (2018) Nicotinic acetylcholine receptors at the single-channel level. *Br J Pharmacol* **175**: 1789-1804 [PMID:28261794]
Chatzidaki A *et al*. (2015) Allosteric modulation of nicotinic acetylcholine receptors. *Biochem Pharmacol***97**: 408-417 [PMID:26231943]
Corradi J *et al*. (2016) Understanding the Bases of Function and Modulation of α7 Nicotinic Receptors: Implications for Drug Discovery. *Mol Pharmacol* **90**: 288-99 [PMID:27190210]
Crespi A *et al*. (2018) Proteins and chemical chaperones involved in neuronal nicotinic receptor expression and function: an update. *Br J Pharmacol* **175**: 1869-1879 [PMID:28294298]
Dineley KT *et al*. (2015) Nicotinic ACh receptors as therapeutic targets in CNS disorders. *Trends Pharmacol Sci* **36**: 96-108 [PMID:25639674]
Lukas RJ *et al*. (1999) International Union of Pharmacology. XX. Current status of the nomenclature for nicotinic acetylcholine receptors and their subunits. *Pharmacol Rev* **51**: 397-401 [PMID:10353988]
Stokes C *et al*. (2015) Looking below the surface of nicotinic acetylcholine receptors. *Trends Pharmacol Sci* **36**: 514-23 [PMID:26067101]
Wang J *et al*. (2018) Orthosteric and allosteric potentiation of heteromeric neuronal nicotinic acetylcholine receptors. *Br J Pharmacol* **175**: 1805-1821 [PMID:28199738]
Wu J *et al*. (2016) Heteromeric α7β2 Nicotinic Acetylcholine Receptors in the Brain. *Trends Pharmacol Sci* **37**: 562-574 [PMID:27179601]

P2X receptors

Ion channels → Ligand-gated ion channels → P2X receptors

Overview: P2X receptors (**nomenclature as agreed by the NC-IUPHAR Subcommittee on P2X Receptors** [253, 698]) have a trimeric stoichiometry [596, 635, 686, 1009] with two putative TM domains per P2X subunit, gating primarily Na^+, K^+ and Ca^{2+}, exceptionally Cl^-. The Nomenclature Subcommittee has recommended that for P2X receptors, structural criteria should be the initial basis for nomenclature where possible. X-ray crystallography indicates that functional P2X receptors are trimeric and three agonist molecules are required to bind to a single trimeric assembly in order to activate it [461, 520, 596, 686, 908]. Native receptors may occur as either homotrimers (*e.g.* P2X1 in smooth muscle) or heterotrimers (*e.g.* P2X2:P2X3 in the nodose ganglion [1450], P2X1:P2X5 in mouse cortical astrocytes [764], and P2X2:P2X5 in mouse dorsal root ganglion, spinal cord and mid pons [254, 1226]. P2X2, P2X4 and P2X7 receptor activation can lead to influx of large cationic molecules, such as $NMDG^+$, Yo-Pro, ethidium or propidium iodide [1098]. The permeability of the P2X7 receptor is modulated by the amount of cholesterol in the plasma membrane [983]. The hemi-channel pannexin-1 was initially implicated in the action of P2X7 [1099], but not P2X2, receptors [201], but this interpretation is probably misleading [1110]. Convincing evidence now supports the view that the activated P2X7 receptor is immediately permeable to large cationic molecules, but influx proceeds at a much slower pace than that of the small cations Na^+, K^+, and Ca^{2+} [317].

Nomenclature	P2X1	P2X2	P2X3
HGNC, UniProt	*P2RX1*, P51575	*P2RX2*, Q9UBL9	*P2RX3*, P56373
Endogenous agonists	–	ATP [615] – Rat	ATP [616]
Agonists	αβ-meATP, BzATP, L-βγ-meATP	–	αβ-meATP, BzATP
Antagonists	TNP-ATP (pIC_{50}~8.9) [1437], Ip_5I (pIC_{50}~8.5) [705], NF023 (pIC_{50}~6.7) [1304], NF449 (pIC_{50}~6.3) [681]	NF770 (pIC_{50} 7–8) [1033], NF778 (pIC_{50} 7–8) [1033], PSB-10211 (pIC_{50}~7) [1033]	TNP-ATP (pIC_{50}~8.9) [1437], AF-906 (pIC_{50} 8.9) [618], gefapixant (pIC_{50} 8.5) [618], sivopixant (pIC_{50} 8.4) [661], eliapixant (pIC_{50} 8.1) [282], camlipixant (pIC_{50} 7.6) [427], A317491 (pIC_{50}~7.5) [623]
Selective allosteric modulators	MRS 2219 (Positive) [617]	–	–

Nomenclature	P2X4	P2X5	P2X6	P2X7
HGNC, UniProt	*P2RX4*, Q99571	*P2RX5*, Q93086	*P2RX6*, O15547	*P2RX7*, Q99572
Endogenous agonists	ATP [616]	ATP [616] – Rat	ATP [616] – Rat	ATP [616]
Agonists	αβ-meATP, BzATP	–	–	–
Antagonists	BAY-1797 (pIC_{50} 7) [1507], PSB-12054 (pIC_{50} 6.7) [534], 5-BDBD (pIC_{50} 5–6) [618, 1033], BX-430 (pIC_{50} 5–6) [618, 1033], PSB-12062 (pIC_{50} 5–6) [618, 1033], paroxetine (pIC_{50} 5–6) [618, 1033]	–	–	AZ10606120 (pK_d 8.9) [941], A804598 (pIC_{50}~8), brilliant blue G (pIC_{50}~8) [636], A839977 (pIC_{50}~7.7) [336, 338, 563], A740003 (pIC_{50} 7.4) [564], decavanadate (pA_2 = 7.4) (pA_2 7.4) [946], A438079 (pIC_{50}~6.9) [336], AZ11657312 (salt free) (pA_2 6.1) [53]
Selective antagonists	–	–	–	JNJ-47965567 (pK_i 7.9) [116]
Allosteric modulators (Positive)	nimodipine [1234]	–	–	GW791343 [941, 943] – Rat, LL-37 (*CAMP*, P49913) [1392], clemastine [1029], ivermectin [1030], polymyxin B [398]
Allosteric modulators (Negative)	amlodipine [1234]	–	–	AZ10606120 [941], GW791343 [941, 943], KN62 [434, 1263]
Selective allosteric modulators	ivermectin (Positive) (pEC_{50}~6.6) [699] – Rat	–	–	chelerythrine (Negative) (pIC_{50} 5.2) [1263], AZ11645373 (Negative) [944, 1318]
Comments	–	–	–	Ginsenoside compounds acts as positive allosteric modulators of P2X7 [1125], however, the effects of allosteric regulators at P2X7 receptors are species-dependent.

Comments: A317491 and RO3 also block the P2X2:P2X3 heteromultimer [411, 623]. NF449, A317491 and RO3 are more than 10-fold selective for P2X1 and P2X3 receptors, respectively.
Agonists listed show selectivity within recombinant P2X receptors of *ca*. one order of magnitude. A804598, A839977, A740003 and A438079 are at least 10-fold selective for P2X7 receptors and show similar affinity across human and rodent receptors [336, 338, 563].
Several P2X receptors (particularly P2X1 and P2X3) may be inhibited by desensitisation using stable agonists (*e.g.* αβ-meATP); suramin and PPADS are non-selective antagonists at rat and human P2X1-3,5 and hP2X4, but not rP2X4,6,7 [163], and can also inhibit ATPase activity [258]. Ip_5I is inactive at rP2X2, an antagonist at rP2X3 (pIC_{50} 5.6) and enhances agonist responses at rP2X4 [705]. Antagonist potency of NF023 at recombinant P2X2, P2X3 and P2X5 is two orders of magnitude lower than that at P2X1 receptors [1304]. The P2X7 receptor may be inhibited in a non-competitive manner by the protein kinase inhibitors KN62 and chelerythrine [1263], while the p38 MAP kinase inhibitor GTPγS and the cyclic imide AZ11645373 show a species-dependent non-competitive action [337, 944, 945, 1318]. The pH-sensitive dye used in culture media, phenol red, is also reported to inhibit

P2X1 and P2X3 containing channels [706]. Some recombinant P2X receptors expressed to high density bind [^{35}S]ATPγS and [^{3}H]αβ-meATP, although the latter can also bind to 5'-nucleotidase [942]. [^{3}H]A317491 and [^{3}H]A804598 have been used as high affinity antagonist radioligands for P2X3 (and P2X2/3) and P2X7 receptors, respectively [338]. Several high affinity radioligands for the P2X7 receptor have been recently synthesized, some with very promising applications in the diagnosis of inflammatory diseases of the central nervous system [387, 857, 1238, 1373, 1617]. Several P2X3 antagonists have entered clinical trials for refractory chronic cough. In 2022, gefapixant was approved in Japan for the management of refractory or unexplained chronic cough [911]. Oxidized ATP covalently binds un-protonated lysine residues in the vicinity of the ATP-binding site and irreversibly inhibits the P2X7 receptor. Other plasma membrane receptors exposing available lysines may also be blocked by oATP [102, 316]. The cryoelectron microscopy structures of full-length rP2X7 receptor in apo and ATP-bound states have been resolved [927]. A proportion (<10%) of screened humans were found to possess full length P2X5 subunits (444 aa), which can assemble into a functional P2X5 receptor [704, 734]. An uncharged region at the N-terminus of P2X6 exerts an inhibitory effect on its assembly and export from the ER [1058]. The P2X6 subunit also lacks nine residues in the left flipper, which is a key element in agonist docking at P2X receptors [1047].

Further reading on P2X receptors

Di Virgilio F *et al.* (2017) The P2X7 Receptor in Infection and Inflammation. *Immunity* **47**: 15-31 [PMID:28723547]

Di Virgilio F *et al.* (2018) The Elusive P2X7 Macropore. *Trends Cell Biol* **28**: 392-404 [PMID:29439897]

Habermacher C *et al.* (2016) Molecular structure and function of P2X receptors. *Neuropharmacology* **104**: 18-30 [PMID:26231831]

Illes P *et al.* (2021) Update of P2X receptor properties and their pharmacology: IUPHAR Review 30. *Br J Pharmacol* **178**: 489-514 [PMID:33125712]

Jacobson KA *et al.* (2016) Medicinal chemistry of adenosine, P2Y and P2X receptors. *Neuropharmacology* **104**: 31-49 [PMID:26686393]

King BF. (2023) Rehabilitation of the P2X5 receptor: a re-evaluation of structure and function. *Purinergic Signal* **19**: 421-439 [PMID:36279087]

McCarthy AE *et al.* (2019) Full-Length P2X$_7$ Structures Reveal How Palmitoylation Prevents Channel Desensitization. *Cell* **179**: 659-670.e13 [PMID:31587896]

Stokes L *et al.* (2017) P2X4 Receptor Function in the Nervous System and Current Breakthroughs in Pharmacology. *Front Pharmacol* **8**: 291 [PMID:28588493]

ZAC

Ion channels → 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 ACh, 5-HT$_3$, GABA$_A$ and strychnine-sensitive glycine receptors [284, 574, 1402]. The channel is likely to exist as a homopentamer of 4TM subunits that form an intrinsic cation selective channel equipermeable to Na^+, K^+ and Cs^+, but impermeable to Ca^{2+} and Mg^{2+} [1402]. ZAC displays constitutive activity that can be blocked by tubocurarine, TTFB and high concentrations of Ca^{2+} [1402]. Although denoted ZAC, the channel is more potently activated by H^+ and Cu^{2+}, with greater and lesser efficacy than Zn^{2+}, respectively [1402]. Orthologs of the human *ZACN* gene are present in a wide range of mammalian genomes, but notably not in the mouse or rat genomes. [284, 574].

Nomenclature	ZAC
HGNC, UniProt	*ZACN*, Q401N2
Endogenous agonists	H^+ [1402], Cu^{2+} [1402], Zn^{2+} [284, 1402]
Antagonists	tubocurarine (pIC$_{50}$ 5.2) [284], Ca^{2+} (pIC$_{50}$ 2) [1402]
Allosteric modulators	TTFB (Antagonist) (pIC$_{50}$ 5.5) [886]
Functional Characteristics	Outwardly rectifying current (both constitutive and evoked by Zn^{2+})

Comments: A *ZACN* gene does not appear to exist in the mouse or rat genomes [284]. Although tabulated as an antagonist, it is possible that tubocurarine acts as a channel blocker. Antagonism by Ca^{2+} is voltage-independent. ZAC is not activated (at 1 mM) by transition metals including Fe^{2+}, Co^{2+}, Ni^{2+}, Cd^{2+}, or Al^{3+} [1402]. The concentration response relationship to Cu^{2+} is biphasic, with concentrations exceeding 30 µM being associated with reduced activation [1402]. The N-(thiazol-2-yl)-benzamide analog TTFB has been identified as a moderately potent negative allosteric modulator of ZAC. TTFB displays negligible activity at representatives of the GABA$_A$, glycine, 5-HT$_3$ and nicotinic ACh receptors, and thus it constitutes a potential pharmacological tool for ZAC.

Further reading on ZAC

Collingridge GL *et al*. (2009) A nomenclature for ligand-gated ion channels. *Neuropharmacology* **56**: 2-5 [PMID:18655795]

Madjroh N *et al*. (2021) Delineation of the functional properties exhibited by the Zinc-Activated Channel (ZAC) and its high-frequency Thr[128]Ala variant (rs2257020) in Xenopus oocytes. *Pharmacol Res* **169**: 105653 [PMID:33962015]

Madjroh N *et al*. (2021) Probing the molecular basis for signal transduction through the Zinc-Activated Channel (ZAC). *Biochem Pharmacol* **193**: 114781 [PMID:34560053]

Madjroh N *et al*. (2021) Discovery and functional characterization of N-(thiazol-2-yl)-benzamide analogs as the first class of selective antagonists of the Zinc-Activated Channel (ZAC). *Biochem Pharmacol* **193**: 114782 [PMID:34560054]

Peralta FA *et al*. (2016) Zinc as Allosteric Ion Channel Modulator: Ionotropic Receptors as Metalloproteins. *Int J Mol Sci* **17**: [PMID:27384555]

Trattnig SM *et al*. (2016) Copper and protons directly activate the zinc-activated channel. *Biochem Pharmacol***103**: 109-17 [PMID:26872532]

Voltage-gated ion channels

Ion channels → Voltage-gated ion channels

Overview: The voltage-gated ion channels and their structural relatives comprise a superfamily encoded by at least 143 genes in the human genome and are therefore one of the largest superfamilies of signal transduction proteins, following the G protein-coupled receptors and the protein kinases in number [185]. In addition to their prominence in signal transduction, these ion channels are also among the most common drug targets. As for other large protein superfamilies, understanding the molecular relationships among family members, developing a unified, rational nomenclature for the ion channel families and subfamilies, and assigning physiological functions and pharmacological significance to each family member has been an important challenge. Some of the ion channels placed under the 'Voltage-gated' umbrella are not in fact gated by voltage, but for the reasons mentioned above it is useful to consider them within this superfamily. The inwardly rectifying potassium channels, two-pore domain potassium channels (K2P), ryanodine receptors (RyR) and transient receptor potential channels (TRP) are those that are NOT voltage-gated.

CatSper and Two-Pore channels (TPC)

Ion channels → Voltage-gated ion channels → CatSper and Two-Pore channels (TPC)

Overview: CatSper channels (CatSper1-4, **nomenclature as agreed by NC-IUPHAR** [246]) are putative 6TM, voltage-gated, alkalinization-activated calcium permeant channels that are presumed to assemble as a tetramer of α-like subunits and mediate the current $I_{CatSper}$ [707]. In mammals, CatSper subunits are structurally most closely related to individual domains of voltage-activated calcium channels (Ca_v) [1172]. CatSper1 [1172], CatSper2 [1153] and CatSpers 3 and 4 [639, 851, 1144], in common with a putative 2TM auxiliary CatSperβ protein [841] and two putative 1TM associated CatSperγ and CatSperδ proteins [237, 1468], are restricted to the testis and localised to the principle piece of sperm tail. The novel cross-species CatSper channel inhibitor, RU1968, has been proposed as a useful tool to aid characterisation of native CatSper channels [1173].

Two-pore channels (TPCs) are structurally related to CatSpers, Ca_Vs and Na_Vs. TPCs have a 2x6TM structure with twice the number of TMs of CatSpers and half that of Ca_Vs. There are three animal TPCs (TPC1-TPC3). Humans have TPC1 and TPC2, but not TPC3. TPC1 and TPC2 are localized in endosomes and lysosomes [170]. TPC3 is also found on the plasma membrane and forms a voltage-activated, non-inactivating Na^+ channel [173]. All the three TPCs are Na^+-selective under whole-cell or whole-organelle patch clamp recording [174, 175, 1534]. The channels may also conduct Ca^{2+} [972].

Nomenclature	CatSper1	CatSper2	CatSper3	CatSper4
HGNC, UniProt	*CATSPER1*, Q8NEC5	*CATSPER2*, Q96P56	*CATSPER3*, Q86XQ3	*CATSPER4*, Q7RTX7
Activators	CatSper1 is constitutively active, weakly facilitated by membrane depolarisation, strongly augmented by intracellular alkalinisation. In human, but not mouse, progesterone (EC_{50} ~ 8 nM) also potentiates the CatSper current ($I_{CatSper}$). [836, 1330]	–	–	–
Channel blockers	ruthenium red (Inhibition) (pIC_{50} 5) [707] – Mouse, HC-056456 (pIC_{50} 4.7) [181], Cd^{2+} (Inhibition) (pIC_{50} 3.7) [707] – Mouse, Ni^{2+} (Inhibition) (pIC_{50} 3.5) [707] – Mouse	–	–	–
Selective channel blockers	NNC55-0396 (Inhibition) (pIC_{50} 5.7) [-80mV – 80mV] [836, 1330], mibefradil (Inhibition) (pIC_{50} 4.4–4.5) [1330]	–	–	–
Functional Characteristics	Calcium selective ion channel (Ba^{2+}>Ca^{2+}≫Mg^{2+}≫Na^+); quasilinear monovalent cation current in the absence of extracellular divalent cations; alkalinization shifts the voltage-dependence of activation towards negative potentials [$V_{\frac{1}{2}}$ @ pH 6.0 = +87 mV (mouse); $V_{\frac{1}{2}}$ @ pH 7.5 = +11mV (mouse) or pH 7.4 = +85 mV (human)]; required for $I_{CatSper}$ and male fertility (mouse and human)	Required for $I_{CatSper}$ and male fertility (mouse and human)	Required for $I_{CatSper}$ and male fertility (mouse)	Required for $I_{CatSper}$ and male fertility (mouse)

Nomenclature	TPC1	TPC2
HGNC, UniProt	*TPCN1*, Q9ULQ1	*TPCN2*, Q8NHX9
Activators	phosphatidyl (3,5) inositol bisphosphate (pEC_{50} 6.5) [174]	phosphatidyl (3,5) inositol bisphosphate (pEC_{50} 6.4) [1484]
Selective activators	–	TPC2-A1-N (pEC_{50} 5.1) [442]
Channel blockers	verapamil (Inhibition) (pIC_{50} 4.6) [174], Cd^{2+} (Inhibition) (pIC_{50} 3.7) [174]	verapamil (Inhibition) (pIC_{50} 5) [1484]
Functional Characteristics	Organelle voltage-gated Na^+-selective channel (Na^+≫K^+≫Ca^{2+}); Required for the generation of action potential-like long depolarization in lysosomes. Voltage-dependence of activation is sensitive to luminal pH (determined from lysosomal recordings). $\psi_{1/2}$ @ pH4.6 = +91 mV; $\psi_{1/2}$ @ pH6.5 = +2.6 mV. Maximum activity requires PI(3,5)P2 and reduced [ATP], or depletion of extracellular amino acids.	Organelle voltage-independent Na^+-selective channel (Na^+≫K^+≫-Ca^{2+}). Sensitive to the levels of PI(3,5)P2. Activated by decreases in [ATP] or depletion of extracellular amino acids

Comments: CatSper channel subunits expressed singly, or in combination, fail to functionally express in heterologous expression systems [1153, 1172]. The properties of CatSper1 tabulated above are derived from whole cell voltage-clamp recordings comparing currents endogenous to spermatozoa isolated from the *corpus epididymis* of wild-type and *Catsper1*$^{(-/-)}$ mice [707] and also mature human sperm [836, 1330]. $I_{CatSper}$ is also undetectable in the spermatozoa of *Catsper2*$^{(-/-)}$, *Catsper3*$^{(-/-)}$, *Catsper4*$^{(-/-)}$, or CatSperδ$^{(-/-)}$ mice, and CatSper 1 associates with CatSper 2, 3, 4, β, γ, and δ [237, 841, 1144]. Moreover, targeted disruption of *Catsper1, 2, 3, 4*, or δ genes results in an identical phenotype in which spermatozoa fail to exhibit the hyperactive movement (whip-like flagellar beats) necessary for penetration of the egg *cumulus* and *zona pellucida* and subsequent fertilization. Such disruptions are associated with a deficit in alkalinization and depolarization-evoked Ca^{2+} entry into spermatozoa [182, 237, 1144]. Thus, it is likely that the CatSper pore is formed by a heterotetramer of CatSpers1-4 [1144] in association with the auxiliary subunits (β, γ, δ) that are also essential for function [237]. CatSper channels are required for the increase in intracellular Ca^{2+} concentration in sperm evoked by egg *zona pellucida* glycoproteins [1534]. Mouse and human sperm swim against the fluid flow and Ca^{2+} signaling through CatSper is required for the rheotaxis [949]. *In vivo*, CatSper1-null spermatozoa cannot ascend the female reproductive tracts efficiently [238, 552]. It has been shown that CatSper channels form four linear Ca^{2+} signaling domains along the flagella, which orchestrate capacitation-associated tyrosine phosphorylation [238].The driving force for Ca^{2+} entry is principally determined by a mildly outwardly rectifying K^+ channel (KSper) that, like CatSpers, is activated by intracellular alkalinization [1000]. Mouse KSper is encoded by *mSlo3*, a protein detected only in testis [915, 1000, 1598]. In human sperm, such alkalinization may result from the activation of H_v1, a proton channel [837]. Mutations in CatSpers are associated with syndromic and non-syndromic male infertility [540]. In human ejaculated spermatozoa, progesterone (<50 nM) potentiates the CatSper current by a non-genomic mechanism and acts synergistically with intracellular alkalinisation [836, 1330]. Sperm cells from infertile patients with a deletion in CatSper2 gene lack $I_{CatSper}$ and the progesterone response [1290]. In addition, certain prostaglandins (*e.g.*$PGF_{1\alpha}$, PGE_1) also potentiate CatSper mediated currents [836, 1330].
In human sperm, CatSper channels are also activated by various small molecules including endocrine disrupting chemicals and proposed as a polymodal sensor [149, 149].
TPCs are the major Na^+ conductance in lysosomes; knocking out TPC1 and TPC2 eliminates the Na^+ conductance and renders the organelle's membrane potential insensitive to changes in $[Na^+]$ (31). The channels are regulated by luminal pH [174], PI(3,5)P2 [1484], intracellular ATP and extracellular amino acids [175]. TPCs are also involved in the NAADP-activated Ca^{2+} release from lysosomal Ca^{2+} stores [170, 972]. Mice lacking TPCs are viable but have phenotypes including compromised lysosomal pH stability, reduced physical endurance [175], resistance to Ebola viral infection [1215] and fatty liver [476]. No major human disease-associated TPC mutation has been reported.

Further reading on CatSper and Two-Pore channels (TPC)

Clapham DE *et al*. (2005) International Union of Pharmacology. L. Nomenclature and structure-function relationships of CatSper and two-pore channels. *Pharmacol Rev* **57**: 451-4 [PMID:16382101]

Grimm C *et al*. (2017) Two-Pore Channels: Catalyzers of Endolysosomal Transport and Function. *Front Pharmacol* **8**: 45 [PMID:28223936]

Kintzer AF *et al*. (2018) On the structure and mechanism of two-pore channels. *FEBS J* **285**: 233-243 [PMID:28656706]

Cyclic nucleotide-regulated channels (CNG)

Ion channels → Voltage-gated ion channels → Cyclic nucleotide-regulated channels (CNG)

Overview: **Cyclic nucleotide-gated (CNG) channels** are responsible for signalling in the primary sensory cells of the vertebrate visual and olfactory systems. CNG channels are voltage-independent cation channels formed as tetramers. Each subunit has 6TM, with the pore-forming domain between TM5 and TM6. CNG channels were first found in rod photoreceptors [400, 685], where light signals through rhodopsin and transducin to stimulate phosphodiesterase and reduce intracellular cyclic GMP level. This results in a closure of CNG channels and a reduced 'dark current'. Similar channels were found in the cilia of olfactory neurons [994] and the pineal gland [342]. The cyclic nucleotides bind to a domain in the C terminus of the subunit protein: other channels directly binding cyclic nucleotides include hyperolarisation-activated, cyclic nucleotide-gated channels (HCN), ether-a-go-go and certain plant potassium channels.
The **HCN channels** are cation channels that are activated by hyperpolarisation at voltages negative to ˜-50 mV. The cyclic nucleotides cyclic AMP and cyclic GMP directly bind to the cyclic nucleotide-binding domain of HCN channels and shift their activation curves to more positive voltages, thereby enhancing channel activity. HCN channels underlie pacemaker currents found in many excitable cells including cardiac cells and neurons [322, 1074]. In native cells, these currents have a variety of names, such as I_h, I_q and I_f. The four known HCN channels have six transmembrane domains and form tetramers. It is believed that the channels can form heteromers with each other, as has been shown for HCN1 and HCN4 [35]. High resolution structural studies of CNG and HCN channels has provided insight into the gating processes of these channels [778, 779, 808]. **A standardised nomenclature for CNG and HCN channels has been proposed by the NC-IUPHAR Subcommittee on voltage-gated ion channels** [556].

Nomenclature	CNGA1	CNGA2	CNGA3	CNGB1	CNGB3
HGNC, UniProt	*CNGA1*, P29973	*CNGA2*, Q16280	*CNGA3*, Q16281	*CNGB1*, Q14028	*CNGB3*, Q9N-QW8
Activators	cyclic GMP (EC_{50} ˜ 30 μM) ≫ cyclic AMP	cyclic GMP > cyclic AMP (EC_{50} ˜ 1 μM)	cyclic GMP (EC_{50} ˜ 30 μM) ≫ cyclic AMP	–	–
Channel blockers	dequalinium (Antagonist) (pIC_{50} 6.7) [0mV] [1189], L-(cis)-diltiazem (Antagonist) (pK_i 4) [-80mV – 80mV] [213]	dequalinium (Antagonist) (pIC_{50} 5.6) [0mV] [1188]	L-(cis)-diltiazem (high affinity binding requires presence of CNGB subunits)	–	L-(cis)-diltiazem (Antagonist) (pIC_{50} 5.5) [0mV] [443] – Mouse
Functional Characteristics	γ = 25-30 pS P_{Ca}/P_{Na} = 3.1	γ = 35 pS P_{Ca}/P_{Na} = 6.8	γ = 40 pS P_{Ca}/P_{Na} = 10.9	–	–
Comments	–	–	–	L-(cis)-diltiazem acts as a channel blocker when CNGB1 is co-expressed with CNGA1.	–

Nomenclature	HCN1	HCN2	HCN3	HCN4
HGNC, UniProt	*HCN1*, O60741	*HCN2*, Q9UL51	*HCN3*, Q9P1Z3	*HCN4*, Q9Y3Q4
Activators	cyclic AMP > cyclic GMP (both weak)	cyclic AMP > cyclic GMP	–	cyclic AMP > cyclic GMP
Channel blockers	MEL57A (pEC_{50} 6.5) [-80mV] [303] – Mouse, ivabradine (Antagonist) (pIC_{50} 5.7) [1314], ZD7288 (Antagonist) (pIC_{50} 4.7) [1313], EC18 (pEC_{50} 4.7) [303] – Mouse, Cs^+ (Antagonist) (pIC_{50} 3.7) [-40mV] [1313]	ivabradine (Antagonist) (pIC_{50} 5.6) [1314] – Mouse, clonidine (Antagonist) (pIC_{50} 5.1) [-40mV] [721] – Mouse, MEL57A (pEC_{50} 4.9) [303] – Mouse, EC18 (pEC_{50} 4.7) [303] – Mouse, ZD7288 (Antagonist) (pIC_{50} 4.4) [1313], Cs^+ (Antagonist) (pIC_{50} 3.7) [-40mV] [1313]	ivabradine (Antagonist) (pIC_{50} 5.7) [1314], ZD7288 (Antagonist) (pIC_{50} 4.5) [1313], Cs^+ (Antagonist) (pIC_{50} 3.8) [-40mV] [1313]	ivabradine (Antagonist) (pIC_{50} 5.7) [1314], EC18 (pEC_{50} 5.4) [-80mV] [303], clonidine (Antagonist) (pIC_{50} 5) [-40mV] [721] – Mouse, ZD7288 (Antagonist) (pIC_{50} 4.7) [1313], MEL57A (pEC_{50} 4.1) [303], Cs^+ (Antagonist) (pIC_{50} 3.8) [-40mV] [1313]

Comments: CNGA1, CNGA2 and CNGA3 express functional channels as homomers. Three additional subunits *CNGA4* (Q8IV77), *CNGB1* (Q14028) and *CNGB3* (Q9NQW8) do not, and are referred to as auxiliary subunits. The subunit composition of the native channels is believed to be as follows. Rod: $CNGA1_3$/CNGB1a [87]; Cone: $CNGA3_3/CNGB3_1$ [1618] ; Olfactory neurons: $CNGA2_2$/CNGA4/CNGB1b [1100, 1505, 1615, 1616, 1622]. HCN channels are permeable to both Na^+ and K^+ ions, with a Na^+/K^+ permeability ratio of about 0.2. Functionally, they differ from each other in terms of time constant of activation with HCN1 the fastest, HCN4 the slowest and HCN2 and HCN3 intermediate. The compounds ZD7288 [140] and ivabradine [162] have proven useful in identifying and studying functional HCN channels in native cells. Zatebradine and cilobradine are also useful blocking agents.

Further reading on Cyclic nucleotide-regulated channels (CNG)

Barret DCA *et al.* (2022) The structure of cyclic nucleotide-gated channels in rod and cone photoreceptors. *Trends Neurosci* **45**: 763-776 [PMID:35934530]

Gerhardt MJ *et al.* (2023) Biology, Pathobiology and Gene Therapy of CNG Channel-Related Retinopathies. *Biomedicines* **11**: [PMID:36830806]

Hennis K *et al.* (2022) Paradigm shift: new concepts for HCN4 function in cardiac pacemaking. *Pflugers Arch* **474**: 649-663 [PMID:35556164]

Napolitano LMR *et al.* (2021) CNG channel structure, function, and gating: a tale of conformational flexibility. *Pflugers Arch* **473**: 1423-1435 [PMID:34357442]

Santoro B *et al.* (2020) Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels as Drug Targets for Neurological Disorders. *Annu Rev Pharmacol Toxicol* **60**: 109-131 [PMID:31914897]

Sartiani L *et al.* (2017) The Hyperpolarization-Activated Cyclic Nucleotide-Gated Channels: from Biophysics to Pharmacology of a Unique Family of Ion Channels. *Pharmacol Rev* **69**: 354-395 [PMID:28878030]

Potassium channels

Ion channels → Voltage-gated ion channels → Potassium channels

Overview: Activation of potassium channels regulates excitability and can control the shape of the action potential waveform. They are present in all cells within the body and can influence processes as diverse as cognition, muscle contraction and hormone secretion. Potassium channels are subdivided into families, based on their structural and functional properties. The largest family consists of potassium channels that activated by membrane depolarization, with other families consisting of channels that are either activated by a rise of intracellular calcium ions or are constitutively active. A standardised nomenclature for potassium channels has been proposed by the **NC-IUPHAR Subcommittees** on potassium channels [460, 494, 754, 1503], which has placed cloned channels into groups based on gene family and structure of channels that exhibit 6, 4 or 2 transmembrane domains (TM).

Calcium- and sodium-activated potassium channels (K_{Ca}, K_{Na})

Ion channels → Voltage-gated ion channels → Potassium channels → Calcium- and sodium-activated potassium channels (K_{Ca}, K_{Na})

Overview: Calcium- and sodium- activated potassium channels are members of the 6TM family of K channels which comprises the voltage-gated K_V subfamilies, including the KCNQ subfamily, the EAG subfamily (which includes hERG channels), the Ca^{2+}-activated Slo subfamily (actually with 6 or 7TM) and the Ca^{2+}- and Na^{+}-activated SK subfamily (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Calcium- and sodium-activated potassium channels** [658]). As for the 2TM family, the pore-forming a subunits form tetramers and heteromeric channels may be formed within subfamilies (*e.g.* K_V1.1 with K_V1.2; KCNQ2 with KCNQ3).

Nomenclature	K_{Ca}1.1
HGNC, UniProt	*KCNMA1*, Q12791
Activators	dehydrosoyasaponin I (pEC_{50}~7) [453], 16,17-EpDPE (pEC_{50} 6.6) [1479], GoSlo-SR-5-69 (pEC_{50} 6.6) [1193], flindokalner (pEC_{50} 6.4–6.5) [629], magnolol (pEC_{50}~6) [1530], BC5 (pEC_{50} 5.6) [1604], BMS-191011 (pEC_{50}~5.6) [1186], NS1619 (pEC_{50} 5.4) [784, 1049], NS004 (pEC_{50} 4.5–5), NS11021 (pEC_{50} 4.7–5) [109], NS19504 (pEC_{50} 5) [999], mefenamic acid (pEC_{50} 4) [1372]
Channel blockers	BmTx2 (pIC_{50} 9.5) [124, 1185], BmTx1 (pIC_{50} 9.2) [1185], slotoxin (blocks channels with β1 auxiliary subunit) (pIC_{50} 8.8) [432], paxilline (pK_i 8.7) [0mV] [1221] – Mouse, Penitrem A (pIC_{50} 8.2) [52], kaliotoxin (pIC_{50} 7.7) [259], BmP09 (pIC_{50} 7.6) [1566], natrin (pIC_{50} 7.5) [1474], ChTX-Lq2 (pIC_{50} 7.4) [866], Lqh Tx 15-1 (pIC_{50} 7.3) [913], butantoxin (pIC_{50} 7.3) [1035], martentoxin (pIC_{50} 7.1) [1369], verruculogen (pIC_{50}~7) [968], charybdotoxin (pIC_{50} 6.6) [428], iberiotoxin (pIC_{50} 6.6) [422], clotrimazole (pIC_{50} 5.5) [1531], tetrandrine (pIC_{50} 5) [1466]
Functional Characteristics	Maxi K_{Ca}

Nomenclature	K_{Ca}2.1	K_{Ca}2.2	K_{Ca}2.3
HGNC, UniProt	*KCNN1*, Q92952	*KCNN2*, Q9H2S1	*KCNN3*, Q9UGI6
Activators	EBIO (Agonist) Concentration range: 2×10^{-3}M [-80mV] [1092, 1500], NS309 (Agonist) Concentration range: 3×10^{-8}M-1×10^{-7}M [-90mV] [1327, 1500]	NS309 (Agonist) (pEC_{50} 6.2) Concentration range: 3×10^{-8}M-1×10^{-7}M [1091, 1327, 1500], NS13001 (Agonist) (pEC_{50} 5.7) [682] – Mouse, rimtuzalcap (pIC_{50}~5.3) [1609], CyPPA (Agonist) (pEC_{50} 4.9) [571], EBIO (Agonist) (pEC_{50} 3.3) [1091, 1500]	NS13001 (Agonist) (pEC_{50} 6.8) [682] – Mouse, CyPPA (Agonist) (pEC_{50} 5.3) [571], EBIO (Agonist) (pEC_{50} 3.8) [1500, 1519], NS309 (Agonist) Concentration range: 3×10^{-8}M [1327, 1500]

Inhibitors	UCL1684 (pIC$_{50}$ 9.1) [1326, 1500], apamin (pIC$_{50}$ 8.4) [760, 1255, 1316, 1326], CM-TPMF (pEC$_{50}$ 7.6) [572]	UCL1684 (pIC$_{50}$ 10.1) [386, 996, 1500], apamin (pK_d 9.4) [619], Lei-Dab7 (pIC$_{50}$ 8.4) [1256], AP14145 (pIC$_{50}$ 6) [323, 1279], AP30663 (pIC$_{50}$ 5.6) [562]	UCL1684 (pIC$_{50}$ 8–9) [386, 1500]
Channel blockers	NS8593 (pIC$_{50}$ 6.4) [0mV] [1325], AP30663 (pIC$_{50}$ 6) [108, 562], tetraethylammonium (pIC$_{50}$ 2.7) [1500]	NS8593 (pIC$_{50}$ 6.4) [1325], AP30663 (pIC$_{50}$ 5.6) [108, 562], tetraethylammonium (pIC$_{50}$ 2.7) [1500]	apamin (Antagonist) (pIC$_{50}$ 8.6) [78, 570, 760] – Rat, AP14145 (pIC$_{50}$ 6) [1279], AP30663 (pIC$_{50}$ 6) [108, 562], tetraethylammonium (pIC$_{50}$ 2.7) [1500]
Functional Characteristics	SK_{Ca}	SK_{Ca}	SK_{Ca}
Comments	The rat isoform does not form functional channels when expressed alone in cell lines. N- or C-terminal chimeric constructs permit functional channels that are insensitive to apamin [1500]. Heteromeric channels are formed between K_{Ca}2.1 and 2.2 subunits that show intermediate sensitivity to apamin [242].	Cryo-EM-derived structures of human K_{Ca}2.2-K_{Ca}3.1 chimeric channels have been deposited to the Protein Data Bank (PDB) with IDs 9O48 (Ca2+ bound state), 9O51 (Ca2+ free state), 9O53 (inhibitor bound state), 9O50 (activator bound state) and 9O52 (apamin bound state).	–

Nomenclature	K_{Ca}3.1	K_{Na}1.1	K_{Na}1.2	K_{Ca}5.1
HGNC, UniProt	*KCNN4*, O15554	*KCNT1*, Q5JUK3	*KCNT2*, Q6UVM3	*KCNU1*, A8MYU2
Activators	NS309 (Agonist) (pEC$_{50}$ 8) [-90mV] [1327, 1500], SKA-121 (Agonist) (pEC$_{50}$ 7) [250], SKA-111 (Agonist) (pEC$_{50}$ 6.9) [250], EBIO (Agonist) (pEC$_{50}$ 4.1–4.5) [-100mV – -50mV] [1092, 1350, 1500]	bithionol (Agonist) (pEC$_{50}$ 5–6) [1557] – Rat, niclosamide (Agonist) (pEC$_{50}$ 5.5) [122], loxapine (Agonist) (pEC$_{50}$ 5.4) [122]	niflumic acid (Agonist) (pEC$_{50}$ 8.7) [271, 433]	–
Gating inhibitors	–	bepridil (pIC$_{50}$ 5–6) [1557] – Rat	–	–
Channel blockers	maurotoxin (Inhibition) (pIC$_{50}$ 9) [184], charybdotoxin (pIC$_{50}$ 7.6–8.7) [630, 649]	PRX-2904 (pIC$_{50}$ 7.4) [474], CPK20 (pIC$_{50}$ 6.7) [601], VU0948578 (pIC$_{50}$ 6.2) [1155], VU0948578 (pIC$_{50}$ 6.2) [1155], quinidine (pIC$_{50}$ 4) [115, 1557] – Rat	CPK20 (pIC$_{50}$ 5.9) [601], compound 43 (pIC$_{50}$ 5.6) [1154], Ba^{2+} (Inhibition) (pIC$_{50}$ 3) [115], quinidine (Inhibition) Concentration range: 1×10^{-3}M [115] – Rat	VU0546110 (pIC$_{50}$ 5.9) [875], quinidine Concentration range: 2×10^{-5}M [1367, 1526] – Mouse
Selective channel blockers	DHP-103 (pIC$_{50}$ 8.2) [1056], NS6180 (Inhibition) (pIC$_{50}$ 8.1) [1324], TRAM-34 (Inhibition) (pK_d 7.6–8) [1532], senicapoc (Inhibition) (pIC$_{50}$ 8) [1315]	–	–	–
Functional Characteristics	IK_{Ca}; K_{Ca}3.1 may form heteromers with K_{Ca}2.1 [539].	K_{Na}	K_{Na}	Sperm pH-regulated K^+ current, KSPER
Comments	Cryo-EM-derived structures of human K_{Ca}2.2-K_{Ca}3.1 chimeric channels have been deposited to the Protein Data Bank (PDB) with IDs 9O48 (Ca2+ bound state), 9O51 (Ca2+ free state), 9O53 (inhibitor bound state), 9O50 (activator bound state) and 9O52 (apamin bound state).	–	–	–

Further reading on Calcium- and sodium-activated potassium channels (K_{Ca}, K_{Na})

Brown BM *et al.* (2020) Pharmacology of Small- and Intermediate-Conductance Calcium-Activated Potassium Channels. *Annu Rev Pharmacol Toxicol* **60**: 219-240 [PMID:31337271]

Dopico AM *et al.* (2018) Calcium- and voltage-gated BK channels in vascular smooth muscle. *Pflugers Arch* **470**: 1271-1289 [PMID:29748711]

Kaczmarek LK *et al.* (2017) International Union of Basic and Clinical Pharmacology. C. Nomenclature and Properties of Calcium-Activated and Sodium-Activated Potassium Channels. *Pharmacol Rev* **69**: 1-11 [PMID:28267675]

Kshatri AS *et al.* (2018) Physiological Roles and Therapeutic Potential of Ca^{2+} Activated Potassium Channels in the Nervous System. *Front Mol Neurosci* **11**: 258 [PMID:30104956]

Inwardly rectifying potassium channels (K_{IR})

Ion channels → Voltage-gated ion channels → Potassium channels → Inwardly rectifying potassium channels (K_{IR})

Overview: The 2TM domain family of K channels are also known as the inward-rectifier K channel family. This family includes the strong inward-rectifier K channels (K_{ir} 2.x) that are constitutively active, the G protein-activated inward-rectifier K channels (K_{ir} 3.x) and the ATP-sensitive K channels (K_{ir} 6.x, which combine with sulphonylurea receptors (SUR1-3)). The pore-forming α subunits form tetramers, and heteromeric channels may be formed within subfamilies (*e.g.* K_{ir} 3.2 with K_{ir} 3.3).

Nomenclature	K_{ir} 1.1
HGNC, UniProt	*KCNJ1*, P48048
Ion Selectivity and Conductance	NH_4^+ [62pS] > K^+ [38. pS] > Tl^+ [21pS] > Rb^+ [15pS] (Rat) [229, 551]
Channel blockers	tertiapin-Q (Inhibition) (pIC_{50} 8.9) [641], Ba^{2+} (Antagonist) (pIC_{50} 2.3–4.2) Concentration range: 1×10^{-4}M [*voltage dependent* 0mV – -100mV] [551, 1623] – Rat, Cs^+ (Antagonist) (pIC_{50} 2.9) [*voltage dependent* -120mV] [1623] – Rat
Functional Characteristics	K_{ir} 1.1 is weakly inwardly rectifying, as compared to classical (strong) inward rectifiers.

Nomenclature	K_{ir} 2.1	K_{ir} 2.2	K_{ir} 2.3	K_{ir} 2.4
HGNC, UniProt	*KCNJ2*, P63252	*KCNJ12*, Q14500	*KCNJ4*, P48050	*KCNJ14*, Q9UNX9
Endogenous activators	PIP_2 (Agonist) Concentration range: 1×10^{-5}M-5×10^{-5}M [-30mV] [581, 1167, 1303] – Mouse	–	–	–
Endogenous inhibitors	–	Intracellular Mg^{2+} (pIC_{50} 5) [40mV] [1554]	–	Intracellular Mg^{2+}
Gating inhibitors	–	Ba^{2+} (Antagonist) Concentration range: 5×10^{-5}M [-150mV – -50mV] [1354] – Mouse, Cs^+ (Antagonist) Concentration range: 5×10^{-6}M-5×10^{-5}M [-150mV – -50mV] [1354] – Mouse	–	–

Endogenous channel blockers	spermine (Antagonist) (pK_d 9.1) [*voltage dependent* 40mV] [609, 1559] – Mouse, spermidine (Antagonist) (pK_d 8.1) [*voltage dependent* 40mV] [1559] – Mouse, putrescine (Antagonist) (pK_d 5.1) [*voltage dependent* 40mV] [609, 1559] – Mouse, Intracellular Mg^{2+} (Antagonist) (pK_d 4.8) [*voltage dependent* 40mV] [1559] – Mouse	–	Intracellular Mg^{2+} (Antagonist) (pK_d 5) [*voltage dependent* 50mV] [854], putrescine (Antagonist) Concentration range: 5×10^{-5}M-1 $\times 10^{-3}$M [-80mV – 80mV] [854], spermidine (Antagonist) Concentration range: 2.5×10^{-5} M-1 $\times 10^{-3}$M [-80mV – 80mV] [854], spermine (Antagonist) Concentration range: 5×10^{-5}M-1 $\times 10^{-3}$M [-80mV – 80mV] [854]	–
Channel blockers	Ba^{2+} (Antagonist) (pK_d 3.9–5.6) Concentration range: 1×10^{-6}M-1 $\times 10^{-4}$M [*voltage dependent* 0mV – -80mV] [25] – Mouse, Cs^+ (Antagonist) (pK_d 1.3–4) Concentration range: 3×10^{-5}M-3 $\times 10^{-4}$M [*voltage dependent* 0mV – -102mV] [8] – Mouse	–	Ba^{2+} (Antagonist) (pIC$_{50}$ 5) Concentration range: 3×10^{-6}M-5 $\times 10^{-4}$ M [-60mV] [898, 1136, 1368], Cs^+ (Antagonist) (pK_i 1.3–4.5) Concentration range: 3×10^{-6}M-3 $\times 10^{-4}$M [0mV – -130mV] [898]	Cs^+ (Antagonist) (pK_d 3–4.1) [*voltage dependent* -60mV – -100mV] [590], Ba^{2+} (Antagonist) (pK_d 3.3) [*voltage dependent* 0mV] [590]
Functional Characteristics	IK_1 in heart, 'strong' inward-rectifier current	IK_1 in heart, 'strong' inward-rectifier current	IK_1 in heart, 'strong' inward-rectifier current	IK_1 in heart, 'strong' inward-rectifier current
Comments	K_{ir} 2.1 is also inhibited by intracellular polyamines	K_{ir} 2.2 is also inhibited by intracellular polyamines	K_{ir} 2.3 is also inhibited by intracellular polyamines	K_{ir} 2.4 is also inhibited by intracellular polyamines

Nomenclature	K_{ir} 3.1	K_{ir} 3.2	K_{ir} 3.3	K_{ir} 3.4
HGNC, UniProt	*KCNJ3*, P48549	*KCNJ6*, P48051	*KCNJ9*, Q92806	*KCNJ5*, P48544
Endogenous activators	PIP_2 (Agonist) (pK_d 6.3) Concentration range: 5×10^{-5}M [physiological voltage] [581]	PIP_2 (Agonist) (pK_d 6.3) Concentration range: 5×10^{-5}M [physiological voltage] [581]	PIP_2 [542]	PIP_2 [90, 542]
Gating inhibitors	–	pimozide (Antagonist) (pEC$_{50}$ 5.5) [-70mV] [724] – Mouse	–	–
Channel blockers	tertiapin-Q (Antagonist) (pIC$_{50}$ 7.9) [640], Ba^{2+} (Antagonist) (pIC$_{50}$ 4.7) [281] – Rat	desipramine (Antagonist) (pIC$_{50}$ 4.4) [-70mV] [725] – Mouse	–	tertiapin-Q (Antagonist) (pIC$_{50}$ 7.9) [640]
Functional Characteristics	G protein-activated inward-rectifier current	G protein-activated inward-rectifier current	G protein-activated inward-rectifier current	G protein-activated inward-rectifier current
Comments	K_{ir} 3.1 is also activated by $G_{\beta\gamma}$. K_{ir} 3.1 is not functional alone. The functional expression of K_{ir} 3.1 in *Xenopus oocytes* requires coassembly with the endogenous *Xenopus* K_{ir} 3.5 subunit. The major functional assembly in the heart is the K_{ir} 3.1/3.4 heteromultimer, while in the brain it is K_{ir} 3.1/3.2, K_{ir} 3.1/3.3 and K_{ir} 3.2/3.3.	K_{ir} 3.2 is also activated by $G_{\beta\gamma}$. K_{ir} 3.2 forms functional heteromers with K_{ir} 3.1/3.3.	K_{ir} 3.3 is also activated by $G_{\beta\gamma}$	K_{ir} 3.4 is also activated by $G_{\beta\gamma}$

Nomenclature	K_{ir} 4.1	K_{ir} 4.2	K_{ir} 5.1
HGNC, UniProt	*KCNJ10*, P78508	*KCNJ15*, Q99712	*KCNJ16*, Q9NPI9
Channel blockers	Ba^{2+} (Antagonist) Concentration range: 3×10^{-6}M-1×10^{-3}M [-160mV – 60mV] [731, 1357, 1364] – Rat, Cs^{+} (Antagonist) Concentration range: 3×10^{-5}M-3×10^{-4}M [-160mV – 50mV] [1357] – Rat	Ba^{2+} (Antagonist) Concentration range: 1×10^{-5}M-1×10^{-4}M [-120mV – 100mV] [1090] – Mouse, Cs^{+} (Antagonist) Concentration range: 1×10^{-5}M-1×10^{-4}M [-120mV – 100mV] [1090] – Mouse	Ba^{2+} (Antagonist) Concentration range: 3×10^{-3}M [-120mV – 20mV] [1363] – Rat
Functional Characteristics	Inward-rectifier current	Inward-rectifier current	Weakly inwardly rectifying

Nomenclature	K_{ir} 6.1	K_{ir} 6.2	K_{ir} 7.1
HGNC, UniProt	*KCNJ8*, Q15842	*KCNJ11*, Q14654	*KCNJ13*, O60928
Associated subunits	SUR1, SUR2A, SUR2B	SUR1, SUR2A, SUR2B	–
Activators	cromakalim, diazoxide (Agonist) Concentration range: 2×10^{-4}M [-60mV] [1552] – Mouse, minoxidil, nicorandil (Agonist) Concentration range: 3×10^{-4}M [-60mV – 60mV] [1552] – Mouse	diazoxide (Agonist) (pEC_{50} 4.2) [physiological voltage] [597] – Mouse, cromakalim (Agonist) Concentration range: 3×10^{-5}M [-60mV] [598] – Mouse, minoxidil, nicorandil	–
Inhibitors	glibenclamide, tolbutamide	glibenclamide, tolbutamide	–
Channel blockers	–	–	Ba^{2+} (Antagonist) (pK_i 3.2) [*voltage dependent* -100mV] [339, 742, 759, 1082], Cs^{+} (Antagonist) (pK_i 1.6) [*voltage dependent* -100mV] [339, 742, 1082]
Functional Characteristics	ATP-sensitive, inward-rectifier current	ATP-sensitive, inward-rectifier current	Inward-rectifier current

Two-pore domain potassium channels (K_{2P})

Ion channels → Voltage-gated ion channels → Potassium channels → Two-pore domain potassium channels (K_{2P})

Overview: The 4TM family of K channels mediate many of the background potassium currents observed in native cells. They are open across the physiological voltage-range and are regulated by a wide array of neurotransmitters and biochemical mediators. The pore-forming α-subunit contains two pore loop (P) domains and two subunits assemble to form one ion conduction pathway lined by four P domains. It is important to note that single channels do not have two pores but that each subunit has two P domains in its primary sequence; hence the name two-pore domain, or K_{2P} channels (and not two-pore channels). Some of the K_{2P} subunits can form heterodimers across subfamilies (*e.g.* K_{2P}3.1 with K_{2P}9.1). The nomenclature of 4TM K channels in the literature is still a mixture of IUPHAR and common names. The suggested division into subfamilies, described in the More detailed introduction online, is based on similarities in both structural and functional properties within subfamilies and this explains the "common abbreviation" nomenclature in the tables below.

Nomenclature	K_{2P}1.1	K_{2P}2.1	K_{2P}3.1	K_{2P}4.1
Common abbreviation	TWIK1	TREK1	TASK1	TRAAK1
HGNC, UniProt	*KCNK1*, O00180	*KCNK2*, O95069	*KCNK3*, O14649	*KCNK4*, Q9NYG8
Endogenous activators	–	arachidonic acid (studied at 1-10 μM) (pEC_{50} 5) [1085]	–	arachidonic acid (studied at 1-10 μM) [402]
Activators	–	GI-530159 (pEC_{50} 6.1) [859], ONO-2920632 (pEC_{50} 5.6) [1567], BL-1249 (pEC_{50} 5.3) [1134], LPS2336 (pEC_{50} 4.9) [146], chloroform (studied at 1-5 mM) Concentration range: 8×10^{-3}M [1084], halothane (studied at 1-5 mM) [1084], isoflurane (studied at 1-5 mM) [1084]	halothane (studied at 1-10 mM) [774]	riluzole (studied at 1-100 μM) [352]
Inhibitors	magnolol (pIC_{50} 5.2) [1473]	ONO-TR-772 (pIC_{50} 7.8) [1362] – Rat, Cpd8l (pIC_{50} 6.1) [842] – Rat, norfluoxetine (pIC_{50} 5.1) [694]	KU124 (pIC_{50} 5.8) [350]	–
Channel blockers	–	–	*R*-(+)-methanandamide (pIC_{50}~6.2) [894], anandamide (pIC_{50}~6.2) [894]	–
Functional Characteristics	Background current	Background current	Background current	Background current
Comments	K_{2P}1.1 is inhibited by acid pH_o external acidification with a pK_a ˜6.7 [1127]. K_{2P}1 forms heterodimers with K_{2P}3 and K_{2P}9 [1128].	K_{2P}2.1 is also activated by membrane stretch, heat and acid pH_i [893, 895]. K_{2P}2 can heterodimerize with K_{2P}4 [126] and K_{2P}10 [802].	Knock-out of the *kcnk3* gene leads to a prolonged QT interval in mice [293] and disrupted development of the adrenal cortex [526]. K_{2P}3.1 is inhibited by acid pH_o with a pK_a of 6.4 [855]. K_{2P}3 forms heterodimers with K_{2P}1 [1128] and K_{2P}9 [269].	K_{2P}4 is activated by membrane stretch [892], and increased temperature (˜12 to 20-fold between 17 and 40°C [667]) and can heterodimerize with K_{2P}2 [126].

Nomenclature	K_{2P}5.1	K_{2P}6.1	K_{2P}7.1	K_{2P}9.1	K_{2P}10.1
Common abbreviation	TASK2	TWIK2	–	TASK3	TREK2
HGNC, UniProt	*KCNK5*, O95279	*KCNK6*, Q9Y257	*KCNK7*, Q9Y2U2	*KCNK9*, Q9NPC2	*KCNK10*, P57789
Endogenous activators	–	–	–	–	arachidonic acid (studied at 1-10 μM) [798]
Activators	–	–	dapagliflozin (pEC_{50} 4) [876]	halothane (studied at 1-5 mM) [1359]	Nb-Activator-67 (pEC_{50} 7) [1156], ONO-2920632 (pEC_{50} 6.5) [1567], Nb-Activator-76 (pEC_{50} 6.4) [1156], GI-530159 [859], halothane (studied at 1-5 mM) [798]
Inhibitors	–	–	–	A-769662 (effective at 300 μM) (pIC_{50} 3.5) [1212], *R*-(+)-methanandamide (studied at 1-10 μM) [1158], anandamide (studied at 1-10 μM) [1158], benzimidazole 991 (effective concentration range 3-30 μM) [1212]	ONO-TR-772 (pIC_{50} 6.8) [1362], Nb-Inhibitor-61 (pIC_{50} 6.2) [1156]
Functional Characteristics	Background current	Unknown	Unknown	Background current	Background current
Comments	K_{2P}5.1 is activated by alkaline pH_o [1175]. Knockout of the kcnk5 gene in mice is associated with metabolic acidosis, hyponatremia and hypotension due to impaired bicarbonate handling in the kidney [1494], as well as deafness [190]. The T108P mutation is associated with Balkan Endemic Nephropathy in humans [1396].	–	–	K_{2P}9.1 is also inhibited by acid pH_o with a pK_a of ˜6 [1158]. Imprinting of the *KCNK9* gene is associated with Birk Barel syndrome [77]. K_{2P}9 can form heterodimers with K_{2P}1 [1128] or K_{2P}3 [269].	K_{2P}10.1 is also activated by membrane stretch [798] and can heterodimerize with K_{2P}2 [802].

Nomenclature	K_{2P}12.1	K_{2P}13.1	K_{2P}15.1	K_{2P}16.1	K_{2P}17.1	K_{2P}18.1
Common abbreviation	THIK2	THIK1	TASK5	TALK1	TALK2	TRESK
HGNC, UniProt	*KCNK12*, Q9HB15	*KCNK13*, Q9HB14	*KCNK15*, Q9H427	*KCNK16*, Q96T55	*KCNK17*, Q96T54	*KCNK18*, Q7Z418
Endogenous inhibitors	–	–	–	–	–	arachidonic acid (studied at 10-50 µM) [1223]
Inhibitors	–	halothane (studied at ˜5 mM) [127]	–	–	–	–
Functional Characteristics	Does not function as a homodimer [1157] but can form a functional heterodimer with K_{2P}13 [127].	Background current	Unknown	Background current	Background current	Background current
Comments	–	Forms a heterodimer with K_{2P}12 [127].	–	K_{2P}16.1 current is increased by alkaline pH_o with a pK_a of 7.8 [668].	K_{2P}17.1 current is increased by alkaline pH_o with a pK_a of 8.8 [668].	A frame-shift mutation (F139WfsX24) in the *KCNK18* gene, is associated with migraine with aura in humans [763]. Sodium butyrate is a TRESK channel activator [550].

Comments: The K_{2P}6, K_{2P}7.1, K_{2P}15.1 and K_{2P}12.1 subtypes, when expressed in isolation, are nonfunctional. All 4TM channels are insensitive to the classical potassium channel blockers tetraethylammonium and fampridine, but are blocked to varying degrees by Ba^{2+} ions.

Further reading on Two-pore domain potassium channels (K_{2P})

Gada K *et al.* (2019) Two-pore domain potassium channels: emerging targets for novel analgesic drugs: IUPHAR Review 26. *Br J Pharmacol* **176**: 256-266 [PMID:30325008]

Jin X *et al.* (2020) Targeting Two-Pore Channels: Current Progress and Future Challenges. *Trends Pharmacol Sci* **41**: 582-594 [PMID:32679067]

Mathie A *et al.* (2021) Two-Pore Domain Potassium Channels as Drug Targets: Anesthesia and Beyond. *Annu Rev Pharmacol Toxicol* **61**: 401-420 [PMID:32679007]

Voltage-gated potassium channels (K_v)

Ion channels → Voltage-gated ion channels → Potassium channels → Voltage-gated potassium channels (K_v)

Overview: The 6TM family of K channels comprises the voltage-gated K_V subfamilies, the EAG subfamily (which includes hERG channels), the Ca^{2+}-activated Slo subfamily (actually with 7TM, termed BK) and the Ca^{2+}-activated SK subfamily. These channels possess a pore-forming α subunit that comprises tetramers of identical subunits (homomeric) or of different subunits (heteromeric). Heteromeric channels can only be formed within subfamilies (e.g. K_v1.1 with K_v1.2; K_v7.2 with K_v7.3). The pharmacology largely reflects the subunit composition of the functional channel.

K_v7 channels K_v7.1-K_v7.5 (KCNQ1-5) K^+ channels are voltage-gated K^+ channels with major roles in neurons, muscle cells and epithelia where they underlie physiologically important K^+ currents, such as the neuronal M-current and the cardiac IKs. Genetic deficiencies in all five KCNQ genes result in human excitability disorders, including epilepsy, autism spectrum disorders, cardiac arrhythmias and deafness. Thanks to the recent knowledge of the structure and function of human KCNQ-encoded proteins, these channels are increasingly used as drug targets for treating diseases [1, 587, 651, 1434].

Nomenclature	K_v1.1	K_v1.2	K_v1.3	K_v1.4	K_v1.5	K_v1.6	K_v1.7
HGNC, UniProt	*KCNA1*, Q09470	*KCNA2*, P16389	*KCNA3*, P22001	*KCNA4*, P22459	*KCNA5*, P22460	*KCNA6*, P17658	*KCNA7*, Q96RP8
Associated subunits	K_v1.2, K_v1.4, $K_v\beta$1 and $K_v\beta$2 [251]	K_v1.1, K_v1.4, $K_v\beta$1 and $K_v\beta$2 [251]	K_v1.1, K_v1.2, K_v1.4, K_v1.6, $K_v\beta$1 and $K_v\beta$2 [251]	K_v1.1, K_v1.2, $K_v\beta$1 and $K_v\beta$2 [251]	$K_v\beta$1 and $K_v\beta$2	$K_v\beta$1 and $K_v\beta$2	$K_v\beta$1 and $K_v\beta$2
Channel blockers	α-dendrotoxin (pEC_{50} 7.7–9) [481, 592] – Rat, margatoxin (Inhibition) (pIC_{50} 8.4) [88], tetraethylammonium (Inhibition) (pK_d 3.5) [481] – Mouse	margatoxin (Inhibition) (pIC_{50} 11.2) [88], α-dendrotoxin (pIC_{50} 7.8–9.4) [481, 592] – Rat, noxiustoxin (pK_d 8.7) [481] – Rat, κM-conotoxin RIIIK (pIC_{50} 6.6) [0mV] [396]	margatoxin (pIC_{50} 10–10.3) [431, 445], noxiustoxin (pK_d 9) [481] – Mouse, maurotoxin (pIC_{50} 6.8) [1181], tetraethylammonium (pK_d 2) [481] – Mouse	fampridine (pIC_{50} 1.9) [1331] – Rat	fampridine (pIC_{50} 4.3) [390]	α-dendrotoxin (pIC_{50} 7.7) [485], tetraethylammonium (pIC_{50} 2.2) [485]	noxiustoxin (pIC_{50} 7.7) [664] – Mouse, fampridine (pIC_{50} 3.6) [664] – Mouse
Selective channel blockers	–	–	correolide (pIC_{50} 7.1) [392]	–	–	–	–
Functional Characteristics	K_V	K_V	K_V	K_A	K_v	K_V	K_V
Comments	–	–	Resistant to dendrotoxins	Resistant to dendrotoxins	Resistant to external TEA	–	–

Nomenclature	K_v1.8	K_v2.1	K_v2.2	K_v3.1	K_v3.2	K_v3.3	K_v3.4
HGNC, UniProt	*KCNA10*, Q16322	*KCNB1*, Q14721	*KCNB2*, Q92953	*KCNC1*, P48547	*KCNC2*, Q96PR1	*KCNC3*, Q14003	*KCNC4*, Q03721
Associated subunits	$K_v\beta$1 and $K_v\beta$2	K_v5.1, K_v6.1-6.4, K_v8.1-8.2 and K_v9.1-9.3	K_v5.1, K_v6.1-6.4, K_v8.1-8.2 and K_v9.1-9.3	–	–	–	MiRP2 is an associated subunit for K_v3.4
Gating inhibitors	–	RY796 (pIC_{50} 6.6) [535], RY785 (pIC_{50} 5.9) [535], GxTx-1E (pIC_{50} 2) [536]	GxTx-1E (pK_d 8.6) [536], RY796 (pIC_{50} 7.1) [535], RY785 (pIC_{50} 6.7) [535]	–	–	–	–
Channel blockers	fampridine (pIC_{50} 2.8) [769]	tetraethylammonium (Pore blocker) (pIC_{50} 2) [524] – Rat	fampridine (pIC_{50} 2.8) [1236], tetraethylammonium (pIC_{50} 2.6) [1236]	fampridine (pIC_{50} 4.5) [481] – Mouse, tetraethylammonium (pIC_{50} 3.7) [481] – Mouse	fampridine (pIC_{50} 4.6) [823] – Rat, tetraethylammonium (pIC_{50} 4.2) [823] – Rat	tetraethylammonium (pIC_{50} 3.9) [1422] – Rat	tetraethylammonium (pIC_{50} 3.5) [1174, 1245] – Rat
Selective channel blockers	–	–	–	–	–	–	sea anemone toxin BDS-I (pIC_{50} 7.3) [329] – Rat
Functional Characteristics	K_V	K_V	–	K_V	K_V	K_A	K_A

Nomenclature	K_v4.1	K_v4.2	K_v4.3
HGNC, UniProt	*KCND1*, Q9NSA2	*KCND2*, Q9NZV8	*KCND3*, Q9UK17
Associated subunits	KChIP 1-4, DP66, DPP10	KChIP 1-4, DPP6, DPP10, $K_v\beta$1, NCS-1, $Na_v\beta$1	KChIP 1-4, DPP6 and DPP10, MinK, MiRPs
Channel blockers	fampridine (pIC_{50} 2) [604]	–	–
Functional Characteristics	K_A	K_A	K_A

Nomenclature	K_v5.1	K_v6.1	K_v6.2	K_v6.3	K_v6.4
HGNC, UniProt	*KCNF1*, Q9H3M0	*KCNG1*, Q9UIX4	*KCNG2*, Q9UJ96	*KCNG3*, Q8TAE7	*KCNG4*, Q8TDN1

Nomenclature	K_v7.1	K_v7.2	K_v7.3	K_v7.4	K_v7.5
HGNC, UniProt	*KCNQ1*, P51787	*KCNQ2*, O43526	*KCNQ3*, O43525	*KCNQ4*, P56696	*KCNQ5*, Q9NR82
Activators	ML277 (pEC_{50} 6.6) [924]	–	gabapentin (pEC_{50} 8.3) [909], retigabine (pEC_{50} 6.2) [1371]	retigabine (pEC_{50} 5.2) [1371]	retigabine (pEC_{50} 5) [353]
Selective activators	–	–	–	retigabine derivative 10g (pEC_{50} 6) [1477]	gabapentin (pEC_{50} 8.7) [909], retigabine derivative 10g (pEC_{50} 6) [1477]
Inhibitors	XE991 (pK_d 6.1) [1471], linopirdine (pIC_{50} 4.4) [1043] – Mouse	XE991 (pIC_{50} 6.2) [1472], linopirdine (pIC_{50} 5.3) [1472]	linopirdine (pIC_{50} 5.4) [1472] – Rat	XE991 (pIC_{50} 5.3) [1299], linopirdine (pIC_{50} 4.9) [1299]	linopirdine (pK_d 4.8) [795]
Sub/family-selective inhibitors	–	–	–	–	XE991 (pIC_{50} 4.2) [1244]
Channel blockers	JNJ303 (pIC_{50} 7.2) [1399]	tetraethylammonium (pIC_{50} 3.5–3.9) [499, 1510]	–	tetraethylammonium (pIC_{50} 1.3) [70]	–
Allosteric modulators	–	retigabine (Activation) (pEC_{50} 5.6) [814, 1371]	–	–	–
Functional Characteristics	cardiac IK_5	M current as a heteromer between K_V7.2 and K_V7.3	M current as heteromeric K_V7.2/K_V7.3 or K_V7.3/K_V7.5	–	M current as heteromeric K_V7.3/K_V7.5

Comments	Polyunsaturated fatty acids (PUFA) activate K_v7.1 (KCNQ1) [772]. The PUFA analogue DHA-glycine is a selective activator of IKS with pEC_{50} 5.2 [133]. A single binding site for ML277 was identified, localized to a pocket lined by the S4-S5 linker, S5 and S6 helices of two separate subunits [878, 1512]. 3D structures have revealed the structural basis of hKCNQ1 modulation and gating [1336, 1337]. ML277 induces an upward movement of the S4-S5 linker and opening of the activation gate without affecting the C-terminal domain [878].	The cryo-EM structure of K_v7.2 channel in its apo state and in complex with two activators, ztz240 or retigabine. While ztz240 binds to the voltage sensor domain, retigabine interacts with the pore doamin [814]. Other K_v7.2 cryo-EM structures have been determined in complex with additional activators such as Ebio1, Ebio2, cannabidiol (CBD), PIP_2 and HN37 revealing the binding of two CBD, one PIP_2, and two HN37 molecules in each K_v7.2 subunit [806, 877, 1610] and with a blocker Ebio3 [806].	Gentisic acid (GA) is found to be selective for K_v7.3 versus other K_v7 homomers; it requires S5 residue K_v7.3-W265 for K_v7.3 channel activation [2].	Two PIP_2 molecules are identified in the open-state structure of K_v7.4 (KCNQ4), which act as a bridge to couple the voltage-sensing domain (VSD) and pore domain (PD) of KCNQ4 leading to the channel opening [812, 1619]. In K_v7.4, retigabine nestles in each fenestration, whereas linopirdine resides in a cytosolic cavity underneath the channel's inner gate [812].	The cryo-EM structure of human KCNQ5-calmodulin (CaM) complex in the apo, PIP_2-bound, and both PIP_2- and the activator HN37-bound states in either a closed or an open conformation was solved [1565].

Nomenclature	K_v8.1	K_v8.2	K_v9.1	K_v9.2	K_v9.3	K_v10.1	K_v10.2
HGNC, UniProt	*KCNV1*, Q6PIU1	*KCNV2*, Q8TDN2	*KCNS1*, Q96KK3	*KCNS2*, Q9ULS6	*KCNS3*, Q9BQ31	*KCNH1*, O95259	*KCNH5*, Q8NCM2

Nomenclature	K_v11.1	K_v11.2	K_v11.3	K_v12.1	K_v12.2	K_v12.3
HGNC, UniProt	*KCNH2*, Q12809	*KCNH6*, Q9H252	*KCNH7*, Q9NS40	*KCNH8*, Q96L42	*KCNH3*, Q9ULD8	*KCNH4*, Q9UQ05
Associated subunits	minK (KCNE1) and MiRP1 (KCNE2)	minK (KCNE1)	minK (KCNE1)	minK (KCNE1)	minK (KCNE1) and MiRP2 (KCNE3)	–
Channel blockers	astemizole (pIC_{50} 9) [1629], terfenadine (pIC_{50} 7.3) [1162], disopyramide (Inhibition) (pIC_{50} 4) [695]	–	–	–	–	–
Sub/family-selective channel blockers	E4031 (pIC_{50} 8.1) [1628]	–	–	–	–	–
Selective channel blockers	dofetilide (Inhibition) (pK_i 8.2) [1282], ibutilide (pIC_{50} 7.6–8) [695, 1106]	–	–	–	–	–
Functional Characteristics	cardiac IK_R	–	–	–	–	–
Comments	RPR260243 is an activator of K_v11.1 [670].	–	–	–	–	–

Further reading on Potassium channels

Aguilar-Bryan L *et al.* (1998) Toward understanding the assembly and structure of KATP channels. *Physiol Rev* **78**: 227-45 [PMID:9457174]

Borsotto M *et al.* (2015) Targeting two-pore domain K(+) channels TREK-1 and TASK-3 for the treatment of depression: a new therapeutic concept. *Br J Pharmacol* **172**: 771-84 [PMID:25263033]

Chang PC *et al.* (2015) SK channels and ventricular arrhythmias in heart failure. *Trends Cardiovasc Med* **25**: 508-14 [PMID:25743622]

Decher N *et al.* (2017) Stretch-activated potassium currents in the heart: Focus on TREK-1 and arrhythmias. *Prog Biophys Mol Biol* **130**: 223-232 [PMID:28526352]

Feliciangeli S *et al.* (2015) The family of K2P channels: salient structural and functional properties. *J Physiol (Lond.)* **593**: 2587-603 [PMID:25530075]

Foster MN *et al.* (2016) KATP Channels in the Cardiovascular System. *Physiol Rev* **96**: 177-252 [PMID:26660852]

Gada K *et al.* (2019) Two-pore domain potassium channels: emerging targets for novel analgesic drugs: IUPHAR Review 26. *Br J Pharmacol* **176**: 256-266 [PMID:30325008]

Goldstein SA *et al.* (2005) International Union of Pharmacology. LV. Nomenclature and molecular relationships of two-P potassium channels. *Pharmacol Rev* **57**: 527-40 [PMID:16382106]

Greene DL *et al.* (2017) Modulation of Kv7 channels and excitability in the brain. *Cell Mol Life Sci* **74**: 495-508 [PMID:27645822]

Gutman GA *et al.* (2003) International Union of Pharmacology. XLI. Compendium of voltage-gated ion channels: potassium channels. *Pharmacol Rev* **55**: 583-6 [PMID:14657415]

Kaczmarek LK *et al.* (2017) International Union of Basic and Clinical Pharmacology. C. Nomenclature and Properties of Calcium-Activated and Sodium-Activated Potassium Channels. *Pharmacol Rev* **69**: 1-11 [PMID:28267675]

Kubo Y *et al.* (2005) International Union of Pharmacology. LIV. Nomenclature and molecular relationships of inwardly rectifying potassium channels. *Pharmacol Rev* **57**: 509-26 [PMID:16382105]

Latorre R *et al.* (2017) Molecular Determinants of BK Channel Functional Diversity and Functioning. *Physiol Rev* **97**: 39-87 [PMID:27807200]

Niemeyer MI *et al.* (2016) Gating, Regulation, and Structure in K2P K+ Channels: In Varietate Concordia? *Mol Pharmacol* **90**: 309-17 [PMID:27268784]

Poveda JA *et al.* (2017) Towards understanding the molecular basis of ion channel modulation by lipids: Mechanistic models and current paradigms. *Biochim Biophys Acta* **1859**: 1507-1516 [PMID:28408206]

Rifkin RA *et al.* (2017) G Protein-Gated Potassium Channels: A Link to Drug Addiction. *Trends Pharmacol Sci* **38**: 378-392 [PMID:28188005]

Taylor KC *et al.* (2017) Regulation of KCNQ/Kv7 family voltage-gated K^+ channels by lipids. *Biochim Biophys Acta* **1859**: 586-597 [PMID:27818172]

Vivier D *et al.* (2016) Perspectives on the Two-Pore Domain Potassium Channel TREK-1 (TWIK-Related K(+) Channel 1). A Novel Therapeutic Target? *J Med Chem* **59**: 5149-57 [PMID:26588045]

Wei AD *et al.* (2005) International Union of Pharmacology. LII. Nomenclature and molecular relationships of calcium-activated potassium channels. *Pharmacol Rev* **57**: 463-72 [PMID:16382103]

Yang KC *et al.* (2016) Mechanisms contributing to myocardial potassium channel diversity, regulation and remodeling. *Trends Cardiovasc Med* **26**: 209-18 [PMID:26391345]

Ryanodine receptors (RyR)

Ion channels → Voltage-gated ion channels → Ryanodine receptors (RyR)

Overview: The ryanodine receptors (RyRs) are found on intracellular Ca^{2+} storage/release organelles. The family of RyR genes encodes three highly related Ca^{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^{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 [1343]. The function of the ryanodine receptor channels may also be influenced by closely associated proteins such as the tacrolimus (FK506)-binding protein, calmodulin [1553], triadin, calsequestrin, junctin and sorcin, and by protein kinases and phosphatases. Recent studies solving the structure of the ryanodine receptor have shed light on the structural basis of ryanodine receptor function [see, for example, Samso (2017) [1220] and Meissner (2017) [937]].

Nomenclature	RyR1	RyR2	RyR3
HGNC, UniProt	*RYR1*, P21817	*RYR2*, Q92736	*RYR3*, Q15413
Endogenous activators	cytosolic ATP (endogenous; mM range), luminal Ca^{2+} (endogenous), cytosolic Ca^{2+} (endogenous; µM range)	cytosolic ATP (endogenous; mM range), cytosolic Ca^{2+} (endogenous; µM range), luminal Ca^{2+} (endogenous)	cytosolic ATP (endogenous; mM range), cytosolic Ca^{2+} (endogenous; µM range)
Activators	caffeine (pharmacological; mM range), ryanodine (pharmacological; nM - µM range), suramin (pharmacological; µM range)	caffeine (pharmacological; mM range), ryanodine (pharmacological; nM - µM range), suramin (pharmacological; µM range)	caffeine (pharmacological; mM range), ryanodine (pharmacological; nM - µM range)
Endogenous antagonists	cytosolic Ca^{2+} Concentration range: >1×10^{-4}M, cytosolic Mg^{2+} (mM range)	cytosolic Ca^{2+} Concentration range: >1×10^{-3}M, cytosolic Mg^{2+} (mM range)	cytosolic Ca^{2+} Concentration range: >1×10^{-3}M, cytosolic Mg^{2+} (mM range)
Antagonists	dantrolene	–	dantrolene
Channel blockers	procaine, ruthenium red, ryanodine Concentration range: >1×10^{-4}M	procaine, ruthenium red, ryanodine Concentration range: >1×10^{-4}M	ruthenium red
Functional Characteristics	Ca^{2+}: (P_{Ca}/P_K6) single-channel conductance: 90 pS (50 mM Ca^{2+}), 770 pS (200 mM K^+)	Ca^{2+}: (P_{Ca}/P_K6) single-channel conductance: 90 pS (50 mM Ca^{2+}), 720 pS (210 mM K^+)	Ca^{2+}: (P_{Ca}/P_K6) single-channel conductance: 140 pS (50 mM Ca^{2+}), 777 pS (250 mM K^+)
Comments	RyR1 is also activated by depolarisation *via* DHP receptor, calmodulin at low cytosolic Ca^{2+} concentrations, CaM kinase and PKA; antagonised by calmodulin at high cytosolic Ca^{2+} concentrations	RyR2 is also activated by CaM kinase and PKA; antagonised by calmodulin at high cytosolic Ca^{2+} concentrations	RyR3 is also activated by calmodulin at low cytosolic Ca^{2+} concentrations; antagonised by calmodulin at high cytosolic Ca^{2+} concentrations

Comments: The modulators of channel function included in this table are those most commonly used to identify ryanodine-sensitive Ca^{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 [423, 1613].

Further reading on Ryanodine receptors (RyR)

Dulhunty AF *et al*. (2017) Physiology and Pharmacology of Ryanodine Receptor Calcium Release Channels. *Adv Pharmacol* **79**: 287-324 [PMID:28528672]

Meissner G. (2017) The structural basis of ryanodine receptor ion channel function. *J Gen Physiol* **149**: 1065-1089 [PMID:29122978]

O'Brien F *et al*. (2015) The ryanodine receptor provides high throughput Ca2+-release but is precisely regulated by networks of associated proteins: a focus on proteins relevant to phosphorylation. *Biochem Soc Trans* **43**: 426-33 [PMID:26009186]

Samsó M. (2017) A guide to the 3D structure of the ryanodine receptor type 1 by cryoEM. *Protein Sci***26**: 52-68 [PMID:27671094]

Van Petegem F. (2015) Ryanodine receptors: allosteric ion channel giants. *J Mol Biol* **427**: 31-53 [PMID:25134758]

Zalk R *et al*. (2017) Ca^{2+} Release Channels Join the 'Resolution Revolution'. *Trends Biochem Sci* **42**: 543-555 [PMID:28499500]

Transient Receptor Potential channels (TRP)

Ion channels → Voltage-gated ion channels → Transient Receptor Potential channels (TRP)

Overview:

The TRP superfamily of channels (**nomenclature as agreed by NC-IUPHAR** [247, 1529]), whose founder member is the *Drosophila* Trp channel, exists in mammals as six families; TRPC, TRPM, TRPV, TRPA, TRPP and TRPML based on amino acid homologies. TRP subunits contain six putative TM domains and assemble as homo- or hetero-tetramers to form cation selective channels with diverse modes of activation and varied permeation properties (reviewed by [1065]). Established, or potential, physiological functions of the individual members of the TRP families are discussed in detail in the recommended reviews and in a number of books [367, 610, 1018, 1631]. The established, or potential, involvement of TRP channels in disease [1592] is reviewed in [711, 1016], [1020] and [727], together with a special edition of *Biochemica et Biophysica Acta* on the subject [1016]. Additional disease related reviews, for pain [971], stroke [1603], sensation and inflammation [1423], itch [183], and airway disease [470, 1508], are available. The pharmacology of most TRP channels has been advanced in recent years. Broad spectrum agents are listed in the tables along with more selective, or recently recognised, ligands that are flagged by the inclusion of a primary reference. See Rubaiy (2019) for a review of pharmacological tools for TRPC1/C4/C5 channels [1195]. Most TRP channels are regulated by phosphoinositides such as PtIns(4,5)P_2 although the effects reported are often complex, occasionally contradictory, and likely to be dependent upon experimental conditions, such as intracellular ATP levels (reviewed by [1021, 1184, 1440]). Such regulation is generally not included in the tables.When thermosensitivity is mentioned, it refers specifically to a high Q10 of gating, often in the range of 10-30, but does not necessarily imply that the channel's function is to act as a 'hot' or 'cold' sensor. In general, the search for TRP activators has led to many claims for temperature sensing, mechanosensation, and lipid sensing. All proteins are of course sensitive to energies of binding, mechanical force, and temperature, but the issue is whether the proposed input is within a physiologically relevant range resulting in a response.

TRPA (ankyrin) family

TRPA1 is the sole mammalian member of this group (reviewed by [430]). TRPA1 activation of sensory neurons contribute to nociception [653, 932, 1321]. Pungent chemicals such as mustard oil (AITC), allicin, and cinnamaldehyde activate TRPA1 by modification of free thiol groups of cysteine side chains, especially those located in its amino terminus [92, 547, 883, 885]. Alkenals with α, β-unsaturated bonds, such as propenal (acrolein), butenal (crotylaldehyde), and 2-pentenal can react with free thiols *via* Michael addition and can activate TRPA1. However, potency appears to weaken as carbon chain length increases [43, 92]. Covalent modification leads to sustained activation of TRPA1. Chemicals including carvacrol, menthol, and local anesthetics reversibly activate TRPA1 by non-covalent binding [675, 790, 1540, 1541]. TRPA1 is not mechanosensitive under physiological conditions, but can be activated by cold temperatures [302, 676]. The electron cryo-EM structure of TRPA1 [1087] indicates that it is a 6-TM homotetramer. Each subunit of the channel contains two short 'pore helices' pointing into the ion selectivity filter, which is big enough to allow permeation of partially hydrated Ca^{2+} ions.

Nomenclature	TRPA1
HGNC, UniProt	*TRPA1*, O75762
Chemical activators	Isothiocyanates (covalent) and 1,4-dihydropyridines (non-covalent)
Oxidative stress compounds	4-oxo-nonenal: pEC_{50} 5.7, H2O2: pEC_{50} 3.6, hypochlorite: EC_{50} 11 ppm (human) and 7 ppm (mouse) (Mouse) [41, 110, 1227]
Physical activators	Cooling (<17°C) (disputed) [653, 989, 1420]
Activators	polygodial (pEC_{50} 6.4) [374], acrolein (Agonist) (pEC_{50} 5.3) [physiological voltage] [92], allicin (Agonist) (pEC_{50} 5.1) [physiological voltage] [93], Δ^9-tetrahydrocannabinol (Agonist) (pEC_{50} 4.9) [-60mV] [653], nicotine (non-covalent) (pEC_{50} 4.8) [-75mV] [1358], thymol (non-covalent) (pEC_{50} 4.7) Concentration range: 6.2×10^{-6}M-2.5×10^{-5}M [786], URB597 (Agonist) (pEC_{50} 4.6) [1015], (-)-menthol (Partial agonist) (pEC_{50} 4–4.5) [675, 1535], allyl isothiocyanate (pEC_{50} 4.2) [547], cinnamaldehyde (Agonist) (pEC_{50} 4.2) [physiological voltage] [72] – Mouse, formalin (covalent. This level of activity is also observed for rat TRPA1) (pEC_{50} 3.4) [885, 932] – Mouse, icilin (Agonist) Concentration range: 1×10^{-4}M [physiological voltage] [1321] – Mouse
Selective activators	JT010 (pEC_{50} 9.2) [1355], PF-4840154 (This compound has similar activity at rat and mouse TRPA1) (pEC_{50} 7.6) [1205], chlorobenzylidene malononitrile (covalent) (pEC_{50} 6.7) [153], ASP7663 (pEC_{50} 6.3) [728]
Channel blockers	AP18 (Inhibition) (pIC_{50} 5.5) [1109], ruthenium red (Inhibition) (pIC_{50} 5.5) [-80mV] [989] – Mouse
Selective channel blockers	GDC-0334 (Inhibition) (pIC_{50} 8.8) [71], AM-0902 (Antagonist) (pIC_{50} 7.7) [1233], A-967079 (Inhibition) (pIC_{50} 7.2) [209]
Functional Characteristics	γ = 87-100 pS; conducts mono- and di-valent cations non-selectively (P_{Ca}/PN_a = 0.84); outward rectification; activated by elevated intracellular Ca^{2+}
Comments	miRNA-711 is a selective activator of TRPA1 (pEC_{50} ~5.0) [504]. GRC 17536 (structure not disclosed) is a TRPA1 antagonist with potential as an anti-tussive therapeutic [980]. Some pathogen-derived molecules activate human TRPA1, such as lipopolysaccharide (LPS) [938], indole (pEC_{50} 4.1) [241] and indole-3-carboxyaldhyde (pEC_{50} 4.1) [1568].

TRPC (canonical) family

Members of the TRPC subfamily (reviewed by [7, 36, 99, 120, 414, 709, 1083, 1143]) fall into the subgroups outlined below. TRPC2 is a pseudogene in humans. It is generally accepted that all TRPC channels are activated downstream of $G_{q/11}$-coupled receptors, or receptor tyrosine kinases (reviewed by [1129, 1405, 1529]). A comprehensive listing of G protein-coupled receptors that activate TRPC channels is given in [7]. Hetero-oligomeric complexes of TRPC channels and their association with proteins to form signalling complexes are detailed in [36] and [710]. TRPC channels have frequently been proposed to act as store-operated channels (SOCs) (or components of multimeric complexes that form SOCs), activated by depletion of intracellular calcium stores (reviewed by [36, 95, 223, 224, 1055, 1094, 1135, 1217, 1591]). However, the weight of the evidence is that they are not directly gated by conventional store-operated mechanisms, as established for STIM-gated Orai channels. TRPC channels are not mechanically gated in physiologically relevant ranges of force. All members of the TRPC family are blocked by 2-APB and SKF96365 [517, 518]. Activation of TRPC channels by lipids is discussed by [99]. Important progress has been recently made in TRPC pharmacology [136, 268, 426, 697, 958, 1195, 1259]. TRPC channels regulate a variety of physiological functions and are implicated in many human diseases [100, 137, 217, 436, 633, 848, 1312, 1341, 1467, 1486].

TRPC1/C4/C5 subgroup

TRPC1 alone may not form a functional ion channel [320]. The structures of the apo and antagonist-bound states of TRPC1/TRPC4 heteromeric channels have been resolved by cryo-EM [1521]. TRPC4/C5 may be distinguished from other TRP channels by their potentiation by micromolar concentrations of La^{3+}. TRPC2 is a pseudogene in humans, but in other mammals appears to be an ion channel localized to microvilli of the vomeronasal organ. It is required for normal sexual behavior in response to pheromones in mice. It may also function in the main olfactory epithelia in mice [826, 1053, 1054, 1574, 1580, 1585, 1639].

TRPC3/C6/C7 subgroup

All members are activated by diacylglycerol independent of protein kinase C stimulation [518].

Nomenclature	TRPC1	TRPC2	TRPC3	TRPC4
HGNC, UniProt	*TRPC1*, P48995	*TRPC2*, –	*TRPC3*, Q13507	*TRPC4*, Q9UBN4
Chemical activators	NO-mediated cysteine S-nitrosylation	Diacylglycerol (SAG, OAG, DOG): strongly inhibited by Ca^{2+}/CaM once activated by DAG [1305]	diacylglycerols	NO-mediated cysteine S-nitrosylation, potentiation by extracellular protons
Physical activators	membrane stretch (likely direct)	DAG kinase; regulates DAG concentration in vomeronasal sensory neurons	–	–
Endogenous activators	–	Intracellular Ca^{2+}	–	–
Activators	–	DOG (Agonist) Concentration range: 1×10^{-4}M [-80mV] [865] – Mouse, SAG (Agonist) Concentration range: 1×10^{-4}M [-80mV] [865] – Mouse	pyrazolopyrimidine 4n (pEC_{50} 7.7) [1150], GSK1702934A (Agonist) (pEC_{50} 7.1) [1548]	(-)-englerin A (Agonist) (pEC_{50} 7.9) [18], tonantzitlolone (pEC_{50} 6.9) [1198], La^{3+} (μM range)
Channel blockers	2-APB (Antagonist) [-70mV] [1329], Gd^{3+} (Antagonist) Concentration range: 2×10^{-5}M [-70mV] [1636], La^{3+} (Antagonist) Concentration range: 1×10^{-4}M [-70mV] [1329]	2-APB (Antagonist) Concentration range: 5×10^{-5}M [-70mV – 80mV] [865] – Mouse, U73122 (Antagonist) Concentration range: 1×10^{-5}M – Mouse	GSK2833503A (pIC_{50} 7.7) [80mV] [1252], GSK417651A (Antagonist) (pIC_{50} 7.1) [1495], Gd^{3+} (Antagonist) (pEC_{50} 7) [-60mV] [502], SAR7334 (pIC_{50} 6.6) [891], BTP2 (Antagonist) (pIC_{50} 6.5) [-80mV] [523], Pyr3 (pIC_{50} 6.2) [715], Pyr10 (Antagonist) (pIC_{50} 6.1) [1235], norgestimate (pK_i 5.5) [947], La^{3+} (Antagonist) (pIC_{50} 5.4) [-60mV] [502], clemizole (pIC_{50} 5) [1176], 2-APB (Antagonist) (pIC_{50} 5) [physiological voltage] [824], Ni^{2+}, SKF96365	HC-070 (Antagonist) (pIC_{50} 7.3) [655], ML204 (pIC_{50} 5.5) [952], M084 (Inhibition) (pIC_{50} 5.3) [1632], clemizole (pIC_{50} 5.2) [1176], La^{3+} (mM range), SKF96365, niflumic acid (Antagonist) Concentration range: 3×10^{-5}M [-60mV] [1459] – Mouse
Functional Characteristics	It is not yet clear that TRPC1 forms a homomer. It does form heteromers with TRPC4 and TRPC5	γ = 42 pS linear single channel conductance in 150 mM symmetrical Na^+ in vomeronasal sensory neurons. P_{Ca}/P_{Na} = 2.7; permeant to Na^+, Cs^+, Ca^{2+}, but not NMDG [1053, 1580]	γ = 66 pS; conducts mono and divalent cations non-selectively (P_{Ca}/P_{Na} = 1.6); monovalent cation current suppressed by extracellular Ca^{2+}; dual (inward and outward) rectification	γ = 30 -41 pS, conducts mono and divalent cations non-selectively (P_{Ca}/P_{Na} = 1.1 - 7.7); dual (inward and outward) rectification

Nomenclature	TRPC5	TRPC6	TRPC7
HGNC, UniProt	*TRPC5*, Q9UL62	*TRPC6*, Q9Y210	*TRPC7*, Q9HCX4
Chemical activators	NO-mediated cysteine S-nitrosylation (disputed), potentiation by extracellular protons	Diacylglycerols	diacylglycerols
Physical activators	Membrane stretch	Membrane stretch	–
Endogenous activators	intracellular Ca^{2+} (at negative potentials) (pEC_{50} 6.2), lysophosphatidylcholine	20-HETE, arachidonic acid, lysophosphatidylcholine	–
Activators	(-)-englerin A (Agonist) (pEC_{50} 8.1) [18], tonantzitlolone (pEC_{50} 7.1) [1198], BTD (pEC_{50} 5.8) [98], riluzole (pEC_{50} 5) [1177], methylprednisolone (pEC_{50} 4.9) [98], rosiglitazone (pEC_{50} 4.5) [897], Gd^{3+} Concentration range: 1×10^{-4}M, La^{3+} (μM range), Pb^{2+} Concentration range: 5×10^{-6}M, genistein (independent of tyrosine kinase inhibition) [1522]	AM-0883 (Agonist) (pEC_{50} 7.3) [68], GSK1702934A (Agonist) (pIC_{50} 6.4) [1548], pyrazolopyrimidine 4n (pEC_{50} 5.9) [1150], OptoBI-1 (photoswitch activation; concentration range: 1-2x10^{-5}M) [1388], OptoDArG (photoswitch activation; concentration range: 3x10^{-5}M) [822], flufenamate, hyp 9 [800], hyperforin [801]	pyrazolopyrimidine 4n (pIC_{50} 6.1) [1150], OptoBI-1 (photoswitch activation; concentration range: 1-2x10^{-5}M) [1388]
Selective activators	AM237 (pEC_{50} 7.7) [957]	–	–
Channel blockers	Pico145 (Inhibition) (pIC_{50} 8.9) [1197], HC-070 (Antagonist) (pIC_{50} 8) [655], AM12 (Inhibition) (pIC_{50} 6.6) [1001], GFB-8438 (Inhibition) (pIC_{50} 6.5) [1587], galangin (pK_i 6.3) [1001], clemizole (pIC_{50} 6) [1176], KB-R7943 (Inhibition) (pIC_{50} 5.9) [736], M084 (Inhibition) (pIC_{50} 5.1) [1632], ML204 (pIC_{50}~5) [952], 2-APB (Antagonist) (pIC_{50} 4.7) [-80mV] [1546], La^{3+} (Antagonist) Concentration range: 5×10^{-3}M [-60mV] [654] – Mouse	AM-1473 (Antagonist) (pIC_{50} 9.7) [68], GSK2833503A (pIC_{50} 8.5) [80mV] [1252], GSK2332255B (Antagonist) (pIC_{50} 8.4) [1252], SAR7334 (pIC_{50} 8) [891], BTDM (Inhibition) (pIC_{50} 8) [1366], DS88790512 (Inhibition) (pIC_{50}~7.9) [976], BI 749327 (Antagonist) (pIC_{50} 7.9) [827], SH045 (pIC_{50} 7.2) [500], larixyl acetate (Inhibition) (pIC_{50} 7) [1414], GSK417651A (Antagonist) (pIC_{50} 6.4) [1495], Pyrazolo-pyrimidine 14a (Inhibition) (pIC_{50}~6) [324], clemizole (pIC_{50} 5.9) [1176], Gd^{3+} (Antagonist) (pIC_{50} 5.7) [-60mV] [599] – Mouse, SKF96365 (Antagonist) (pIC_{50} 5.4) [-60mV] [599] – Mouse, norgestimate (pIC_{50} 5.3) [947], La^{3+} (pIC_{50}~5.2), amiloride (Antagonist) (pIC_{50} 3.9) [-60mV] [599] – Mouse, Cd^{2+} (Antagonist) (pIC_{50} 3.6) [-60mV] [599] – Mouse, 2-APB, ACAA, GsMTx-4, Extracellular H^{+}, KB-R7943, ML9	SH045 (pIC_{50}~7.7) [500], SAR7334 (pIC_{50} 6.7) [891], BI 749327 (Antagonist) (pIC_{50} 6.3) [827], larixyl acetate (Inhibition) (pIC_{50}~6.3) [1414], 2-APB, La^{3+} (Antagonist) Concentration range: 1×10^{-4}M [-60mV] [1045] – Mouse, SKF96365 (Antagonist) Concentration range: 2.5×10^{-5}M [-60mV] [1045] – Mouse, amiloride
Selective channel blockers	AC1903 (Inhibition) (pIC_{50} 4.8) [1627]	–	–
Functional Characteristics	γ = 41-63 pS; conducts mono-and di-valent cations non-selectively (P_{Ca}/P_{Na} = 1.8 - 9.5); dual rectification (inward and outward) as a homomer, outwardly rectifying when expressed with TRPC1 or TRPC4	γ = 28-37 pS; conducts mono and divalent cations with a preference for divalents (P_{Ca}/P_{Na} = 4.5-5.0); monovalent cation current suppressed by extracellular Ca^{2+} and Mg^{2+}, dual rectification (inward and outward), or inward rectification	γ = 25-75 pS; conducts mono and divalent cations with a preference for divalents (P_{Ca}/ P_{Cs} = 5.9); modest outward rectification (monovalent cation current recorded in the absence of extracellular divalents); monovalent cation current suppressed by extracellular Ca^{2+} and Mg^{2+}

TRPM (melastatin) family

Members of the TRPM subfamily (reviewed by [408, 517, 1094, 1620]) fall into the five subgroups outlined below.

TRPM1/M3 subgroup

In darkness, glutamate released by the photoreceptors and ON-bipolar cells binds to the metabotropic glutamate receptor 6, leading to activation of Go . This results in the closure of TRPM1. When the photoreceptors are stimulated by light, glutamate release is reduced, and TRPM1 channels are more active, resulting in cell membrane depolarization. Human TRPM1 mutations are associated with congenital stationary night blindness (CSNB), whose patients lack rod function. TRPM1 is also found melanocytes. Isoforms of TRPM1 may present in melanocytes, melanoma, brain, and retina. In melanoma cells, TRPM1 is prevalent in highly dynamic intracellular vesicular structures [602, 1037]. TRPM3 (reviewed by [1040]) exists as multiple splice variants which differ significantly in their biophysical properties. TRPM3 is expressed in somatosensory neurons and may be important in development of heat hyperalgesia during inflammation (see review [1375]). TRPM3 is frequently coexpressed with TRPA1 and TRPV1 in these neurons. TRPM3 is expressed in pancreatic beta cells as well as brain, pituitary gland, eye, kidney, and adipose tissue [1039, 1374]. TRPM3 may contribute to the detection of noxious heat [1447].

TRPM2

TRPM2 is activated under conditions of oxidative stress (respiratory burst of phagocytic cells). The direct activators are calcium, adenosine diphosphate ribose (ADPR) [1413] and cyclic ADPR (cADPR) [1588]. As for many ion channels, PI(4,5)P2 must also be present [1574]. Numerous splice variants of *TRPM2* exist which differ in their activation mechanisms [345]. Recent studies have reported structures of human (hs) TRPM2, which demonstrate two ADPR binding sites in hsTRPM2, one in the N-terminal MHR1/2 domain and the other in the C-terminal NUDT9-H domain. In addition, one Ca^{2+} binding site in the intracellular S2-S3 loop is revealed and proposed to mediate Ca^{2+} binding that induces conformational changes leading the ADPR-bound closed channel to open [588, 1476]. Meanwhile, a quadruple-residue motif (979FGQI982) was identified as the ion selectivity filter and a gate to control ion permeation in hsTRPM2 [1589]. TRPM2 is involved in warmth sensation [1252], and contributes to several diseases [107]. TRPM2 interacts with extra synaptic NMDA receptors (NMDAR) and enhances NMDAR activity in ischemic stroke [1637]. Activation of TRPM2 in macrophages promotes atherosclerosis [1612, 1638]. Moreover, silica nanoparticles induce lung inflammation in mice *via* ROS/PARP/TRPM2 signaling-mediated lysosome impairment and autophagy dysfunction [1478]. Recent studies have designed various compounds for their potential to selectively inhibit the TRPM2 channel, including ACA derivatives A23, and 2,3-dihydroquinazolin-4(1H)-one derivatives [1606, 1608].

TRPM4/5 subgroup

TRPM4 and TRPM5 have the distinction within all TRP channels of being impermeable to Ca^{2+} [1529]. A splice variant of TRPM4 (*i.e.*TRPM4b) and TRPM5 are molecular candidates for endogenous calcium-activated cation (CAN) channels [488]. TRPM4 is active in the late phase of repolarization of the cardiac ventricular action potential. TRPM4 deletion or knockout enhances beta adrenergic-mediated inotropy [922]. Mutations are associated with conduction defects [614, 922, 1307]. TRPM4 has been shown to be an important regulator of Ca^{2+} entry in to mast cells [1426] and dendritic cell migration [76]. TRPM5 in taste receptor cells of the tongue appears essential for the transduction of sweet, amino acid and bitter stimuli [825] TRPM5 contributes to the slow afterdepolarization of layer 5 neurons in mouse prefrontal cortex [792]. Both TRPM4 and TRPM5 are required transduction of taste stimuli [356].

TRPM6/7 subgroup

TRPM6 and 7 combine channel and enzymatic activities ('chanzymes') [245]. These channels have the unusual property of permeation by divalent (Ca^{2+}, Mg^{2+}, Zn^{2+}) and monovalent cations, high single channel conductances, but overall extremely small inward conductance when expressed to the plasma membrane. They are inhibited by internal Mg^{2+} at ˜0.6 mM, around the free level of Mg^{2+} in cells. Whether they contribute to Mg^{2+} homeostasis is a contentious issue. PIP2 is required for TRPM6 and TRPM7 activation [1202, 1536]. When either gene is deleted in mice, the result is embryonic lethality [638, 1524]. The C-terminal kinase region of TRPM6 and TRPM7 is cleaved under unknown stimuli, and the kinase phosphorylates nuclear histones [740, 741]. TRPM7 is responsible for oxidant- induced Zn^{2+} release from intracellular vesicles [6] and contributes to intestinal mineral absorption essential for postnatal survival [961]. The putative metal transporter proteins CNNM1-4 interact with TRPM7 and regulate TRPM7 channel activity [69, 730].

TRPM8

Is a channel activated by cooling and pharmacological agents evoking a 'cool' sensation and participates in the thermosensation of cold temperatures [94, 249, 315] reviewed by [723, 850,

902, 1441]. Direct chemical agonists include menthol and icilin[1545]. Besides, linalool can promote ERK phosphorylation in human dermal microvascular endothelial cells, down-regulate intracellular ATP levels, and activate TRPM8 [97]. Recent studies have found that TRPM8 has typical S4-S5 connectomes with clear selective filters and exowell rings [791], and have identified cryo-electron microscopy structures of mouse TRPM8 in closed, intermediate, and open states along the ligand- and PIP_2-dependent gated pathways [1575]. Moreover, the last 36 amino acids at the carboxyl terminal of TRPM8 are key protein sequences for TRPM8's temperature-sensitive function [270]. TRPM8 deficiency reduced the expression of S100A9 and increased the expression of HNF4α in the liver of mice, which reduced inflammation and fibrosis progression in mice with liver fibrosis, and helped to alleviate the symptoms of bile duct disease [844]. Channel deficiency also shortens the time of hypersensitivity reactions in migraine mouse models by promoting the recovery of normal sensitivity [26]. A cyclic peptide DeC-1.2 was designed to inhibit ligand activation of TRPM8 but not cold activation, which can eliminate the side effects of cold dysalgesia in oxaliplatin-treated mice without changing body temperature [17]. Analysis of clinical data shows that TRPM8-specific blockers WS12 can reduce tumor growth in colorectal cancer xenografted mice by reducing transcription and activation of Wnt signaling regulators and β-catenin and its target oncogenes, such as C-Myc and Cyclin D1 [1067].

Nomenclature	TRPM1	TRPM2
HGNC, UniProt	*TRPM1*, Q7Z4N2	*TRPM2*, O94759
Chemical activators	–	Agents producing reactive oxygen (e.g. H_2O_2) and nitrogen (e.g. GEA 3162) species
Physical activators	–	Heat ˜ 35°C
Endogenous activators	pregnenolone sulphate [766]	intracellular cADPR (Agonist) (pEC_{50} 5) [-80mV – -60mV] [96, 729, 1390], intracellular ADP ribose (Agonist) (pEC_{50} 3.9–4.4) [-80mV] [1105], intracellular Ca^{2+} (perhaps *via* calmodulin), H_2O_2 (Agonist) Concentration range: 5×10^{-7}M-5×10^{-5}M [physiological voltage] [410, 514, 738, 1291, 1502], membrane PIP_2 [1397], arachidonic acid (Potentiation) Concentration range: 1×10^{-5}M-3×10^{-5}M [physiological voltage] [514]
Activators	–	GEA 3162
Endogenous channel blockers	Zn^{2+} (pIC_{50} 6)	Zn^{2+} (pIC_{50} 6), extracellular H^+
Channel blockers	–	2-APB (Antagonist) (pIC_{50} 6.1) [-60mV] [1391], ACAA (Antagonist) (pIC_{50} 5.8) [physiological voltage] [737], clotrimazole (Antagonist) Concentration range: 3×10^{-6}M-3×10^{-5}M [-60mV – -15mV] [544], econazole (Antagonist) Concentration range: 3×10^{-6}M-3×10^{-5}M [-60mV – -15mV] [544], flufenamic acid (Antagonist) Concentration range: 5×10^{-5}M-1×10^{-3}M [-60mV – -50mV] [543, 1391], miconazole (Antagonist) Concentration range: 1×10^{-5}M [-60mV] [1391]
Functional Characteristics	Conducts mono- and di-valent cations non-selectively, dual rectification (inward and outward)	γ = 52-60 pS at negative potentials, 76 pS at positive potentials; conducts mono- and di-valent cations non-selectively (P_{Ca}/P_{Na} = 0.6-0.7); non-rectifying; inactivation at negative potentials; activated by oxidative stress probably *via* PARP-1, PARP inhibitors reduce activation by oxidative stress, activation inhibited by suppression of APDR formation by glycohydrolase inhibitors.
Comments	–	Additional endogenous activators include 2'-deoxy-ADPR, 3'-deoxy-ADPR, 2'-phospho-ADPR, 2-F-ADPR and ADP-ribose-2'-phosphate (ADPRP) [409, 1398]. 8-Br-cADPR acts as a gating inhibitor [729].

Nomenclature	TRPM3	TRPM4
HGNC, UniProt	*TRPM3*, Q9HCF6	*TRPM4*, Q8TD43
Other channel blockers	–	Intracellular nucleotides including ATP, ADP, adenosine 5′-monophosphate and AMP-PNP with an IC_{50} range of 1.3-1.9 μM
Physical activators	heat (Q_{10} = 7.2 between 15 - 25°C), hypotonic cell swelling [479, 1447, 1448]	Membrane depolarization ($V_{0.5}$ = -20 mV to + 60 mV dependent upon conditions) in the presence of elevated $[Ca^{2+}]_i$, heat (Q_{10} = 8.5 @ +25 mV between 15 and 25°C)
Endogenous activators	pregnenolone sulphate (pEC_{50} 4.9) [1452], sphingosine (Agonist) (pEC_{50} 4.9) [physiological voltage] [480], dihydrosphingosine (Agonist) (pEC_{50} 4.7) [480], epipregnanolone sulphate [896]	intracellular Ca^{2+} (Agonist) (pEC_{50} 3.9–6.3) [-100mV – 100mV] [1019, 1023, 1024, 1356]
Activators	CIM0216 (pEC_{50} 6.1) [529, 1375], nifedipine, pentafluoro-trityl clotrimazole analogue 29a (Agonist) [660]	BTP2 (Agonist) (pEC_{50} 8.1) [-80mV] [1356], decavanadate (Agonist) (pEC_{50} 5.7) [-100mV] [1023]
Gating inhibitors	2-APB (Antagonist) (pIC_{50} 4) [1546]	flufenamic acid (Antagonist) (pIC_{50} 5.6) [100mV] [1413] – Mouse, clotrimazole (Antagonist) Concentration range: 1×10^{-6}M-1×10^{-5}M [100mV] [1027]
Endogenous channel blockers	Mg^{2+} (Antagonist) (pIC_{50} 2) [1038] – Mouse, extracellular Na^+ (TRPM3α2 only)	–
Channel blockers	isosakuranetin (pIC_{50} 7.3) [1322], primidone (pIC_{50} 6.2) [751], maprotiline (pIC_{50} 5.8) [751], (*S*)-liquiritigenin (pIC_{50} 5.2) [1322], diclofenac (pIC_{50} 5.2) [1345], naringenin (pIC_{50} 5.2) [1322, 1323], Gd^{3+} (Antagonist) (pIC_{50} 4) [479, 785], La^{3+} (Antagonist) (pIC_{50} 4) [479, 785], chloroform (Antagonist) (pIC_{50} 3.8) [690], halothane (Antagonist) (pIC_{50} 3.3) [690]	NBA (pIC_{50} 6.4) [1317], LBA (pIC_{50} 5.8) [1317], CBA (Antagonist) (pIC_{50} 5.7) [1066], meclofenamic acid (pIC_{50} 5.5) [1421], 9-phenanthrol (pIC_{50} 4.6–4.8) [471], spermine (Antagonist) (pIC_{50} 4.2) [100mV] [1025], adenosine (pIC_{50} 3.2)
Functional Characteristics	$TRPM3_{1325}$: γ = 83 pS (Na^+ current), 65 pS (Ca^{2+} current); conducts mono and di-valent cations non-selectively (P_{Ca}/P_{Na} = 1.6) TRPM3α1: selective for monovalent cations (P_{Ca}/P_{Cs} ˜0.1); TRPM3α2: conducts mono- and di-valent cations non-selectively (P_{Ca}/P_{Cs} = 1-10); In- and outwardly rectifying currents by co-application of pregnenolone sulphate and clotrimazole or single application of CIM0216 [529, 1446]. TRPM3α1 is activated by clotrimazole but not by pregnenolone sulphate [528].	γ = 23 pS (within the range 60 to +60 mV); permeable to monovalent cations; impermeable to Ca^{2+}; strong outward rectification; slow activation at positive potentials, rapid deactivation at negative potentials, deactivation blocked by decavanadate
Comments	G protein βγ subunits can act as endogenous inhibitors of TRPM3 channel activity [63, 309, 1152].	–

Nomenclature	TRPM5	TRPM6
HGNC, UniProt	*TRPM5*, Q9NZQ8	*TRPM6*, Q9BX84
EC number	–	2.7.11.1
Other chemical activators	–	constitutively active, activated by reduction of intracellular Mg^{2+}
Physical activators	membrane depolarization ($V_{\frac{1}{2}}$ = 0 to + 120 mV dependent upon conditions), heat (Q_{10} = 10.3 @ -75 mV between 15 and 25°C)	–
Endogenous activators	intracellular Ca^{2+} (Agonist) (pEC_{50} 4.5–6.2) [-80mV – 80mV] [557, 840, 1413] – Mouse	extracellular H^+ (Potentiation), intracellular Mg^{2+}
Activators	compound 39 (Agonist) (pEC_{50} 7.5) [1206]	2-APB (Agonist) (pEC_{50} 3.4–3.7) [-120mV – 100mV] [807]
Endogenous channel blockers	–	Mg^{2+} (inward current mediated by monovalent cations is blocked) (pIC_{50} 5.5–6), Ca^{2+} (inward current mediated by monovalent cations is blocked) (pIC_{50} 5.3–5.3)
Channel blockers	flufenamic acid (pIC_{50} 4.6), intracellular spermine (pIC_{50} 4.4), Extracellular H^+ (pIC_{50} 3.2)	ruthenium red (pIC_{50} 7) [*voltage dependent* -120mV]
Allosteric modulators	APV207095A (Potentiation) (pEC_{50} 5) [1436], APV207094A (Potentiation) (pEC_{50} 4.4) [1436], APV207010A (Potentiation) (pEC_{50} 4.4) [1436], APV206690A (Potentiation) (pEC_{50} 4) [1436]	–
Functional Characteristics	γ = 15-25 pS; conducts monovalent cations selectively (P_{Ca}/P_{Na} = 0.05); strong outward rectification; slow activation at positive potentials, rapid inactivation at negative potentials; activated and subsequently desensitized by $[Ca^{2+}]_I$	γ= 40-87 pS; permeable to mono- and di-valent cations with a preference for divalents ($Mg^{2+} > Ca^{2+}$; P_{Ca}/P_{Na} = 6.9), conductance sequence $Zn^{2+} > Ba^{2+} > Mg^{2+} = Ca^{2+} = Mn^{2+} > Sr^{2+} > Cd^{2+} > Ni^{2+}$; strong outward rectification abolished by removal of extracellular divalents, inhibited by intracellular Mg^{2+} (IC_{50} = 0.5 mM) and ATP
Comments	TRPM5 is not blocked by ATP. APV206512A and APV206513A are TRPM5 blockers, with IC_{50}s of 15 μM [1436]. Steviol glycosides (sweet-tasting organic molecules) act as positive modulators of TRPM5 activity [1111].	–

Nomenclature	TRPM7	TRPM8
HGNC, UniProt	*TRPM7*, Q96QT4	*TRPM8*, Q7Z2W7
EC number	2.7.11.1	–
Chemical activators	–	agonist activities are temperature dependent and potentiated by cooling
Physical activators	–	depolarization ($V_{0.5}$ ~ +50 mV at 15°C), cooling (< 22-26°C)
Endogenous activators	Extracellular H^+ (Potentiation) (pEC_{50} 4.5) [634]	–
Activators	2-APB Concentration range: >1×10^{-3}M [807] – Mouse, naltriben [558]	icilin (Agonist) (pEC_{50} 6.7–6.9) [physiological voltage] [40, 101] – Mouse, tacrolimus (Agonist) (pEC_{50} 4.8) [49], (-)-menthol (inhibited by intracellular Ca^{2+}) (pEC_{50} 4.6) [-120mV – 160mV] [1439]
Selective activators	–	acoltremon (Full agonist) (pEC_{50} 4.9) [physiological voltage] [879, 1267] – Rat
Selective antagonists	–	KPR-5714 (pIC_{50} 7.6) [995]
Channel blockers	sphingosine (Inhibition) (pIC_{50} 6.2) [-100mV – 100mV] [1149] – Mouse, fingolimod (Inhibition) (pIC_{50} 6.1) [-100mV – 100mV] [1149] – Mouse, spermine (Inhibition) (pK_i 5.6) [-110mV – 80mV] [735] – Rat, 2-APB (Inhibition) (pIC_{50} 3.8) [-100mV – 100mV] [807] – Mouse, carvacrol (Inhibition) (pIC_{50} 3.5) [-100mV – 100mV] [1080] – Mouse, Mg^{2+} (Antagonist) (pIC_{50} 2.5) [80mV] [988] – Mouse, La^{3+} (Antagonist) Concentration range: 2×10^{-3}M [-100mV – 100mV] [1203] – Mouse	BCTC (Antagonist) (pIC_{50} 6.1) [physiological voltage] [101] – Mouse, scutellarein (pIC_{50} 5.8) [1222], 2-APB (Antagonist) (pIC_{50} 4.9–5.1) [100mV – -100mV] [578, 1002] – Mouse, capsazepine (Antagonist) (pIC_{50} 4.7) [physiological voltage] [101] – Mouse
Selective channel blockers	–	PF-05105679 (Antagonist) (pIC_{50} 7) [*voltage dependent*] [44]
Functional Characteristics	γ = 40-105 pS at negative and positive potentials respectively; conducts mono-and di-valent cations with a preference for monovalents (P_{Ca}/P_{Na} = 0.34); conductance sequence $Ni^{2+} > Zn^{2+} > Ba^{2+} = Mg^{2+} > Ca^{2+} = Mn^{2+} > Sr^{2+} > Cd^{2+}$; outward rectification, decreased by removal of extracellular divalent cations; inhibited by intracellular Mg^{2+}, Ba^{2+}, Sr^{2+}, Zn^{2+}, Mn^{2+} and Mg.ATP (disputed); activated by and intracellular alkalinization; sensitive to osmotic gradients	γ = 40-83 pS at positive potentials; conducts mono- and di-valent cations non-selectively (P_{Ca}/P_{Na} = 1.0-3.3); pronounced outward rectification; demonstrates densensitization to chemical agonists and adaptation to a cold stimulus in the presence of Ca^{2+}; modulated by lysophospholipids and PUFAs
Comments	2-APB acts as a channel blocker in the µM range. Recent study shows cAMP inhibits TRPM7-mediated Ca^{2+} influx [152]. Waixenicin-A specifically inhibits TRPM7 [1634].	Cannabidiol and Δ^9-tetrahydrocannabinol are examples of cannabinoid activators. TRPM8 is insensitive to ruthenium red. Icilin requires intracellular Ca^{2+} for full agonist activity.

TRPML (mucolipin) family

The TRPML family [264, 1140, 1146, 1544, 1596] consists of three mammalian members (TRPML1-3). TRPML channels are probably restricted to intracellular vesicles and mutations in the gene (*MCOLN1*) encoding TRPML1 (mucolipin-1) cause the neurodegenerative disorder mucolipidosis type IV (MLIV) in man. TRPML1 is a cation selective ion channel that is important for sorting/transport of endosomes in the late endocytotic pathway and specifically, fission from late endosome-lysosome hybrid vesicles and lysosomal exocytosis [1219]. TRPML2 and TRPML3 show increased channel activity in low luminal sodium and/or increased luminal pH, and are activated by similar small molecules [206, 477, 1306]. A naturally occurring gain of function mutation in TRPML3 (*i.e.* A419P) results in the varitint waddler (V*a*) mouse phenotype (reviewed by [1022, 1146]).

Nomenclature	TRPML1	TRPML2	TRPML3
HGNC, UniProt	*MCOLN1*, Q9GZU1	*MCOLN2*, Q8IZK6	*MCOLN3*, Q8TDD5
Endogenous activators	phosphatidyl (3,5) inositol bisphosphate (Also activates other TRPMLs) (pEC_{50} 7.3) [334]	–	–
Activators	ML SA1 (pEC_{50} 7.3) [-140mV] [1264], MK6-83 (pEC_{50} 7) [208], SF-22 (pEC_{50} 6.3) [-200mV] [208], ML-SA5 (pEC_{50} 5.3) [1586], SF-51 (pEC_{50} 4.5) [1264], ML1-SA1 [1306] TRPML1^{Va}: Constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification)	ML SA1 Concentration range: 1×10^{-5}M [-140mV] [1264], phosphatidyl (3,5) inositol bisphosphate Concentration range: 1×10^{-6}M [-140mV] [334] TRPML2^{Va}: Constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification)	SF-11 (pEC_{50} 6.6) [478], EVP-21 (pEC_{50} 4.3) [1170], ML SA1 Concentration range: 1×10^{-5}M [-140mV] [1264], phosphatidyl (3,5) inositol bisphosphate Concentration range: 1×10^{-6}M [-140mV] [334]
Selective activators	–	ML2-SA1 (Agonist) (pEC_{50} 1.2) [1131]	ML3-SA1 (pEC_{50} 5.1) [1306] – Mouse
Channel blockers	estradiol 3-methyl ether (pIC_{50} 6.7) [1200], PRU-12 (Inhibition) (pIC_{50} 6.6) [1200], estradiol 3-methyl ether (pIC_{50} 6.2) [1200]	–	Gd^{3+} (Antagonist) (pIC_{50} 4.7) [-80mV] [990] – Mouse
Functional Characteristics	TRPML1^{Va}: γ = 40 pS and 76-86 pS at very negative holding potentials with Fe^{2+} and monovalent cations as charge carriers, respectively; conducts $Na^+ \cong K^+ > Cs^+$ and divalent cations ($Ba^{2+} > Mn2^+ > Fe^{2+} > Ca^{2+} > Mg^{2+} > Ni^{2+} > Co^{2+} > Cd^{2+} > Zn^{2+} \gg Cu^{2+}$); monovalent cation flux suppressed by divalent cations (*e.g.* Ca^{2+}, Fe^{2+}); inwardly rectifying	Conducts Na^+; monovalent cation flux suppressed by divalent cations; inwardly rectifying	TRPML3^{Va}: γ = 49 pS at very negative holding potentials with monovalent cations as charge carrier; conducts $Na^+ > K^+ > Cs^+$ with maintained current in the presence of Na^+, conducts Ca^{2+} and Mg^{2+}, but not Fe^{2+}, impermeable to protons; inwardly rectifying Wild type TRPML3: γ = 59 pS at negative holding potentials with monovalent cations as charge carrier; conducts $Na^+ > K^+ > Cs^+$ and Ca^{2+} ($P_{Ca}/P_K \cong 350$), slowly inactivates in the continued presence of Na^+ within the extracellular (extracytosolic) solution; outwardly rectifying
Comments	TRPML1 current is potentiated by acidic pH and sphingosine [1264].	TRPML2 current is inhibited by intralysosomal acidification [1131].	Current is activated by Na^+-free extracellular (extracytosolic) solution, and is inhibited by extracellular acidification (equivalent to intra-lysosomal acidification). Channel blockers include the ML-SI series of compounds (*e.g.* ML-SI1; concentration range 5×10^{-5} M; -120mV) [940].

TRPP (polycystin) family

The TRPP family (reviewed by [306, 308, 452, 555, 1520]) or PKD2 family is comprised of PKD2 (PC2), PKD2L1 (PC2L1), PKD2L2 (PC2L2), which have been renamed TRPP1, TRPP2 and TRPP3, respectively [1529]. It should also be noted that the nomenclature of PC2 was TRPP2 in old literature. However, PC2 has been uniformed to be called TRPP2 [516]. PKD2 family channels are clearly distinct from the PKD1 family, whose function is unknown. PKD1 and PKD2 form a hetero-oligomeric complex with a 1:3 ratio. [1333]. Although still being sorted out, TRPP family members appear to be 6TM spanning nonselective cation channels.

Nomenclature	TRPP1	TRPP2	TRPP3
HGNC, UniProt	*PKD2*, Q13563	*PKD2L1*, Q9P0L9	*PKD2L2*, Q9NZM6
Activators	–	Calmidazolium (in primary cilia): 10 µM	–
Channel blockers	–	phenamil (pIC_{50} 6.9), benzamil (pIC_{50} 6), ethylisopropylamiloride (pIC_{50} 5), amiloride (pIC_{50} 3.8), Gd^{3+} Concentration range: 1×10^{-4}M [-50mV] [218], La^{3+} Concentration range: 1×10^{-4}M [-50mV] [218], flufenamate	–
Functional Characteristics	TRPP1 (PKD2) forms a cation channel (as a homomer consisting of 4 PKD2 subunits or as a heteromer combining 3 PKD2 subunits with one PKD1 subunit) that is expressed on primary cilia of kidney epithelial cells [847]. In kidney epithelial cells TRPP1 is only functional in the ciliary membrane, but not in the plasma membrane. In oocyte overexpression TRPP1 forms functional homomeric and heteromeric channels. Gain of function mutations in TRPP1 in either the S4-S5 linker (F604P) or in the lower gate (L677A, N681A) result in constitutively active channels [50, 495, 1492]. TRPP1 prefers monovalent cations over divalent cations in the order of K^+>Na^+>Ca^{2+} (permeability 1:0.4:0.025), showing low selectivity for Ca^{2+}. The conductance of TRPP1 varies depending on the ion (K^+ : 144 pS, Na^+: 89 pS, Ca^{2+}: 4pS) [847]. TRPP1 homomeric channel produces a larger conductance of 82 pS than the PC-1/TRPP1 heteromeric channel (79.5 pS) with higher absolute open probability (TRPP1 homomeric channel: 0.58, PC-1/TRPP1 heteromeric channel: 0.08) in primary cilia [495]. Specific activators or channel blockers of TRPP1 remain unknown.	TRPP2 is a nonselective cation channel functionally expressed on primary cilia and/or the plasma membrane depending on cell type. It can form a functional channel with PC1-L1 on primary cilia of retinal pigmented epithelial cells. TRPP2 (PKD2L1) displays calcium dependent activation. Calcium accumulation due to prolonged channel activity may lead to outward-moving Ca^{2+} ions within the pore to close the channel [292]. TRPP2 permeates K^+, Na^+ and Ca^{2+} with the single-channel conductance of 189 pS for K^+, 156 for Na^+, and 53 pS for Ca^{2+}, respectively [373]. PKD2L1 forms a heteromeric channel with PC-1L3 (*PKD1L3*) that may be activated by intracellular Ca^{2+} [1332].	TRPP3 is not fully characterized yet. One report suggests the single channel activity of PKD2L2 in HEK293 cells as a 25 pS conductance [1344], but these recordings have not been confirmed.
Comments	Several studies have reported that TRPP1 forms heteromeric ion channels with other TRP channels such as TRPM3 and TRPM4, but the physiological significance of these potential heteromers remains unclear [407, 717]. TRPP1 has also been reported to function as a heteromeric channel with PC-1-L1 (*PKD1L1*) in the embryonic node, but the biophysical characteristics of this heteromeric channel have not yet been characterized [684].	–	–

TRPV (vanilloid) family

Members of the TRPV family (reviewed by [1427]) can broadly be divided into the non-selective cation channels, TRPV1-4 and the more calcium selective channels TRPV5 and TRPV6.

TRPV1-V4 subfamily

TRPV1 is involved in the development of thermal hyperalgesia following inflammation and may contribute to the detection of noxious heat (reviewed by [1118, 1308, 1351]). Numerous splice variants of TRPV1 have been described, some of which modulate the activity of TRPV1, or act in a dominant-negative manner when co-expressed with TRPV1 [1247]. The pharmacology of TRPV1 channels is discussed in detail in [490] and [1445]. TRPV2 is probably not a thermosensor in man [1077], but has recently been implicated in innate immunity [834]. Functional TRPV2 expression is described in placental trophoblast cells of mouse [286]. TRPV3 and TRPV4 are both thermosensitive. There are claims that TRPV4 is also mechanosensitive, but this has not been established to be within a physiological range in a native environment [177, 820].

TRPV5/V6 subfamily

TRPV5 and TRPV6 are highly expressed in placenta, bone, and kidney. Under physiological conditions, TRPV5 and TRPV6 are calcium selective channels involved in the absorption and reabsorption of calcium across intestinal and kidney tubule epithelia (reviewed by [287, 389, 987, 1518]).TRPV6 is reported to play a key role in calcium transport in the mouse placenta [1516].

Nomenclature	TRPV1	TRPV2
HGNC, UniProt	*TRPV1*, Q8NER1	*TRPV2*, Q9Y5S1
Other chemical activators	NO-mediated cysteine S-nitrosylation	–
Physical activators	depolarization ($V_{0.5}$ ˜ 0 mV at 35°C), noxious heat (> 43°C at pH 7.4)	–
Endogenous activators	extracellular H^+ (at 37°C) (pEC_{50} 5.4), 12S-HPETE (Agonist) (pEC_{50} 5.1) [-60mV] [595] – Rat, anandamide (pEC_{50} 5) [14], LTB_4 (Agonist) (pEC_{50} 4.9) [-60mV] [595] – Rat, 5S-HETE	–
Activators	resiniferatoxin (Agonist) (pEC_{50} 8.4) [physiological voltage] [1287], capsaicin (Agonist) (pEC_{50} 7.5) [-100mV – 160mV] [1439], RhTx (pEC_{50} 6.3) [1562], piperine (Agonist) (pEC_{50} 4.4–5) [-70mV] [933], camphor, diphenylboronic anhydride, phenylacetylrinvanil [47]	2-APB (pEC_{50} 5) [1004, 1148] – Rat, Δ^9-tetrahydrocannabinol (pEC_{50} 4.8) [1148] – Rat, cannabidiol (pEC_{50} 4.5) [1148], probenecid (pEC_{50} 4.5) [73] – Rat, 2-APB (Agonist) (pEC_{50} 3.8–3.9) [physiological voltage] [578, 656] – Mouse, diphenylboronic anhydride (Agonist) Concentration range: 1×10^{-4}M [-80mV] [239, 656] – Mouse
Selective activators	olvanil (Agonist) (pEC_{50} 7.7) [physiological voltage] [1287], DkTx (pEC_{50} 6.6) [physiological voltage] [135] – Rat	–
Channel blockers	5′-iodoresiniferatoxin (pIC_{50} 8.4), 6-iodo-nordihydrocapsaicin (pIC_{50} 8), AMG 9810 (Inhibition) (pIC_{50} 7.8) [physiological voltage] [437], BCTC (Antagonist) (pIC_{50} 7.5) [200], capsazepine (Antagonist) (pIC_{50} 7.4) [-60mV] [930], ruthenium red (pIC_{50} 6.7–7)	ruthenium red (pIC_{50} 6.2), tranilast (Inhibition) (pIC_{50} 4–5) [1010], SKF96365 (pIC_{50} 4) [656], TRIM (Inhibition) Concentration range: 5×10^{-4}M [656] – Mouse
Selective channel blockers	AMG517 (pIC_{50} 9) [128], AMG628 (pIC_{50} 8.4) [1470] – Rat, A425619 (pIC_{50} 8.3) [366], A778317 (pIC_{50} 8.3) [117], SB366791 (pIC_{50} 8.2) [492], JYL1421 (Antagonist) (pIC_{50} 8) [1489] – Rat, JNJ17203212 (Antagonist) (pIC_{50} 7.8) [physiological voltage] [1347], SB452533 (Antagonist) (p_B 7.7), SB705498 (Antagonist) (pIC_{50} 7.1) [491]	SET2 (pIC_{50} 6.3) [193], loratadine (Inhibition) (pIC_{50} 5.5) [1418]
Allosteric modulators (Positive)	s-RhTx (pEC_{50} 6.1) [1605], MRS-1477 [683]	–

Labelled ligands	[^{3}H]A778317 (Channel blocker) (pK_d 8.5) [117], [^{125}I]resiniferatoxin (Channel blocker, Antagonist) (pIC$_{50}$ 8.4) [-50mV] [1453] – Rat, [^{3}H]resiniferatoxin (Activator)	–
Functional Characteristics	γ = 35 pS at - 60 mV; 77 pS at + 60 mV, conducts mono and di-valent cations with a selectivity for divalents (P_{Ca}/P_{Na} = 9.6); voltage- and time- dependent outward rectification; potentiated by ethanol; activated/potentiated/upregulated by PKC stimulation; extracellular acidification facilitates activation by PKC; desensitisation inhibited by PKA; inhibited by Ca^{2+}/ calmodulin; cooling reduces vanilloid-evoked currents; may be tonically active at body temperature	Conducts mono- and di-valent cations (P_{Ca}/P_{Na} = 0.9-2.9); dual (inward and outward) rectification; current increases upon repetitive activation by heat; translocates to cell surface in response to IGF-1 to induce a constitutively active conductance, translocates to the cell surface in response to membrane stretch. Cannabidiol sensitizes TRPV2 channels to activation by 2APB [458].

Nomenclature	TRPV3	TRPV4
HGNC, UniProt	*TRPV3*, Q8NET8	*TRPV4*, Q9HBA0
Other chemical activators	NO-mediated cysteine S-nitrosylation	Epoxyeicosatrieonic acids and NO-mediated cysteine S-nitrosylation
Physical activators	depolarization ($V_{0.5}$ ˜ +80 mV, reduced to more negative values following heat stimuli), heat (23°C - 39°C, temperature threshold reduces with repeated heat challenge)	Constitutively active, heat (> 24°C - 32°C), mechanical stimuli
Activators	incensole acetate (pEC$_{50}$ 4.8) [978] – Mouse, 2-APB (Full agonist) (pEC$_{50}$ 4.6) [-80mV – 80mV] [240] – Mouse, diphenylboronic anhydride (Full agonist) (pEC$_{50}$ 4.1–4.2) [*voltage dependent* -80mV – 80mV] [239] – Mouse, thymol (Full agonist) (pEC$_{50}$ 3.3) [1541] – Mouse, eugenol (Full agonist) (pEC$_{50}$ 2.5) [1541] – Mouse, camphor (Full agonist) (pEC$_{50}$ 2) [970] – Mouse, (-)-menthol (pEC$_{50}$ 1.7) [-80mV – 80mV] [884] – Mouse, carvacrol (Full agonist) Concentration range: 5×10^{-4}M [-80mV – 80mV] [1541] – Mouse	phorbol 12-myristate 13-acetate (Agonist) (pEC$_{50}$ 7.9) [physiological voltage] [1539], quinazolin-4(3H) derivative 36 (pEC$_{50}$ 7.2) [57], curcumin (pEC$_{50}$ 5.2) [1257], arachidonic acid (pEC$_{50}$ 5) [1496] – Mouse, puerarin (pEC$_{50}$ 4.8) [1626], vildagliptin (pEC$_{50}$ 3) [424]
Selective activators	KS0365 (pEC$_{50}$ 5.3) [890], 6-tert-butyl-*m*-cresol (pEC$_{50}$ 3.4) [1443] – Mouse	GSK1016790A (pEC$_{50}$ 8.7) [physiological voltage] [1387], 4α-PDH (pEC$_{50}$ 7.1) [physiological voltage] [716] – Mouse, 4α-PDD (Agonist) (pEC$_{50}$ 6.5) [1539], RN1747 (pEC$_{50}$ 6.1) [physiological voltage] [1435], bisandrographolide (Agonist) (pEC$_{50}$ 6) [-60mV] [1292] – Mouse
Inhibitors	–	GSK2798745 (pIC$_{50}$ 8.8) [155], GSK-Bz derivative 2b (pIC$_{50}$ 7.7) [16], paracetamol (pIC$_{50}$ 6.5) [992], cimifugin (pIC$_{50}$ 5.8) [1555], propofol (pIC$_{50}$ 4.4) [1464], Crotamiton [714]
Channel blockers	forsythoside B (Inhibition) (pIC$_{50}$ 6.2) [1607], ruthenium red (Inhibition) (pIC$_{50}$ 6) [1096] – Mouse, diphenyltetrahydrofuran (Antagonist) (pIC$_{50}$ 5–5.2) [-80mV – 80mV] [239] – Mouse, Citrusinine II (Inhibition) (pIC$_{50}$ 4.9) [505], osthole (Inhibition) (pIC$_{50}$ 4.4) [1340]	NSC151066 (Inhibition) (pIC$_{50}$ 6.8) [331], ruthenium red (Inhibition) (pIC$_{50}$ 6.7) [489] – Rat, Gd^{3+}, La^{3+}
Selective channel blockers	Trpvicin (Inhibition) (pIC$_{50}$ 6.4) [385], Isochlorogenic acid B (Inhibition) (pIC$_{50}$ 6.1) [1145], Isochlorogenic acid A (Inhibition) (pIC$_{50}$ 5.6) [1145], verbascoside (Inhibition) (pIC$_{50}$ 4.8) [1338]	HC067047 (Inhibition) (pIC$_{50}$ 7.3) [-40mV] [382], RN-9893 (Antagonist) (pIC$_{50}$ 6.2) [1504], RN1734 (Inhibition) (pIC$_{50}$ 5.6) [physiological voltage] [1435]
Functional Characteristics	γ = 197 pS at = +40 to +80 mV, 48 pS at negative potentials; conducts mono- and di-valent cations; outward rectification; potentiated by arachidonic acid	γ = ˜60 pS at -60 mV, ˜90-100 pS at +60 mV; conducts mono- and di-valent cations with a preference for divalents (P_{Ca}/P_{Na} =6-10); dual (inward and outward) rectification; potentiated by intracellular Ca^{2+}*via* Ca^{2+}/ calmodulin; inhibited by elevated intracellular Ca^{2+}*via* an unknown mechanism (IC$_{50}$ = 0.4 μM)

Nomenclature	TRPV5	TRPV6
HGNC, UniProt	*TRPV5*, Q9NQA5	*TRPV6*, Q9H1D0
Other channel blockers	Pb^{2+} = Cu^{2+} = Gd^{3+} > Cd^{2+} > Zn^{2+} > La^{3+} > Co^{2+} > Fe^2	–
Activators	constitutively active (with strong buffering of intracellular Ca^{2+})	acetaldehyde (pEC_{50} 6.7) [935], ethanol (pEC_{50} 0.8) [935], 2-APB (Potentiation) constitutively active (with strong buffering of intracellular Ca^{2+})
Inhibitors	gentamicin (pIC_{50} 6) [1419], tetrahydrocannabivarin (pIC_{50} 5.4) [622], oxoglaucine (pIC_{50} 4.8) [1621]	GSK3527497 (pIC_{50} 7.9) [154], SOR-C13 (pIC_{50} 7.8) [144], TRPV6 inhibitor cis-22 a (pIC_{50} 6.5) [1280], tetrahydrocannabivarin (pIC_{50} 5.1) [622]
Channel blockers	ruthenium red (pIC_{50} 6.9), Mg^{2+}	ruthenium red (Antagonist) (pIC_{50} 5) [-80mV] [554] – Mouse, Cd^{2+}, La^{3+}, Mg^{2+}
Functional Characteristics	γ = 59-78 pS for monovalent ions at negative potentials, conducts mono- and di-valents with high selectivity for divalents (P_{Ca}/P_{Na} > 107); voltage- and time- dependent inward rectification; inhibited by intracellular Ca^{2+} promoting fast inactivation and slow down-regulation; feedback inhibition by Ca^{2+} reduced by calcium binding protein 80-K-H; inhibited by extracellular and intracellular acidosis; upregulated by 1,25-dihydrovitamin D3	γ = 58-79 pS for monovalent ions at negative potentials, conducts mono- and di-valents with high selectivity for divalents (P_{Ca}/P_{Na} > 130); voltage- and time-dependent inward rectification; inhibited by intracellular Ca^{2+} promoting fast and slow inactivation; gated by voltage-dependent channel blockade by intracellular Mg^{2+}; slow inactivation due to Ca^{2+}-dependent calmodulin binding; phosphorylation by PKC inhibits Ca^{2+}-calmodulin binding and slow inactivation; upregulated by 1,25-dihydroxyvitamin D3

Comments:

TRPA (ankyrin) family

Agents activating TRPA1 in a covalent manner are thiol reactive electrophiles that bind to cysteine and lysine residues within the cytoplasmic domain of the channel [547, 882]. TRPA1 is activated by a wide range of endogenous and exogenous compounds and only a few representative examples are mentioned in the table: an exhaustive listing can be found in [75]. In addition, TRPA1 is potently activated by intracellular zinc (EC_{50} = 8 nM) [42, 577]. A gain-of-function mutation in TRPA1 was found to cause familial episodic pain syndrome [746].

TRPM (melastatin) family

Ca^{2+} activates all splice variants of TRPM2, but other activators listed are effective only at the full length isoform [345]. Inhibition of TRPM2 by clotrimazole, miconazole, econazole, flufenamic acid is largely irreversible. Co-application of pregnenolone sulphate and clotrimazole caused TRPM3 currents to acquire an inwardly rectifying component at negative voltages, resulting in a biphasic conductance-voltage relationship. Evidence was presented that the inward current might reflect the permeation of cations through the opening of a non-canonical pore [1446]. TRPM3 activity is impaired in chronic fatigue syndrome/myalgic encephalomyelitis patients suggesting changes in intracellular Ca^{2+} concentration, which may impact natural killer cellular functions [167]. TRPM4 exists as multiple spice variants: data listed are for TRPM4b. The sensitivity of TRPM4b and TRPM5 to activation by $[Ca^{2+}]_i$ demonstrates a pronounced and time-dependent reduction following excision of inside-out membrane patches [1413]. The $V_{0.5}$ for activation of TRPM4 and TRPM5 demonstrates a pronounced negative shift with increasing temperature. Activation of TRPM8 by depolarization is strongly temperature-dependent via a channel-closing rate that decreases with decreasing temperature. The $V_{0.5}$ is shifted in the hyperpolarizing direction both by decreasing temperature and by exogenous agonists, such as (-)-menthol [1439] whereas antagonists produce depolarizing shifts in $V_{0.5}$ [901]. The $V_{0.5}$ for the native channel is far more positive than that of heterologously expressed TRPM8 [901]. It should be noted that (-)-menthol and structurally related compounds can elicit release of Ca^{2+} from the endoplasmic reticulum independent of activation of TRPM8 [889]. Intracellular pH modulates activation of TRPM8 by cold and icilin, but not (-)-menthol [40].

TRPML (mucolipin) family

Data in the table are for TRPML proteins mutated (*i.e* $TRPML1^{Va}$, $TRPML2^{Va}$ and $TRPML3^{Va}$) at loci equivalent to TRPML3 A419P to allow plasma membrane expression when expressed in HEK-293 cells and subsequent characterisation by patch-clamp recording [333, 475, 702, 990, 1542]. Data for wild type TRPML3 are also tabulated [702, 703, 990, 1542]. It should be noted that alternative methodologies, particularly in the case of TRPML1, have resulted in channels with differing biophysical characteristics (reviewed by [1140]). Initial functional characteristics of TRPML channels are performed on their Va mutations of TRPMLs at loci equivalent to TRPML3 A419P. Current pharmacological characterization of channel activators and blockers are conducted on wild-type channel proteins using endolysosomal patch-clamp [208, 334, 1131, 1264].

TRPP (polycystin) family

Data in the table are extracted from [272, 308] and [1269]. Broadly similar single channel conductance, mono- and di-valent cation selectivity and sensitivity to blockers are observed for TRPP2 co-expressed with TRPP1 [307]. Ca^{2+}, Ba^{2+} and Sr^{2+} permeate TRPP3, but reduce inward currents carried by Na^{+}. Mg^{2+} is largely impermeant and exerts a voltage dependent inhibition that increases with hyperpolarization.

TRPV (vanilloid) family

Activation of TRPV1 by depolarisation is strongly temperature-dependent via a channel opening rate that increases with increasing temperature. The $V_{0.5}$ is shifted in the hyperpolarizing direction both by increasing temperature and by exogenous agonists [1439]. TRPV3 channel dysfunction caused by genetic gain-of-function mutations is implicated in the pathogenesis of skin inflammation, dermatitis, and chronic itch. In rodents, a spontaneous gain-of-function mutation of the TRPV3 gene causes the development of skin lesions with pruritus and dermatitis [51, 830]. In contrast to other thermoTRP channels, TRPV3 sensitizes rather than desensitizes, upon repeated stimulation with either heat or agonists [240, 839, 1543]. The sensitivity of TRPV4 to heat, but not 4α-PDD is lost upon patch excision. TRPV4 is activated by anandamide and arachidonic acid following P450 epoxygenase-dependent metabolism to 5,6-epoxyeicosatrienoic acid (reviewed by [1026]). Activation of TRPV4 by cell swelling, but not heat, or phorbol esters, is mediated via the formation of epoxyeicosatrieonic acids. Phorbol esters bind directly to TRPV4. Different TRPV4 mutations load to a broad spectrum of dominant skeletal dysplasias [739, 1182] and spinal muscular atrophies and hereditary motor and sensory neuropathies [59, 311]. Similar mutations were also found in patients with Charcot-Marie-Tooth disease type 2C [768]. TRPV5 preferentially conducts Ca^{2+} under physiological conditions, but in the absence of extracellular Ca^{2+}, conducts monovalent cations. Single channel conductances listed for TRPV5 and TRPV6 were determined in divalent cation-free extracellular solution. Ca^{2+}-induced inactivation occurs at hyperpolarized potentials when Ca^{2+} is present extracellularly. Single channel events cannot be resolved (probably due to greatly reduced conductance) in the presence of extracellular divalent cations. Measurements of P_{Ca}/P_{Na} for TRPV5 and TRPV6 are dependent upon ionic conditions due to anomalous mole fraction behaviour. Blockade of TRPV5 and TRPV6 by extracellular Mg^{2+} is voltage-dependent. Intracellular Mg^{2+} also exerts a voltage dependent block that is alleviated by hyperpolarization and contributes to the time-dependent activation and deactivation of TRPV6 mediated monovalent cation currents. TRPV5 and TRPV6 differ in their kinetics of Ca^{2+}-dependent inactivation and recovery from inactivation. TRPV5 and TRPV6 function as homo- and hetero-tetramers.

Further reading on Transient Receptor Potential channels (TRP)

Aghazadeh Tabrizi M *et al*. (2017) Medicinal Chemistry, Pharmacology, and Clinical Implications of TRPV1 Receptor Antagonists. *Med Res Rev* **37**: 936-983 [PMID:27976413]

Basso L *et al*. (2017) Transient Receptor Potential Channels in neuropathic pain. *Curr Opin Pharmacol* **32**: 9-15 [PMID:27835802]

Ciardo MG *et al*. (2017) Lipids as central modulators of sensory TRP channels. *Biochim Biophys Acta* **1859**: 1615-1628 [PMID:28432033]

Clapham DE *et al*. (2003) International Union of Pharmacology. XLIII. Compendium of voltage-gated ion channels: transient receptor potential channels. *Pharmacol Rev* **55**: 591-6 [PMID:14657417]

Diaz-Franulic I *et al*. (2016) Allosterism and Structure in Thermally Activated Transient Receptor Potential Channels. *Annu Rev Biophys* **45**: 371-98 [PMID:27297398]

Emir TLR. (2017) Neurobiology of TRP Channels *Neurobiology of TRP Channels* [PMID:29356487]

Grayson TH *et al*. (2017) Transient receptor potential canonical type 3 channels: Interactions, role and relevance - A vascular focus. *Pharmacol Ther* **174**: 79-96 [PMID:28223224]

Nilius B *et al*. (2014) Mammalian transient receptor potential (TRP) cation channels. Preface. *Handb Exp Pharmacol* **223**: v - vi [PMID:25296415]

Rubaiy HN. (2019) Treasure troves of pharmacological tools to study transient receptor potential canonical 1/4/5 channels. *Br J Pharmacol* **176**: 832-846 [PMID:30656647]

Wu LJ *et al*. (2010) International Union of Basic and Clinical Pharmacology. LXXVI. Current progress in the mammalian TRP ion channel family. *Pharmacol Rev* **62**: 381-404 [PMID:20716668]

Zhu MX. (2011) Various *TRP Channels (CRC Press/Taylor & Francis)* [PMID:22593967]

Zierler S *et al*. (2017) TRPM channels as potential therapeutic targets against pro-inflammatory diseases. *Cell Calcium* **67**: 105-115 [PMID:28549569]

Voltage-gated calcium channels (Ca_V)

Ion channels → Voltage-gated ion channels → Voltage-gated calcium channels (Ca_V)

Overview: Ca^{2+} channels are voltage-gated ion channels present in the membrane of most excitable cells. The nomenclature for Ca^{2+}channels was proposed by [372] and **approved by the NC-IUPHAR Subcommittee on Ca^{2+} channels** [188]. Most Ca^{2+} channels form hetero-oligomeric complexes. The α1 subunit is pore-forming and provides the binding site(s) for practically all agonists and antagonists. The 10 cloned α1-subunits can be grouped into three families: (1) the high-voltage activated dihydropyridine-sensitive (L-type, $Ca_V1.x$) channels; (2) the high- to moderate-voltage activated dihydropyridine-insensitive ($Ca_V2.x$) channels and (3) the low-voltage-activated (T-type, $Ca_V3.x$) channels. Each α1 subunit has four homologous repeats (I-IV), each repeat having six transmembrane domains (S1-S6) forming a voltage-sensing domain (VSD, S1-S4) coupled to a pore-forming module (S5, S6 and their connecting linker that contains the selectivity filter. Voltage-dependent gating is driven by voltage-induced transmembrane movements of the S4-helix enabled by conserved positive charges interacting with negative counter-charges within the VSD [186]. All of the α1-subunit genes give rise to alternatively spliced products. At least for high-voltage activated channels, it is likely that native channels comprise co-assemblies of α1, β and α2-δ subunits. CACHD1 is an α2δ-like protein that modulates Ca_v3 channel activity [257]. The γ subunits have not been proven to associate with channels other than the α1s skeletal muscle $Ca_v1.1$ channel. The α2-δ1 and α2-δ2 subunits bind gabapentin and pregabalin [221].

Nomenclature	$Ca_v1.1$	$Ca_v1.2$	$Ca_v1.3$	$Ca_v1.4$
HGNC, UniProt	*CACNA1S*, Q13698	*CACNA1C*, Q13936	*CACNA1D*, Q01668	*CACNA1F*, O60840
Activators	FPL64176 (pEC_{50}~7.8), (-)-(S)-BayK8644 (pEC_{50}~7.8)	(-)-(S)-BayK8644 (pEC_{50}~7.8), FPL64176 Concentration range: 1×10^{-7}M-1×10^{-6}M [669, 843]	FPL64176 (pEC_{50}~7.8), (-)-(S)-BayK8644 (pEC_{50}~7.8)	(-)-(S)-BayK8644 (pEC_{50}~7.8)
Gating inhibitors	nifedipine (Antagonist) (pIC_{50} 6.3) [*voltage dependent* -90mV] [765] – Rat, nimodipine (Antagonist) (pIC_{50}~6) [-70mV]	amlodipine (pIC_{50} 9.3) [589] – Rabbit, isradipine (Antagonist) (pIC_{50} 8.8) [1059], nifedipine (Antagonist) (pIC_{50} 8.1–8.7) [-40mV] [1102, 1117] – Rat, isradipine (Antagonist) (pIC_{50} 8.5) [1059], nimodipine (Antagonist) (pIC_{50} 6.8) [-80mV] [1547] – Rat	nitrendipine (Inhibition) (pIC_{50} 8.4) [1283], isradipine (dopamine neuron-like activity; splice variant-dependent) (pIC_{50} 7.8–8.2) [1059], nifedipine (Antagonist) (pIC_{50} 7.7) [1283], nimodipine (Antagonist) (pIC_{50} 5.7–6.6) [-80mV – -40mV] [1210, 1547] – Rat	nifedipine (Antagonist) (pIC_{50} 6) [-100mV] [934], nimodipine (Antagonist) (pIC_{50}~6) [-70mV], nitrendipine (Antagonist) (pIC_{50}~6) [-70mV]
Channel blockers	verapamil (Antagonist) (pIC_{50}~5) [100mV] [1461] – Rabbit, diltiazem (Antagonist) (pIC_{50} 4.2) [-100mV] [1461] – Rabbit	verapamil (Antagonist) (pIC_{50} 5.3–6.5) [645] – Rat, diltiazem (Antagonist) (pIC_{50} 6.3) [666] – Ferret	verapamil (Antagonist) (pIC_{50} 3.7) [-70mV] [1370] – Mouse, diltiazem (pIC_{50} 3.5) [-70mV] [1370] – Mouse	diltiazem (pIC_{50} 4) [-80mV] [91] – Mouse, verapamil Concentration range: 1×10^{-4}M [-80mV] [91] – Mouse
Sub/family-selective channel blockers	–	calciseptine (Antagonist) (pIC_{50} 7.1–7.8) [86, 291, 939, 1498]	–	–
Functional Characteristics	L-type calcium current: High voltage-activated, very slow voltage dependent inactivation	L-type calcium current: High voltage-activated, voltage- and calcium-dependent inactivation	L-type calcium current: more negative activation voltage range than $Ca_v1.2$, calcium-dependent inactivation	L-type calcium current: More negative activation voltage range than $Ca_v1.2$, no/weak calcium-dependent inactivation

Comments	Serves primarily as voltage-sensor for excitation contraction coupling in skeletal muscle. The adaptor protein STAC3 binds to Ca_v1.1 α1 and is essential for transmitting its conformational changes to ryanodine receptor-mediated excitation contraction coupling [1133].	Amlodopine, isradipine, nifedipine and nimodipine are examples of dihydropyridine calcium channel antagonists. Verapamil is a phenylalkylamine calcium channel blocker. Diltiazem is an example of a benzothiazepine calcium channel blocker. Inhibition by dihydropyridines (*e.g.* nifedipine or isradipine) is voltage-dependent with a higher apparent affinity at more depolarised potentials [1352]; phenylalkylamines and diltiazem exhibit strong use-dependence with a higher apparent affinity at higher stimulation frequencies. Calciseptin is a potent inhibitor of Ca_v1.2 but not of Ca_v1.3 [939].	Ca_v1.3 is about 5-10 fold less sensitive to dihydropyridine antagonists [1352].	Ca_v1.4 is less sensitive to dihydropyridine antagonists than other Ca_v1 channels

Nomenclature	Ca_v2.1	Ca_v2.2	Ca_v2.3
HGNC, UniProt	*CACNA1A*, O00555	*CACNA1B*, Q00975	*CACNA1E*, Q15878
Gating inhibitors	–	NP118809 (pIC_{50} 7) [-80mV] [1594] – Rat	–
Selective gating inhibitors	ω-agatoxin IVA (Antagonist) (pIC_{50} 7–8.7) [-100mV – -90mV] [142, 960] – Rat, ω-agatoxin IVB (Antagonist) (pK_d 8.5) [-80mV] [12] – Rat	C2230 (pIC_{50} 6) [-50mV] [1365]	SNX482 (Antagonist) (pIC_{50} 7.5–8) [physiological voltage] [1005]
Channel blockers	–	–	Ni^{2+} (Antagonist) (pIC_{50} 4.6) [-90mV] [1515]
Sub/family-selective channel blockers	ω-conotoxin MVIIC (Antagonist) (pIC_{50} 8.2–9.2) Concentration range: 2×10^{-6}M-5×10^{-6}M [physiological voltage] [803] – Rat	ω-conotoxin GVIA (Antagonist) (pIC_{50} 10.4) [-80mV] [803] – Rat, ω-conotoxin MVIIC (Antagonist) (pIC_{50} 6.1–8.5) [-80mV] [546, 803, 929] – Rat	–
Functional Characteristics	P/Q-type calcium current: High voltage-activated, moderate voltage-dependent inactivation	N-type calcium current: High voltage-activated, moderate voltage-dependent inactivation	R-type calcium current: Moderate voltage-activated, fast voltage-dependent inactivation
Comments	All three Ca_v2.x types directly contribute towards triggering neurotransmitter release at fast synapses in the mammalian nervous system. In many cell types, P- and Q-current components cannot be adequately separated and many researchers in the field have therefore adopted the terminology 'P/Q-type' current when referring to either component. Both of these physiologically defined current types are conducted by alternative forms of Ca_v2.1 [815]. Ziconotide (a synthetic peptide equivalent to omega-Conotoxin-MVIIA) has been approved for the treatment of chronic pain [1514].	–	–

Nomenclature	$Ca_v3.1$	$Ca_v3.2$	$Ca_v3.3$
HGNC, UniProt	*CACNA1G*, O43497	*CACNA1H*, O95180	*CACNA1I*, Q9P0X4
Gating inhibitors	kurtoxin (Antagonist) (pIC_{50} 7.3–7.8) [-90mV] [236, 1273] – Rat	kurtoxin (Antagonist) (pIC_{50} 7.3–7.6) [-90mV] [236, 1273] – Rat	–
Channel blockers	ACT-709478 (Inhibition) (pIC_{50} 8.2) [114], ulixacaltamide (Pore blocker) (pIC_{50} 7.3) [-80mV] [1406], TTA-A2 (Pore blocker) (pIC_{50} 7) [-75mV] [413], mibefradil (Antagonist) (pIC_{50} 6–6.6) [-110mV – -100mV] [914], Ni^{2+} (Antagonist) (pIC_{50} 3.6–3.8) [*voltage dependent* -90mV] [782] – Rat	TTA-A2 (Pore blocker) (pIC_{50} 8) [-75mV] [413], ACT-709478 (Inhibition) (pIC_{50} 7.7) [114], mibefradil (Pore blocker) (pIC_{50} 5.9–7.2) [-110mV – -80mV] [914], and derivatives pimozide (Pore blocker) (pIC_{50} 6.8) [679], ulixacaltamide (Pore blocker) (pIC_{50} 6.8) [-75mV] [1406], efonidipine (Pore blocker) (pIC_{50} 6.4) [788], ABT-639 (Pore blocker) (pIC_{50} 5.7) [-70mV] [46, 625], Ni^{2+} (Pore blocker) (pIC_{50} 4.9–5.2) [*voltage dependent* -90mV] [782]	ACT-709478 (Inhibition) (pIC_{50} 8.1) [114], TTA-A2 (Pore blocker) (pIC_{50} 7.5) [-75mV] [413], ulixacaltamide (Pore blocker) (pIC_{50} 7) [-75mV] [1406], mibefradil (Antagonist) (pIC_{50} 5.8) [-110mV] [914], Ni^{2+} (Antagonist) (pIC_{50} 3.7–4.1) [*voltage dependent* -90mV] [782] – Rat
Functional Characteristics	T-type calcium current: Low voltage-activated, fast voltage-dependent inactivation	T-type calcium current: Low voltage-activated, fast voltage-dependent inactivation	T-type calcium current: Low voltage-activated, moderate voltage-dependent inactivation

Further reading on Voltage-gated calcium channels (Ca_V)

Catterall WA. (2023) Voltage gated sodium and calcium channels: Discovery, structure, function, and Pharmacology. *Channels (Austin)* **17**: 2281714 [PMID:37983307]

Catterall WA *et al.* (2005) International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. *Pharmacol Rev* **57**: 411-25 [PMID:16382099]

Catterall WA *et al.* (2015) Deciphering voltage-gated Na(+) and Ca(2+) channels by studying prokaryotic ancestors. *Trends Biochem Sci* **40**: 526-34 [PMID:26254514]

Chen Z *et al.* (2023) EMC chaperone-Ca_V structure reveals an ion channel assembly intermediate. *Nature***619**: 410-419 [PMID:37196677]

Dolphin AC. (2018) Voltage-gated calcium channels: their discovery, function and importance as drug targets. *Brain Neurosci Adv* **2**: [PMID:30320224]

Filippini L *et al.* (2023) Ca_v 1.3-selective inhibitors of voltage-gated L-type Ca^{2+} channels: Fact or (still) fiction? *Br J Pharmacol* **180**: 1289-1303 [PMID:36788128]

Huang J *et al.* (2017) Regulation of voltage gated calcium channels by GPCRs and post-translational modification. *Curr Opin Pharmacol* **32**: 1-8 [PMID:27768908]

Nanou E *et al.* (2018) Calcium Channels, Synaptic Plasticity, and Neuropsychiatric Disease. *Neuron* **98**: 466-481 [PMID:29723500]

Papa A *et al.* (2022) Adrenergic Regulation of Calcium Channels in the Heart. *Annu Rev Physiol* **84**: 285-306 [PMID:34752709]

Pelizzari S *et al.* (2024) $Ca_V1.1$ voltage-sensing domain III exclusively controls skeletal muscle excitation-contraction coupling. *Nat Commun* **15**: 7440 [PMID:39198449]

Rougier JS *et al.* (2016) Cardiac voltage-gated calcium channel macromolecular complexes. *Biochim Biophys Acta* **1863**: 1806-12 [PMID:26707467]

Weiss N *et al.* (2024) The T-type calcium channelosome. *Pflugers Arch* **476**: 163-177 [PMID:38036777]

Yao X *et al.* (2024) Structural biology of voltage-gated calcium channels. *Channels (Austin)* **18**: 2290807 [PMID:38062897]

Zamponi GW. (2016) Targeting voltage-gated calcium channels in neurological and psychiatric diseases. *Nat Rev Drug Discov* **15**: 19-34 [PMID:26542451]

Zamponi GW *et al.* (2015) The Physiology, Pathology, and Pharmacology of Voltage-Gated Calcium Channels and Their Future Therapeutic Potential. *Pharmacol Rev* **67**: 821-70 [PMID:26362469]

Voltage-gated proton channel (H_v1)

Ion channels → Voltage-gated ion channels → Voltage-gated proton channel (H_v1)

Overview: The voltage-gated proton channel (provisionally denoted H_v1) is a putative 4TM proton-selective channel gated by membrane depolarization and which is sensitive to the transmembrane pH gradient [178, 294, 295, 1165, 1225]. The structure of H_v1 is homologous to the voltage-sensing domain (VSD) of the superfamily of voltage-gated ion channels (*i.e.* segments S1 to S4) and contains no discernable pore region [1165, 1225]. Proton flux through Hv1 is instead most likely mediated by a hydrogen-bonded chain [296, 991] formed in a crevice of the protein when the voltage-sensing S4 helix moves in response to a change in transmembrane potential [1164, 1523]. Proton selective conduction requires an aspartate residue at the center of the pore [202, 986, 1294]. Both selectivity and conduction may result from obligatory protonation by each conducted proton [297, 349]. H_v1 expresses largely as a dimer mediated by intracellular C-terminal coiled-coil interactions [811] but individual promoters nonetheless support gated H^+ flux *via* separate conduction pathways [726, 787, 1108, 1393]. Within dimeric structures, the two protomers do not function independently, but dis-

play co-operative interactions during gating resulting in increased voltage sensitivity, but slower activation, of the dimeric,*versus* monomeric, complexes [462, 1394]. The otopetrin proteins appear to form proton-selective ion channels and to date 3 subtypes have been identified in eukaryotes; otopetrin 1 [1163, 1409], otopetrin 2 [856] and otopetrin 3 [591].

Nomenclature	H_v1
HGNC, UniProt	*HVCN1*, Q96D96
Channel blockers	Zn^{2+} (pIC_{50}~5.7–6.3), Cd^{2+} (pIC_{50}~5)
Functional Characteristics	Activated by membrane depolarization mediating macroscopic currents with time-, voltage- and pH-dependence; outwardly rectifying; voltage dependent kinetics with relatively slow current activation sensitive to extracellular pH and temperature, relatively fast deactivation; voltage threshold for current activation determined by pH gradient ($\Delta pH = pH_o - pH_i$) across the membrane

Comments: The voltage threshold (V_{thr}) for activation of Hv1 is not fixed but is set by the pH gradient across the membrane such that V_{thr} is positive to the Nernst potential for H^+, which ensures that only outwardly directed flux of H^+ occurs under physiological conditions [178, 227, 294, 295]. Phosphorylation of H_v1 within the N-terminal domain by PKC enhances the gating of the channel [298, 299, 984]. Tabulated IC_{50} values for Zn^{2+} and Cd^{2+} are for heterologously expressed human and mouse H_v1 [1165, 1225]. Zn^{2+} is not a conventional pore blocker, but is coordinated by two, or more, external protonation sites involving histamine residues [1165]. Zn^{2+} binding may occur at the dimer interface between pairs of histamine residues from both monomers where it may interfere with channel opening [985]. Mouse knockout studies [365, 973, 1166] support the view that H_v1 participates in both charge compensation and pH regulation in granulocytes during the respiratory burst of NADPH oxidase-dependent reactive oxygen species production that assists in the clearance of bacterial pathogens [300, 531, 673, 1243]. Additional physiological functions of H_v1 are reviewed by [178].

Further reading on Voltage-gated proton channel (H_v1)

Castillo K *et al.* (2015) Voltage-gated proton (H(v)1) channels, a singular voltage sensing domain. *FEBS Lett* **589**: 3471-8 [PMID:26296320]

DeCoursey TE. (2018) Gating currents indicate complex gating of voltage-gated proton channels. *Proc Natl Acad Sci USA* **115**: 9057-9059 [PMID:30135099]

DeCoursey TE. (2018) Voltage and pH sensing by the voltage-gated proton channel, H_V1. *J R Soc Interface* **15**: [PMID:29643227]

Fernández A *et al.* (2016) Pharmacological Modulation of Proton Channel Hv1 in Cancer Therapy: Future Perspectives. *Mol Pharmacol* **90**: 385-402 [PMID:27260771]

Okamura Y *et al.* (2015) Gating mechanisms of voltage-gated proton channels. *Annu Rev Biochem* **84**: 685-709 [PMID:26034892]

Voltage-gated sodium channels (Na_V)

Ion channels → Voltage-gated ion channels → Voltage-gated sodium channels (Na_V)

Overview: Sodium channels are voltage-gated sodium-selective ion channels present in the membrane of most excitable cells. Sodium channels comprise one pore-forming α subunit, which may be associated with either one or two β subunits [611]. α-Subunits consist of four homologous domains (I-IV), each containing six transmembrane segments (S1-S6) and a pore-forming loop. The positively charged fourth transmembrane segment (S4) acts as a voltage sensor and is involved in channel gating. The crystal structure of the bacterial NavAb channel has revealed a number of novel structural features compared to earlier potassium channel structures including a short selectivity filter with ion selectivity determined by interactions with glutamate side chains [1088]. Interestingly, the pore region is penetrated by fatty acyl chains that extend into the central cavity which may allow the entry of small, hydrophobic pore-blocking drugs [1088]. Auxiliary β1, β2, β3 and β4 subunits consist of a large extracellular N-terminal domain, a single transmembrane segment and a shorter cytoplasmic domain. Pharmacological targeting of voltage-gated sodium channels has long been a cornerstone of clinical treatment for a range of conditions. Classical sodium channel blockers, many of which act by occluding the central pore, are widely used as local anesthetics, antiarrhythmic agents, and anticonvulsants [412]. More recently, suzetrigine, a highly selective $Na_v1.8$ inhibitor, received FDA approval for the treatment of acute post-operative pain [652, 1499].

The nomenclature for sodium channels was proposed by Goldin *et al.*, (2000) [459] **and approved by the NC-IUPHAR Subcommittee on sodium channels (Catterall *et al.*, 2005,** [185]**).**

Nomenclature	$Na_v1.1$	$Na_v1.2$	$Na_v1.3$	$Na_v1.4$	$Na_v1.5$
HGNC, UniProt	*SCN1A*, P35498	*SCN2A*, Q99250	*SCN3A*, Q9NY46	*SCN4A*, P35499	*SCN5A*, Q14524
Sub/family-selective activators	batrachotoxin, veratridine	batrachotoxin (Agonist) (pK_d 9.1) [physiological voltage] [831] – Rat, veratridine (Partial agonist) (pK_d 5.2) [physiological voltage] [187] – Rat	batrachotoxin, veratridine	batrachotoxin (Full agonist) Concentration range: 5×10^{-6} M [-100mV] [1481] – Rat, veratridine (Partial agonist) Concentration range: 2×10^{-4} M [-100mV] [1481] – Rat	batrachotoxin (Full agonist) (pK_d 7.6) [physiological voltage] [1262] – Rat, veratridine (Partial agonist) (pEC_{50} 6.3) [-30mV] [1465] – Rat
Channel blockers	tetrodotoxin (Pore blocker) (pK_d 8) [-100mV] [1293] – Rat, cannabidiol (pIC_{50} 5.5) [-70mV] [449], cannabidiol (pIC_{50} 4.9) [-100mV] [449]	cannabidiol (pIC_{50} 5.5) [-45mV] [449]	cannabidiol (pIC_{50} 5.5) [-45mV] [449]	cannabidiol (pIC_{50} 5.7) [-45mV] [449], cannabidiol (pIC_{50} 5) [-110mV] [446]	cannabidiol (pIC_{50} 5.4) [-60mV] [449]
Sub/family-selective channel blockers	ICA-121431 (pIC_{50} 7.7) [928], Hm1a [1062] – Rat, saxitoxin (Pore blocker)	saxitoxin (Pore blocker) (pIC_{50} 8.8) [-120mV] [150] – Rat, tetrodotoxin (Pore blocker) (pIC_{50} 8) [-120mV] [150] – Rat, XPC-5462 (pIC_{50} 8) [-45mV] [463], lacosamide (Antagonist) (pIC_{50} 4.5) [-80mV] [3] – Rat	tetrodotoxin (Pore blocker) (pIC_{50} 8.4) [220], ICA-121431 (pIC_{50} 7.7) [928], saxitoxin (Pore blocker)	saxitoxin (Pore blocker) (pIC_{50} 8.4) [-100mV] [1101] – Rat, tetrodotoxin (Pore blocker) (pIC_{50} 7.6) [-120mV] [192], μ-conotoxin GIIIA (Pore blocker) (pIC_{50} 5.9) [-100mV] [192]	tetrodotoxin (Pore blocker) (pK_d 5.8) [-80mV] [260, 1597] – Rat
Functional Characteristics	Activation $V_{0.5}$ = -20 mV. Fast inactivation (τ = 0.7 ms for peak sodium current).	Activation $V_{0.5}$ = -24 mV. Fast inactivation (τ = 0.8 ms for peak sodium current).	Activation $V_{0.5}$ = -24 mV. Fast inactivation (0.8 ms)	Activation $V_{0.5}$ = -30 mV. Fast inactivation (0.6 ms)	Activation $V_{0.5}$ = -26 mV. Fast inactivation (τ = 1 ms for peak sodium current).
Comments	–	The anti-sense oligonucleotide elsunersen is designed to reduce expression of gain-of-function SCN2A, as a proposed therapy for SCN2A-driven early-onset developmental and epileptic encephalopathy (DEE) [809].	–	–	–

Nomenclature	$Na_v1.6$	$Na_v1.7$	$Na_v1.8$	$Na_v1.9$
HGNC, UniProt	*SCN8A*, Q9UQD0	*SCN9A*, Q15858	*SCN10A*, Q9Y5Y9	*SCN11A*, Q9UI33
Sub/family-selective activators	batrachotoxin, veratridine	batrachotoxin, veratridine	–	–
Channel blockers	cannabidiol (pIC_{50} 5.5) [-45mV] [449]	cannabidiol (pIC_{50} 5.5–6.7) [449, 583], cannabigerol (pIC_{50} 5.3) [-90mV] [448], amorolfine (pIC_{50} 5.2) [-80mV] [450], ANP-230 (At resting state) (pIC_{50} 5.2) [665], cannabinol (pIC_{50} 5) [-90mV] [447], cannabigerol (pIC_{50} 4.7) [-110mV] [448], cannabinol (pIC_{50} 4.5) [-100mV] [447], amorolfine (pIC_{50} 4) [-100mV] [450]	cannabidiol (pIC_{50} 5.7) [451] – Mouse, cannabigerol (pIC_{50} 5.3) [451], ANP-230 (AT resting state) (pIC_{50} 4.9) [665], cannabinol (pIC_{50} 4.8) [451] – Mouse	ANP-230 (At resting state) (pIC_{50} 5.2) [665]
Sub/family-selective channel blockers	tetrodotoxin (Pore blocker) (pIC_{50} 9) [-130mV] [321] – Rat, XPC-5462 (pIC_{50} 8) [-45mV] [463], XPC-7224 (pIC_{50} 7.1) [-45mV] [463], saxitoxin (Pore blocker)	PF-05089771 (pIC_{50} 7.5–8) [34, 642], tetrodotoxin (Pore blocker) (pIC_{50} 7.6) [-100mV] [720], PF-04856264 (pIC_{50} 7.6) [928], saxitoxin (Pore blocker) (pIC_{50} 6.2) [1458]	suzetrigine (pIC_{50} 9.6) [643, 1417], A-887826 (pIC_{50} 8) [643, 1611], VX-150 (pIC_{50} 7.8) [1417], LTGO-33 (pIC_{50} 7.5–7.6) [455, 643], PF-01247324 (Pore blocker) (pIC_{50} 6.7) [*voltage dependent*] [1089], tetrodotoxin (Pore blocker) (pIC_{50} 4.2) [-60mV] [20] – Rat	tetrodotoxin (Pore blocker) (pIC_{50} 4.4) [-120mV] [267] – Rat
Functional Characteristics	Activation $V_{0.5}$ = -29 mV. Fast inactivation (1 ms)	Activation $V_{0.5}$ = -27 mV. Fast inactivation (0.5 ms)	Activation $V_{0.5}$ = -16 mV. Inactivation (6 ms)	Activation $V_{0.5}$ = -32 mV. Slow inactivation (16 ms)
Comments	$Na_v1.6$ is the target of the potential anti-epileptic channel blocker zandatrigine (NBI-921352) [646, 809].	–	–	–

Comments: Sodium channels are also blocked by local anaesthetic agents, antiarrythmic drugs and antiepileptic drugs. In general, these drugs are not highly selective among channel subtypes. There are two clear functional fingerprints for distinguishing different subtypes. These are sensitivity to tetrodotoxin ($Na_V1.5$, $Na_V1.8$ and $Na_V1.9$ are much less sensitive to block) and rate of fast inactivation ($Na_V1.8$ and particularly $Na_V1.9$ inactivate more slowly). All sodium channels also have a slow inactivation process that is engaged during long depolarizations (>100 ms) or repetitive trains of stimuli. All sodium channel subtypes are blocked by intracellular QX-314.

Further reading on Voltage-gated sodium channels (Na_V)

Alsaloum M *et al*. (2025) Voltage-gated sodium channels in excitable cells as drug targets. *Nat Rev Drug Discov* **24**: 358-378 [PMID:39901031]

Catterall WA *et al*. (2005) International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. *Pharmacol Rev* **57**: 397-409 [PMID:16382098]

Catterall WA *et al*. (2017) The chemical basis for electrical signaling. *Nat Chem Biol* **13**: 455-463 [PMID:28406893]

Deuis JR *et al*. (2017) The pharmacology of voltage-gated sodium channel activators. *Neuropharmacology* **127**: 87-108 [PMID:28416444]

Ghovanloo MR *et al*. (2022) Cannabidiol and Sodium Channel Pharmacology: General Overview, Mechanism, and Clinical Implications. *Neuroscientist* **28**: 318-334 [PMID:34027742]

Jiang D *et al*. (2018) Structural basis for gating pore current in periodic paralysis. *Nature* **557**: 590-594 [PMID:29769724]

Kanellopoulos AH *et al*. (2016) Voltage-gated sodium channels and pain-related disorders. *Clin Sci* **130**: 2257-2265 [PMID:27815510]

Shen H *et al*. (2018) Structural basis for the modulation of voltage-gated sodium channels by animal toxins. *Science* **362**: [PMID:30049784]

Terragni B *et al*. (2018) Post-translational dysfunctions in channelopathies of the nervous system. *Neuropharmacology* **132**: 31-42 [PMID:28571716]

Waxman SG. (2023) Targeting a Peripheral Sodium Channel to Treat Pain. *N Engl J Med* **389**: 466-469 [PMID:37530829]

Comments on Voltage-gated ion channels: The voltage-dependent anion channels (VDACs) plays a key role in regulating metabolic and energetic flux across the outer mitochondrial membrane. It is involved in the transport of ATP, ADP, pyruvate, malate, and other metabolites, and thus communicates extensively with enzymes from metabolic pathways. They are a class of porin ion channel located on the outer mitochondrial membrane. VDAC1, VDAC2 and VDAC3 are involved in the regulation of apoptosis, cell metabolism, mitochondrial apoptosis, and spermatogenesis [888, 1271].
The calcium homeostasis modulator (CALHM) ion channels are apparently voltage- and extracellular Ca^{2+}-gated, and constitute a novel ion channel family that is widely expressed in the brain and taste buds throughout vertebrates and in sensory neurons and body wall muscles in *C. elegans*. In humans, the CALHM family encompasses six paralogs, some of which function as non-selective channels that are permeable to large substances such as ATP. CALHM channels are thought to play important roles in neuronal excitability, neurotransmission of tastes, and muscle cell function. The voltage- and extracellular Ca^{2+}-dependent gating mechanisms, structural features that define the gate and ion permeation pathway and additional physiological roles, remain to be discovered [881].

Other ion channels

Ion channels → Other ion channels

Overview: A number of ion channels in the human genome do not fit readily into the classification of either ligand-gated or voltage-gated ion channels. These are identified below.

Aquaporins

Ion channels → Other ion channels → Aquaporins

Overview: Aquaporins and aquaglyceroporins are membrane channels that allow the permeation of water and certain other small solutes across the cell membrane, or in the case of AQP6, AQP11 and AQP12A, intracellular membranes, such as vesicles and the endoplasmic reticulum membrane [745]. Since the isolation and cloning of the first aquaporin (AQP1) [1137], 12 additional mammalian members of the family have been identified, although little is known about the functional properties of one of these (*AQP12A*; Q8IXF9) and it is thus not tabulated. The other 12 aquaporins can be broadly divided into three families: orthodox aquaporins (AQP0,-1,-2,-4,-5, -6 and -8) permeable mainly to water, but for some additional solutes [285]; aquaglyceroporins (AQP3,-7 -9 and -10), additionally permeable to glycerol and for some isoforms urea [712], and superaquaporins (AQP11 and 12) located within cells [608]. Some aquaporins also conduct ammonia and/or H_2O_2 giving rise to the terms 'ammoniaporins' ('aquaammoniaporins') and 'peroxiporins', respectively. Aquaporins are impermeable to protons and other inorganic and organic cations, with the possible exception of AQP1, although this is controversial [712]. One or more members of this family of proteins have been found to be expressed in almost all tissues of the body [reviewed in Yang (2017) [1556]]. AQPs are involved in numerous processes that include systemic water homeostasis, adipocyte metabolism, brain oedema, cell migration and fluid secretion by epithelia. Loss of function mutations of some human AQPs, or their disruption by autoantibodies further underscore their importance [reviewed by Verkman *et al*. (2014) [1429], Kitchen *et al*. (2105) [712]]. Functional AQPs exist as homotetramers that are the water conducting units wherein individual AQP subunits (each a protomer) have six TM helices and two half helices that constitute a seventh 'pseudotransmembrane domain' that surrounds a narrow water conducting channel [745]. In addition to the four pores contributed by the protomers, an additional hydrophobic pore exists within the center of the complex [745] that may mediate the transport through AQP1. Although numerous small molecule inhibitors of aquaporins, particularly AQP1, have been reported primarily from *Xenopus* oocyte swelling assays, the activity of most has subsequently been disputed upon retesting using assays of water transport that are less prone to various artifacts [377] and they are therefore excluded from the tables [see Tradtrantip *et al*. (2017) [1400] for a review].

Nomenclature	AQP0	AQP1	AQP2	AQP3
HGNC, UniProt	*MIP*, P30301	*AQP1*, P29972	*AQP2*, P41181	*AQP3*, Q92482
Endogenous activator	AQP0 is gated by calmodulin [712]	cGMP (see comment)	–	–
Permeability	water (rat single channel permeability 0.25 x $10^{-14}cm^3s^{-1}$) (Rat) [1558]	water (rat single channel permeability 6.0 x $10^{-14}cm^3s^{-1}$), ammonia, H_2O_2 [444, 1558]	water (rat single channel permeability 3.3 x $10^{-14}cm^3s^{-1}$) [880]	water (rat single channel permeability 2.1 x $10^{-14}cm^3s^{-1}$), glycerol, ammonia, H_2O_2 [119, 444, 1558]
Inhibitors	Hg^{2+}	compound 1 (pIC_{50} 5.1) [1249], Ag^+, Hg^{2+}, pCMBS	Hg^{2+}	Auphen (pIC_{50} 6.1) [916], Audien (pIC_{50} 4.8) [916], Hg^{2+}
Channel blockers	–	5-Hydroxymethyl-2-furfural (Inhibition) (pIC_{50} 6.4) [232]	–	–
Comments	–	Permeability to H_2O_2 has been demonstrated for rat, but not human, AQP1 [119]. Numerous small molecule inhibitors of AQP1 have been proposed, but re-evaluation indicates that they have no significant effect upon water permeability at concentrations in excess of their originally reported IC_{50} values [435]. A fifth pore located at the central axis of the tetrameric complex has, controversially, been described as a cation conductance activated by cGMP and phosphorylation by protein kinases A and C. Evidence in support and against this proposal is discussed in detail by Kitchen *et al*. (2015) [712].	–	AQP3 is also inhibited by acid pH: permeability to urea is controversial [712].

Nomenclature	AQP4	AQP5
HGNC, UniProt	*AQP4*, P55087	*AQP5*, P55064
Permeability	water (rat single channel permeability 24 x $10^{-14}cm^3s^{-1}$ [1558]	water (rat single channel permeability 5.0 x $10^{-14}cm^3s^{-1}$), H_2O_2 [663]
Inhibitors	–	Hg^{2+}
Comments	AQP4 is inhibited by PKC activation (although this is probably due to phosphorylation-dependent protein localisation rather than inhibition of the channel *per se*), but not by $HgCl_2$. AQP4 is predicted to be permeable to NO [1490]. Recent work suggests that the membrane trafficking of AQP4 could be an alternative target to pore-blockers [713].	AQP5 may conduct CO_2 [444].

Nomenclature	AQP6	AQP7	AQP8	AQP9	AQP10
HGNC, UniProt	*AQP6*, Q13520	*AQP7*, O14520	*AQP8*, O94778	*AQP9*, O43315	*AQP10*, Q96PS8
Permeability	water (zero, or very low basal, permeability is enhanced by low pH and in mouse and rat by Hg^{2+}), glycerol, ammonia, urea, anions [444, 561, 712, 1159]	water (high), glycerol, ammonia, urea [444, 606]	water (mouse single channel permeability 8.2 x $10^{-14}cm^3s^{-1}$), ammonia, H_2O_2 [119, 444, 712, 880]	water (low), glycerol, ammonia, urea, H_2O_2, monocarboxylates [444, 560, 1159, 1497]	water (low), glycerol, urea [607]
Activators	Hg^{2+}	–	–	–	–
Inhibitors	–	Auphen (Effective at 15 µM), Hg^{2+}	Hg^{2+}	Hg^{2+}, phloretin	Hg^{2+}
Comments	AQP6 is an intracellular channel that localises to acid secreting intercalated cells of the renal collecting ducts. Notably, AQP6 is activated by Hg^{2+} and by low pH and is unusually permeable to anions (with the permeability sequence $NO_3^- > I^- \gg Br^- > Cl^- \gg Fl^-$) as well as water, both through the monomeric pore [712, 1159].	AQP7 also transports silicon [435].	Permeability to urea is controversial, but might be explained by differences between mouse and human caused by a pore-lining amino acid residue that differs between species [712].	AQP9 may transport silicon [435].	It is not known if AQP10 is permeable to ammonia. Permeability to silicon has been described [435].

Further reading on Aquaporins

Abir-Awan M *et al.* (2019) Inhibitors of Mammalian Aquaporin Water Channels. *Int J Mol Sci* **20**: [PMID:30934923]
Agre P. (2006) The aquaporin water channels. *Proc Am Thorac Soc* **3**: 5-13 [PMID:16493146]
Beitz E *et al.* (2015) Challenges and achievements in the therapeutic modulation of aquaporin functionality. *Pharmacol Ther* **155**: 22-35 [PMID:26277280]
Bill RM. (2024) Drugging aquaporins. *Biochim Biophys Acta Biomembr* **1866**: 184164 [PMID:37146744]
Carbrey JM *et al.* (2009) Discovery of the aquaporins and development of the field. *Handb Exp Pharmacol* 3-28 [PMID:19096770]
Geng X *et al.* (2017) Transport Characteristics of Aquaporins. *Adv Exp Med Biol* **969**: 51-62 [PMID:28258565]
Kitchen P *et al.* (2015) Beyond water homeostasis: Diverse functional roles of mammalian aquaporins. *Biochim Biophys Acta* **1850**: 2410-21 [PMID:26365508]
Tesse A *et al.* (2018) Aquaporins as Targets of Dietary Bioactive Phytocompounds. *Front Mol Biosci* **5**: 30 [PMID:29721498]
Tradtrantip L *et al.* (2017) Aquaporin-Targeted Therapeutics: State-of-the-Field. *Adv Exp Med Biol* **969**: 239-250 [PMID:28258578]
Yang B. (2017) *In Advances in Experimental Medicine and Biology* Edited by Yang B: Springer: 1-276 [ISBN: 9789402410570]

Chloride channels

Ion channels → Other ion channels → Chloride channels

Overview: Chloride channels are a functionally and structurally diverse group of anion selective channels involved in processes including the regulation of the excitability of neurones, skeletal, cardiac and smooth muscle, cell volume regulation, transepithelial salt transport, the acidification of internal and extracellular compartments, the cell cycle and apoptosis (reviewed in [354]). Excluding the transmittergated $GABA_A$ and glycine receptors (see separate tables), well characterised chloride channels can be classified as certain members of the voltage-sensitive ClC subfamily, calcium-activated channels, high (maxi) conductance channels, the cystic fibrosis transmembrane conductance regulator (CFTR) and volume regulated channels [1430]. No official recommendation exists regarding the classification of chloride channels. Functional chloride channels that have been cloned from, or characterised within, mammalian tissues are listed with the exception of several classes of intracellular channels (*e.g.* CLIC) that are reviewed by in [362].

ClC family

Ion channels → Other ion channels → Chloride channels → ClC family

Overview: The mammalian ClC family (reviewed in [10, 212, 354, 357, 632]) contains 9 members that fall, on the basis of sequence homology, into three groups; ClC-1, ClC-2, hClC-Ka (rClC-K1) and hClC-Kb (rClC-K2); ClC-3 to ClC-5, and ClC-6 and -7. ClC-1 and ClC-2 are plasma membrane chloride channels. ClC-Ka and ClC-Kb are also plasma membrane channels (largely expressed in the kidney and inner ear) when associated with barttin (*BSND*, Q8WZ55), a 320 amino acid 2TM protein [378]. The localisation of the remaining members of the ClC family is likely to be predominantly intracellular *in vivo*, although they may traffic to the plasma membrane in overexpression systems. Numerous recent reports indicate that ClC-4, ClC-5, ClC-6 and ClC-7 (and by inference ClC-3) function as Cl^-/H^+ antiporters (secondary active transport), rather than classical Cl^- channels [472, 793, 1003, 1113, 1232]; reviewed in [10, 1142]). It has recently been reported that the activity of ClC-5 as a Cl^-/H^+ exchanger is important for renal endocytosis [1034]. Alternative splicing increases the structural diversity within the ClC family. The crystal structure of two bacterial ClC proteins has been described [358] and a eukaryotic ClC transporter (CmCLC) has recently been described at 3.5 Å resolution [394]. Each ClC subunit, with a complex topology of 18 intramembrane segments, contributes a single pore to a dimeric 'double-barrelled' ClC channel that contains two independently gated pores, confirming the predictions of previous functional and structural investigations (reviewed in [212, 357, 632, 1142]). As found for ClC-4, ClC-5, ClC-6 and ClC-7, the prokaryotic ClC homologue (ClC-ec1) and CmCLC function as H^+/Cl antiporters, rather than as ion channels [9, 394]. The generation of monomers from dimeric ClC-ec1 has firmly established that each ClC subunit is a functional unit for transport and that cross-subunit interaction is not required for Cl^-/H^+ exchange in ClC transporters [1180].

Nomenclature	ClC-1	ClC-2
HGNC, UniProt	*CLCN1*, P35523	*CLCN2*, P51788
Endogenous activators	–	arachidonic acid
Activators	–	lubiprostone, omeprazole
Inhibitors	NMD670 (pEC_{50} 5.8) [1285]	–
Channel blockers	9-anthroic acid, *S*-(-)CPB, *S*-(-)CPP, Cd^{2+}, Zn^{2+}, fenofibric acid, niflumic acid	GaTx2 (pK_d 10.8) [*voltage dependent* -100mV], Cd^{2+}, NPPB, Zn^{2+}, diphenylamine-2-carboxylic acid
Functional Characteristics	γ = 1-1.5 pS; voltage-activated (depolarization) (by fast gating of single protopores and a slower common gate allowing both pores to open simultaneously); inwardly rectifying; incomplete deactivation upon repolarization, ATP binding to cytoplasmic cystathionine β-synthase related (CBS) domains inhibits ClC-1 (by closure of the common gate), depending on its redox status	γ = 2-3 pS; voltage-activated by membrane hyperpolarization by fast protopore and slow cooperative gating; channels only open negative to E_{Cl} resulting in steady-state inward rectification; voltage dependence modulated by permeant anions; activated by cell swelling, PKA, and weak extracellular acidosis; potentiated by SGK1; inhibited by phosphorylation by p34(cdc2)/cyclin B; cell surface expression and activity increased by association with Hsp90
Comments	CIC-1 is constitutively active	CIC-2 is also activated by amidation

Nomenclature	ClC-Ka	ClC-Kb	ClC-3	ClC-4
HGNC, UniProt	*CLCNKA*, P51800	*CLCNKB*, P51801	*CLCN3*, P51790	*CLCN4*, P51793
Activators	niflumic acid (pEC_{50} 3–5)	niflumic acid (pEC_{50} 3–5)	–	–
Channel blockers	3-phenyl-CPP, DIDS, niflumic acid	3-phenyl-CPP, DIDS	phloretin (pIC_{50} 4.5)	Zn^{2+} (pIC_{50} 4.3) [1063], Cd^{2+} (pIC_{50} 4.2) [1063]
Functional Characteristics	γ = 26 pS; linear current-voltage relationship except at very negative potentials; no time dependence; inhibited by extracellular protons (p*K* = 7.1); potentiated by extracellular Ca^{2+}	Bidirectional rectification; no time dependence; inhibited by extracellular protons; potentiated by extracellular Ca^{2+}	Cl^-/H^+ antiporter [923]; pronounced outward rectification; slow activation, fast deactivation; activity enhanced by CaM kinase II; inhibited by intracellular Ins(3,4,5,6)P4 and extracellular acidosis	Cl^-/H^+ antiporter ($2Cl^-:1H^+$) [30, 1113, 1232]; extreme outward rectification; voltage-dependent gating with mid-point of activation at +73 mV [1057]; rapid activation and deactivation; inhibited by extracellular acidosis; non-hydrolytic nucleotide binding required for full activity
Comments	ClC-Ka is constitutively active (when co-expressed with barttin), and can be blocked by benzofuran derivatives	ClC-Kb is constitutively active (when co-expressed with barttin), and can be blocked by benzofuran derivatives	insensitive to the channel blockers DIDS, NPPB and tamoxifen (10 μM)	–

Nomenclature	ClC-5	ClC-6	ClC-7
HGNC, UniProt	*CLCN5*, P51795	*CLCN6*, P51797	*CLCN7*, P51798
Channel blockers	–	DIDS (pIC_{50} 3)	DIDS (pIC_{50} 4.4) [1246], NS5818 (pIC_{50} 4.3) [1246], NPPB (pIC_{50} 3.8) [1246]
Functional Characteristics	Cl^-/H^+ antiporter ($2Cl^-:1H^+$) [1113, 1232, 1288, 1635]; extreme outward rectification; voltage-dependent gating with midpoint of activation of 116.0 mV; rapid activation and deactivation; potentiated and inhibited by intracellular and extracellular acidosis, respectively; ATP binding to cytoplasmic cystathionine β-synthase related (CBS) domains activates ClC-5	Cl^-/H^+ antiporter ($2Cl^-:1H^+$) [1003]; outward rectification, rapid activation and deactivation	Cl^-/H^+ antiporter ($2Cl^-:1H^+$) [472, 793, 1246]; strong outward rectification; voltage-dependent gating with a threshold more positive than ˜ + 20 mV; very slow activation and deactivation
Comments	Insensitive to the channel blockers DIDS (1 mM), diphenylamine-2-carboxylic acid (1 mM), 9-anthroic acid (2 mM), NPPB (0.5 mM) and niflumic acid (1 mM)	–	active when co-expressed with Ostm1

Comments: ClC channels display the permeability sequence $Cl^- > Br^- > I^-$ (at physiological pH). ClC-1 has significant opening probability at resting membrane potential, accounting for 75% of the membrane conductance at rest in skeletal muscle, and is important for stabilization of the membrane potential. *S*-(-)CPP, 9-anthroic acid and niflumic acid act intracellularly and exhibit a strongly voltage-dependent block with strong inhibition at negative voltages and relief of block at depolarized potentials ([818] and reviewed in [1141]). Inhibition of ClC-2 by the peptide GaTx2, from *Leiurus quinquestriatus herbareus* venom, is likely to occur through inhibition of channel gating, rather than direct open channel blockade [1383]. Although ClC-2 can be activated by cell swelling, it does not correspond to the VRAC channel (see below). Alternative potential physiological functions for ClC-2 are reviewed in [1126]. Functional expression of human ClC-Ka and ClC-Kb requires the presence of barttin [378, 1239] reviewed in [384]. The properties of ClC-Ka/barttin and ClC-Kb/barttin tabulated are those observed in mammalian expression systems: in oocytes the channels display time- and voltage-dependent gating. The rodent homologue (ClC-K1) of ClC-Ka demonstrates limited expression as a homomer, but its function is enhanced by barttin which increases both channel opening probablility in the physiological range of potentials [378, 404, 1239] reviewed in [384]). ClC-Ka is approximately 5 to 6-fold more sensitive to block by 3-phenyl-CPP and DIDS than ClC-Kb, while newly synthesized benzofuran derivatives showed the same blocking affinity (<10 μM) on both CLC-K isoforms [819]. The biophysical and pharmacological properties of ClC-3, and the relationship of the protein to the endogenous volume-regulated anion channel(s) VRAC [31, 486] are controversial and further complicated by the

possibility that ClC-3 may function as both a Cl^-/H^+ exchanger and an ion channel [31, 1113, 1485]. The functional properties tabulated are those most consistent with the close structural relationship between ClC-3, ClC-4 and ClC-5. Activation of heterologously expressed ClC-3 by cell swelling in response to hypotonic solutions is disputed, as are many other aspects of its regulation. Dependent upon the predominant extracellular anion (*e.g.* SCN^- versus Cl^-), CIC-4 can operate in two transport modes: a slippage mode in which behaves as an ion channel and an exchanger mode in which unitary transport rate is 10-fold lower [30]. Similar findings have been made for ClC-5 [1595]. ClC-7 associates with a β subunit, Ostm1, which increases the stability of the former [770] and is essential for its function [793].

CFTR

Ion channels → Other ion channels → Chloride channels → CFTR

Overview: CFTR is a member of the ABC transporter superfamily, but, uniquely, it is an ion channel, allowing electrodiffusion of Cl^- and HCO_3^-. It is activated by phosphorylation, mainly by PKA on its regulatory domain (R domain). Conserved nucleotide binding domains (NBD1 and NBD2) couple ATP binding and hydrolysis to gate opening and closing, respectively [262]. CFTR is expressed apically in polarized epithelial cells in various organs where it controls volume and pH of fluid secretions as well as mucin unfolding and release [904]. CFTR transcripts are present in secretory and ionocyte cells in airway epithelia [1048, 1130], crypt enterocytes, goblet and CFTR-high expressing cells in the intestine [113, 180], pancreatic duct cells [397], intra- and extra-hepatic cholangiocytes 33318612 [1432] and others.

Mutations in the CFTR gene cause the genetic disease cystic fibrosis (CF) [1272]. The most common mutation, F508del, is present in at least one gene copy in ˜80% of patients worldwide, but there are ˜1000 different variants known to cause CF. Mutations affect CFTR biogenesis (folding, maturation, trafficking, metabolic stability) and/or ion-channel function. Vertex Pharmaceuticals developed small-molecule CFTR modulator drugs that improve biogenesis (“correctors”) or open probability (“potentiators”) of defective CFTR variants. Triple combination therapies, including two correctors and one potentiator (*e.g.* Trikafta®: elexacaftor, tezacaftor, ivacaftor), are standard of care for patients carrying at least one copy of the F508del variant. Patients carrying mutations only affecting ion-channel function (“gating mutations” *e.g.* G551D) are treated with ivacaftor (potentiator) alone. Cryo-EM structures of Trikafta-bound F508del-E1371Q-CFTR reveal that all three compounds bind at the protein-membrane interface, in shallow pockets on CFTR’s surface [401].

While low/absent CFTR activity causes CF, over-activation of CFTR (due to bacterial toxins such as cholera toxin) results in secretory diarrhoeas, causing large intestinal loss of fluid and alkali [288]. No inhibitors have been approved yet for emergency treatment of secretory diarrhoeas.

Nomenclature	CFTR
HGNC, UniProt	*CFTR*, P13569
Activators	ivacaftor (Potentiation) (pEC_{50} 9.3) [261], ivacaftor (Potentiation) (pEC_{50} 8.5) [496], elexacaftor (Correction) (pEC_{50} 6.4–7.2) [4, 689], GLPG1837 (Potentiation) (pEC_{50} 6.6) [1569], deutivacaftor (Potentiation) (pEC_{50} 6.6) [515], tezacaftor (Correction) (pEC_{50} 6.6) [1194], felodipine (Potentiation) (pEC_{50} 5.7) [1093], vanzacaftor (Correction) [688]
Inhibitors	(R)-BPO-27 (pIC_{50} 8.4) [1297], $CFTR_{inh}$ -172 (pIC_{50} 7.1) [425], GaTx1 (pIC_{50} 7) [419]
Channel blockers	GlyH-101 (Pore blocker) (pIC_{50} 5.4) [*voltage dependent*] [979], glibenclamide (Pore blocker) (pK_i 4.7) [*voltage dependent*] [1266]
Functional Characteristics	γ = 6-9 pS; permeability ratio sequence: $SCN^- > NO_3^- > Br^- > Cl^- > I^- >$ formate$^-$ $> F^-$; conductance ratio sequence: $Cl^- > NO_3^- > Br^-$ ˜ formate$^-$ $> SCN^- > I^-$. Slight outward rectification, only observed in intact cells, is probably due to cytosolic anions resulting in voltage-dependent channel block [835]. Activated by binding of and phosphorylation by PKA [948]. Opening of the channel gate follows ATP binding at two nucleotide binding domains (NBD1 and NBD2), and formation of an intramolecular NBD1/NBD2 tight dimer [1428]; closing is coupled to ATP hydrolysis and dimer dissociation [263]. Positively regulated by PKC [197] and PKGII (in enterocytes) [1250, 1416].
Comments	UCCF-339, UCCF-029, apigenin and genistein are examples of flavones. UCCF-853 and NS004 are examples of benzimidazolones. CBIQ is an example of a benzoquinoline. Felodipine and nimodipine are examples of 1,4-dihydropyridines. Phenylglycine-01 is an example of a phenylglycine. Sulfonamide-01 is an example of a sulfonamide. Malonic acid hydrazide conjugates are also CFTR channel blockers (see Verkman and Galietta, 2009 [1430])

Comments: Cystic fibrosis mouse models have been useful in studies of the intestinal symptoms of CF (*e.g.* [1361]). However, they do not develop severe lung symptoms typically observed in humans with CF [487]. CF pigs [1319] exhibit respiratory defects and mucus accumulation similar to humans [1311]. More recently, several ferret (*Mustela putorius furo*) CF models have also been developed, by providing *in utero* treatment with CFTR modulators to reduce mortality in the foetal and neonatal period [380, 1339].

Further reading on CFTR

Fiedorczuk K *et al*. (2022) Mechanism of CFTR correction by type I folding correctors. *Cell* **185**: 158-168.e11 [PMID:34995514]

Levring J *et al*. (2023) CFTR function, pathology and pharmacology at single-molecule resolution. *Nature* **616**: 606-614 [PMID:36949202]

Calcium activated chloride channel (CaCC)

Ion channels → Other ion channels → Chloride channels → Calcium activated chloride channel (CaCC)

Overview: Chloride channels activated by intracellular Ca^{2+} (CaCC) are widely expressed in excitable and non-excitable cells where they perform diverse functions [519]. CaCCs are activated by a rise in intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$), typically following activation of G_q protein coupled receptors (G_q-PCR). This section centres on CaCC channels encoded by the TMEM16A gene (HUGO gene nomenclature: Anoctamin 1). The TMEM16 family consists of 10 paralogs (TMEM16A-K; Anoctamin 1-10). The TMEM16A and TMEM16B genes (*ANO1* and *ANO2*) encode for CaCCs, while the other members function as lipid scramblases or have combined scramblase and non-selective ion channel function [13, 395, 522, 1116, 1242]. TMEM16A has a broad tissue distribution and a variety of established cellular roles, while the main physiological role for TMEM16B identified thus far is in olfaction [319, 776]. Alternative splicing regulates the voltage- and Ca^{2+}-dependence of TMEM16A and such post-transcriptional process may be tissue-specific and contribute to functional diversity [399]. TMEM16A is a potential drug target for a variety of conditions spanning from respiratory to vascular (see "Comments" section for further detail).

Nomenclature	CaCC
HGNC, UniProt	*ANO1*, Q5XXA6
Endogenous activators	intracellular Ca^{2+}
Activators	PAM_16A (pEC_{50} 8.4) [21], E_{act} [1431]
Endogenous inhibitors	Ins(3,4,5,6)P_4
Inhibitors	MONNA (pIC_{50} 7.1) [130, 1042, 1407], T16Ainh-A01 (pIC_{50}~6) [130, 1114], crofelemer (pIC_{50} 5.2) [1401], 9-anthroic acid, CaCCinh-A01 [130, 289], DCDPC, DIDS, NPPB, SITS, flufenamic acid, fluoxetine, mibefradil, niflumic acid, tannic acid
Selective inhibitors	TM_{inh} -23 (pIC_{50} 7.5) [1407], Ani9 (pIC_{50} 7) [1253]
Functional Characteristics	γ = 0.5-5 pS; permeability sequence, $SCN^- > NO_3^- > I^- > Br^- > Cl^- > F^-$; relative permeability of $SCN^-:Cl^-$ ~8. $I^-:Cl^-$ ~3, aspartate:Cl^- ~0.15, outward rectification (decreased by increasing $[Ca^{2+}]_i$); sensitivity to activation by $[Ca^{2+}]_i$ decreased at hyperpolarized potentials; slow activation at positive potentials (accelerated by increasing $[Ca^{2+}]_i$); rapid deactivation at negative potentials, deactivation kinetics modulated by anions binding to an external site; modulated by redox status
Comments	TMEM16A has been reported to regulate a wide variety of physiological processes ranging from sensory transduction to smooth muscle contraction and epithelial secretion [582]. A CaCC (TMEM16A) potentiator compound (GDC-6988/ETD002, undisclosed structure; acquired by Roche from Enterprise Therapeutics) entered Phase 1 clinical evaluation as a novel approach that has potential to provide benefit to all patients with cystic fibrosis (mentioned in [1120]). Up-regulating chloride transport *via* CaCC is proposed to mitigate the effect of loss of chloride transport *via* CFTR in CF. See Enterprise Therapeutics' reports of CaCC potentiator ETX001 for more detailed background information [273, 278].

Comments: **Therapeutic indications:** TMEM16A regulates a wide variety of physiological processes ranging from nociception to smooth muscle contraction and epithelial secretion [582]. In airway epithelial cells, TMEM16A expression is enhanced by inflammatory stimuli that also lead to goblet cell metaplasia and increased mucus secretion. Thus, pharmacological modulation of TMEM16A could help to improve mucociliary clearance in cystic fibrosis (CF) and chronic obstructive respiratory disease [274, 421]. TMEM16A activation might also be of potential therapeutic benefit in Sjögren's syndrome. Given the established role of TMEM16A role in smooth muscle and cerebral pericyte contraction, pharmacological inhibitors of TMEM16A are expected to promote vasodilation and could have therapeutic use in a range of diseases of altered vessel tone including stoke, hypertension and vascular dementia [23, 440]. Other suggested therapeutic indications in which TMEM16A could be targeted include neuropathic pain, given the identified role of TMEM16A in dorsal root ganglion (DRG) neurons [838]. TMEM16A is also expressed in interstitial cells of Cajal and may be involved in the control of gastric emptying and motility [243]; thus, TMEM16A modulators could be used to modulate gastric contractility. TMEM16A was also reported in the smooth muscle of the bladder, uterus, and internal urethral sphincter; therefore, TMEM16A modulators could have a role in the treatment of overactive bladder and urinary incontinence [391] and to

foster myometrium relaxation [1525]. TMEM16A is overexpressed in a variety of cancer types and TMEM16A inhibitors have been suggested as a potential anticancer treatment [580, 1151].

Pharmacology: A CaCC (TMEM16A) activator compound (GDC-6988/ETD002, undisclosed structure; acquired by Roche from Enterprise Therapeutics) entered Phase 1 clinical evaluation as a novel approach that has potential to provide benefit to all patients with cystic fibrosis (CF) (mentioned in [1120]). Upregulating chloride transport *via* CaCC is proposed to mitigate the effect of loss of Cl- transport *via* CFTR in CF. See Enterprise Therapeutics' reports of CaCC potentiator ETX001 for more detailed background information [273, 278]. The compound Eact has been reported to directly activate TMEM16A [1431]. However, recent data have challenged this direct activation of TMEM16A and indicate that Eact induces an increase in $[Ca^{2+}]_i$ through an agonist effect on TRPV1 and TRPV4 [438, 845]. Many of the listed TMEM16A channel blockers are recognised as being unselective [22, 130, 439]. Ani9 demonstrates selectivity for TMEM16A versus TMEM16B [1253] and, in contrast to several of the other inhibitors, (i) has no effects on intracellular Ca^{2+} signalling in human airway epithelial cells [276] and (ii) does not affect a range of other ion current types [22]. Ani9 possess an imine/hydrazone group that might render the compound unstable and potentially reactive *in vivo*. TMinh-23 is one the most potent TMEM16A inhibitors reported thus far (IC_{50} ~30 nM) [244, 1407]. However, the selectivity of this compound is not fully defined, and the compound might be metabolically unstable *in vivo* due to potential hydrolysis of one or both amide groups present in this molecule. TMEM16A is inhibited by the therapeutic drugs tamsulosin (IC_{50} ~ 7 µM) [810]. The anthelminthic niclosamide was also reported to inhibit TMEM16A [959], but further studies demonstrated that niclosamide can act both as an inhibitor or an activator depending on the membrane potential and $[Ca^{2+}]_i$ [276, 687, 816]. A range of natural compounds including gallotannins [997], evodiamine and rutecarpine [1614], theaflavin [1268] and allicin [67] are non-selective, low potency TMEM16A inhibitors. CaCC currents in CFPAC-1 have also been reported to be inhibited by Ins(3,4,5,6)P4 [553]. Complex effects on native CaCC and cloned TMEM16A and TMEM16B currents have been observed for a range of compounds including extracellular niflumic acid; DCDPC and 9-anthroic acid (but not DIDS) enhancing and inhibiting inwardly and outwardly directed currents in a manner dependent upon $[Ca^{2+}]_i$ and membrane potential [226, 1121, 1209, 1353] (and [777] for summary). Blockade of CaCC currents by niflumic acid, DIDS and 9-anthroic acid is voltage-dependent, whereas block by NPPB is voltage-independent [519]. Considerable crossover in pharmacology with large conductance Ca^{2+}-activated K^+ channels also exists (see [473] for overview).

Maxi chloride channel

Ion channels → Other ion channels → Chloride channels → Maxi chloride channel

Overview: Maxi Cl- channels are high conductance, anion selective, channels initially characterised in skeletal muscle and subsequently found in many cell types including neurones, glia, cardiac muscle, lymphocytes, secreting and absorbing epithelia, macula densa cells of the kidney and human placenta syncytiotrophoblasts [1208]. The physiological significance of the maxi Cl- channel is uncertain, but roles in cell volume regulation and apoptosis have been claimed. Evidence suggests a role for maxi Cl- channels as a conductive pathway in the swelling-induced release of ATP from mouse mammary C127i cells that may be important for autocrine and paracrine signalling by purines [355, 1207]. A similar channel mediates ATP release from macula densa cells within the thick ascending of the loop of Henle in response to changes in luminal NaCl concentration [106]. A family of human high conductance Cl- channels (TTYH1-3) that resemble Maxi Cl- channels has been cloned [1346], but alternatively, Maxi Cl- channels have also been suggested to correspond to the voltage-dependent anion channel, VDAC, expressed at the plasma membrane [65, 1044].

Nomenclature	Maxi Cl-
Activators	cytosolic GTPγS, extracellular chlorpromazine, extracellular tamoxifen, extracellular toremifene, extracellular triflupromazine
Endogenous channel blockers	intracellular arachidonic acid
Channel blockers	DIDS (pIC_{50} 4.4) [1246], extracellular Zn^{2+} (pIC_{50} 4.3) [1063], NPPB (pIC_{50} 3.8) [1246], extracellular Gd^{3+}, SITS, diphenylamine-2-carboxylic acid
Functional Characteristics	γ = 280-430 pS (main state); permeability sequence, I > Br > Cl > F > gluconate (P_{Cl} P_{Cl} = ~1.5); ATP is a voltage dependent permeant blocker of single channel activity (P_{ATP} /P_{Cl} = 0.08-0.1); channel activity increased by patch-excision; channel opening probability (at steady-state) maximal within approximately ± 20 mV of 0 mV, opening probability decreased at more negative and (commonly) positive potentials yielding a bell-shaped curve; channel conductance and opening probability regulated by annexin 6
Comments	Maxi Cl- is also activated by G protein-coupled receptors and cell swelling. Tamoxifen and toremifene are examples of triphenylethylene anti-oestrogens

Comments: Differing ionic conditions may contribute to variable estimates of γ reported in the literature. Inhibition by arachidonic acid (and cis-unsaturated fatty acids) is voltage-independent, occurs at an intracellular site, and involves both channel shut down (K_d = 4-5 µM) and a reduction of γ (K_d = 13-14 µM). Blockade of channel activity by SITS, DIDS, Gd^{3+} and arachidonic acid is paralleled by decreased swelling-induced release of ATP [355, 1207]. Channel activation by anti-oestrogens in whole cell recordings requires the presence of intracellular nucleotides and is prevented by pre-treatment with 17β-estradiol, bucladesine, or intracellular dialysis with GDPβS [318]. Activation by tamoxifen is suppressed by low concentrations of okadaic acid, suggesting that a dephosphorylation event by protein phosphatase PP2A occurs in the activation pathway [318]. In contrast, 17β-estradiol and tamoxifen appear to directly inhibit the maxi Cl- channel of human placenta reconstituted into giant liposomes and recorded in excised patches [1178].

Volume regulated chloride channels (VRAC)

Ion channels → Other ion channels → Chloride channels → Volume regulated chloride channels (VRAC)

Overview: Volume activated chloride channels (also termed VSOAC, volume-sensitive organic osmolyte/anion channel; VRC, volume regulated channel and VSOR, volume expansion-sensing outwardly rectifying anion channel) participate in regulatory volume decrease (RVD) in response to cell swelling. VRAC may also be important for several other processes including the regulation of membrane excitability, transcellular Cl^- transport, angiogenesis, cell proliferation, necrosis, apoptosis, glutamate release from astrocytes, insulin (*INS*, P01308) release from pancreatic β cells and resistance to the anti-cancer drug, cisplatin (reviewed by [111, 981, 1017, 1046]). VRAC may not be a single entity, but may instead represent a number of different channels that are expressed to a variable extent in different tissues and are differentially activated by cell swelling. In addition to ClC-3 expression products (see above) several former VRAC candidates including *MDR1* (ABCB1 P-glycoprotein), Icln, Band 3 anion exchanger and phospholemman are also no longer considered likely to fulfil this function (see reviews [1017, 1224]).

Nomenclature	VRAC
Activators	GTPγS
Endogenous channel blockers	intracellular Mg^{2+}, arachidonic acid
Channel blockers	1,9-dideoxyforskolin, 9-anthroic acid, DCPIB, DIDS, IAA-94, NPPB, NS3728, carbenoxolone, clomiphene, diBA-(5)-C4, gossypol, mefloquine, mibefradil, nafoxidine, nordihydroguiaretic acid, quinidine, quinine, tamoxifen
Functional Characteristics	γ = 10-20 pS (negative potentials), 50-90 pS (positive potentials); permeability sequence SCN > I > NO_3^- >Br^- > Cl^- > F^- > gluconate; outward rectification due to voltage dependence of γ; inactivates at positive potentials in many, but not all, cell types; time dependent inactivation at positive potentials; intracellular ionic strength modulates sensitivity to cell swelling and rate of channel activation; rate of swelling-induced activation is modulated by intracellular ATP concentration; ATP dependence is independent of hydrolysis and modulated by rate of cell swelling; inhibited by increased intracellular free Mg^{2+} concentration; swelling induced activation of several intracellular signalling cascades may be permissive of, but not essential to, the activation of VRAC including: the Rho-Rho kinase-MLCK; Ras-Raf-MEK-ERK; PIK3-NOX-H_2O_2 and Src-PLCγ-Ca^{2+} pathways; regulation by PKCα required for optimal activity; cholesterol depletion enhances activity; activated by direct stretch of β1-integrin
Comments	VRAC is also activated by cell swelling and low intracellular ionic strength. VRAC is also blocked by chromones, extracellular nucleotides and nucleoside analogues

Comments: In addition to conducting monovalent anions, in many cell types the activation of VRAC by a hypotonic stimulus can allow the efflux of organic osmolytes such as amino acids and polyols that may contribute to RVD.

Comments on Chloride channels: Other chloride channels

In addition to some intracellular chloride channels that are not considered here, plasma membrane channels other than those listed have been functionally described. Many cells and tissues contain outwardly rectifying chloride channels (ORCC) that may correspond to VRAC active under isotonic conditions. A cyclic AMP-activated Cl^- channel that does not correspond to CFTR has been described in intestinal Paneth cells [1408]. A Cl channel activated by cyclic GMP with a dependence on raised intracellular Ca^{2+} has been recorded in various vascular smooth muscle cells types, which has a pharmacology and biophysical characteristics very different from the 'conventional' CaCC [920, 1122]. It has been proposed that bestrophin-3 (*BEST3*, Q8N1M1) is an essential component of the cyclic GMP-activated channel [921]. A proton-activated, outwardly rectifying anion channel has also been described [767].

The chloride intracellular channel proteins (CLICs) are non-canonical ion channels with six homologs, distinct from most ion channels in that they have both soluble and integral membrane forms. The physiological role of CLICs appears to be maintenance of intracellular membranes, which is associated with tubulogenesis but may involve other substructures [493].

Further reading on Chloride channels

Adkins GB *et al.* (2015) Potential role of cardiac chloride channels and transporters as novel therapeutic targets. *Pharmacol Ther* **145**: 67-75 [PMID:25160469]

Huang F *et al.* (2012) International Union of Basic and Clinical Pharmacology. LXXXV: calcium-activated chloride channels. *Pharmacol Rev* **64**: 1-15 [PMID:22090471]

Kamaleddin MA. (2018) Molecular, biophysical, and pharmacological properties of calcium-activated chloride channels. *J Cell Physiol* **233**: 787-798 [PMID:28121009]
Kunzelmann K. (2015) TMEM16, LRRC8A, bestrophin: chloride channels controlled by Ca(2+) and cell volume. *Trends Biochem Sci* **40**: 535-43 [PMID:26254230]
Pedersen SF *et al*. (2016) Biophysics and Physiology of the Volume-Regulated Anion Channel (VRAC)/Volume-Sensitive Outwardly Rectifying Anion Channel (VSOR). *Pflugers Arch* **468**: 371-83 [PMID:26739710]
Peretti M *et al*. (2015) Chloride channels in cancer: Focus on chloride intracellular channel 1 and 4 (CLIC1 AND CLIC4) proteins in tumor development and as novel therapeutic targets. *Biochim Biophys Acta***1848**: 2523-31 [PMID:25546839]
Sabirov RZ *et al*. (2016) The properties, functions, and pathophysiology of maxi-anion channels. *Pflugers Arch* **468**: 405-20 [PMID:26733413]
Zegarra-Moran O *et al*. (2017) CFTR pharmacology. *Cell Mol Life Sci* **74**: 117-128 [PMID:27704174]

Connexins and Pannexins

Ion channels → Other ion channels → Connexins and Pannexins

Overview: Gap junctions are essential for many physiological processes including cardiac and smooth muscle contraction, regulation of neuronal excitability and epithelial electrolyte transport [161, 255, 381]. Gap junction channels allow the passive diffusion of molecules of up to 1,000 Daltons which can include nutrients, metabolites and second messengers (such as IP_3) as well as cations and anions. 21 connexin genes and 3 pannexin genes which are structurally related to the invertebrate innexin genes, code for gap junction proteins in humans. Each connexin gap junction comprises 2 hemichannels or 'connexons' which are themselves formed from 6 connexin molecules. The various connexins have been observed to combine into both homomeric and heteromeric combinations, each of which may exhibit different functional properties. It is also suggested that individual hemichannels formed by a number of different connexins might be functional in at least some cells [537]. Connexins have a common topology, with four α-helical transmembrane domains, two extracellular loops, a cytoplasmic loop, and N- and C-termini located on the cytoplasmic membrane face. In mice, the most abundant connexins in electrical synapses in the brain seem to be Cx36, Cx45 and Cx57 [1300]. Mutations in connexin genes are associated with the occurrence of a number of pathologies, such as peripheral neuropathies, cardiovascular diseases and hereditary deafness. The pannexin genes Px1 and Px2 are widely expressed in the mammalian brain [1442]. Like the connexins, at least some of the pannexins can form hemichannels [161, 1099].

Nomenclature	Cx23	Cx25	Cx26	Cx30	Cx30.2	Cx30.3	Cx31
HGNC, UniProt	*GJE1*, A6NN92	*GJB7*, Q6PEY0	*GJB2*, P29033	*GJB6*, O95452	*GJC3*, Q8NFK1	*GJB4*, Q9NTQ9	*GJB3*, O75712
Endogenous inhibitors	extracellular Ca^{2+} (blocked by raising external Ca^{2+})						
Inhibitors	carbenoxolone, flufenamic acid, octanol						

Nomenclature	Cx31.1	Cx31.9	Cx32	Cx36	Cx37	Cx40	Cx40.1
HGNC, UniProt	*GJB5*, O95377	*GJD3*, Q8N144	*GJB1*, P08034	*GJD2*, Q9UKL4	*GJA4*, P35212	*GJA5*, P36382	*GJD4*, Q96KN9
Endogenous inhibitors	extracellular Ca^{2+} (blocked by raising external Ca^{2+})						
Inhibitors	carbenoxolone, flufenamic acid, octanol						

Nomenclature	Cx43	Cx45	Cx46	Cx47	Cx50	Cx59	Cx62
HGNC, UniProt	*GJA1*, P17302	*GJC1*, P36383	*GJA3*, Q9Y6H8	*GJC2*, Q5T442	*GJA8*, P48165	*GJA9*, P57773	*GJA10*, Q969M2
Endogenous inhibitors	extracellular Ca^{2+} (blocked by raising external Ca^{2+})						
Inhibitors	carbenoxolone, flufenamic acid, octanol						

Nomenclature	Px1	Px2	Px3
HGNC, UniProt	*PANX1*, Q96RD7	*PANX2*, Q96RD6	*PANX3*, Q96QZ0
Inhibitors	EG-2184 (pIC_{50} 7.3) [761], carbenoxolone, flufenamic acid (little block by flufenamic acid)	carbenoxolone, flufenamic acid (little block by flufenamic acid)	carbenoxolone, flufenamic acid (little block by flufenamic acid)
Comments	Electrophysiological studies demonstrate that endogenously expressed hPx1 forms intercellular channels with distinct voltage-dependent properties [1068]. Channel function is unaffected by raising external Ca^{2+}.	Unaffected by raising external Ca^{2+}	Unaffected by raising external Ca^{2+}

Comments: Connexins are most commonly named according to their molecular weights, so, for example, Cx23 is the connexin protein of 23 kDa. This can cause confusion when comparing between species- for example, the mouse connexin Cx57 is orthologous to the human connexin Cx62. No natural toxin or specific inhibitor of junctional channels has been identified yet however two compounds often used experimentally to block connexins are carbenoxolone and flufenamic acid [1216]. At least some pannexin hemichannels are more sensitive to carbenoxolone than connexins but much less sensitive to flufenamic acid [160]. It has been suggested that 2-aminoethoxydiphenyl borate (2-APB) may be a more effective blocker of some connexin channel subtypes (Cx26, Cx30, Cx36, Cx40, Cx45, Cx50) compared to others (Cx32, Cx43, Cx46, [66]).

Further reading on Connexins and Pannexins

Decrock E *et al*. (2015) Connexin and pannexin signaling pathways, an architectural blueprint for CNS physiology and pathology? *Cell Mol Life Sci* **72**: 2823-51 [PMID:26118660]

Esseltine JL *et al*. (2016) Next-Generation Connexin and Pannexin Cell Biology. *Trends Cell Biol* **26**: 944-955 [PMID:27339936]

Freund-Michel V *et al*. (2016) Expression and role of connexin-based gap junctions in pulmonary inflammatory diseases. *Pharmacol Ther* **164**: 105-19 [PMID:27126473]

Harris AL. (2018) Electrical coupling and its channels. *J Gen Physiol* **150**: 1606-1639 [PMID:30389716]

Navis KE *et al*. (2020) Pannexin 1 Channels as a Therapeutic Target: Structure, Inhibition, and Outlook. *ACS Chem Neurosci* **11**: 2163-2172 [PMID:32639715]

Palacios-Prado N *et al*. (2022) Endogenous pannexin1 channels form functional intercellular cell-cell channels with characteristic voltage-dependent properties. *Proc Natl Acad Sci U S A* **119**: e2202104119 [PMID:35486697]

Sáez JC *et al*. (2015) Regulation of pannexin and connexin channels and their functional role in skeletal muscles. *Cell Mol Life Sci* **72**: 2929-35 [PMID:26084874]

Willebrords J *et al*. (2017) Inhibitors of connexin and pannexin channels as potential therapeutics. *Pharmacol Ther* **180**: 144-160 [PMID:28720428]

Piezo channels

Ion channels → Other ion channels → Piezo channels

Overview: PIEZO proteins are the pore-forming subunits of trimeric ion channels that open rapidly in response to mechanical stimuli such as membrane stretch, allowing positively charged ions such as the calcium ion to flow into the cell to change cellular structure and function. The proteins are eukaryotic, not prokaryotic, and lack sequence or structural homology to other proteins. There are two main types: In humans, there is PIEZO1 of 2521 amino acids and PIEZO2 of 2752 amino acids, which can form homomeric PIEZO1 and PIEZO2 channels. Membrane stretching causes complex changes in the channels that include a reduced inward curvature, an expansion of the N-terminal transmembrane helical units and an opening of the central ion pore region comprising the last two C-terminal helices. When there is sustained membrane stretching, the channels may adapt by inactivating at various rates depending on the cell type and context. There are many roles of the channels in diverse organ systems including cardiovascular, gastrointestinal, haematological, hepatobiliary, immune, integumental, musculoskeletal, neuronal, reproductive, respiratory and urinary systems as well as adipose tissue and cancers. The expression and functions of PIEZO1 are broad and diverse across many cell types and organs, whereas PIEZO2 is more restricted.

Nomenclature	Piezo1	Piezo2
HGNC, UniProt	*PIEZO1*, Q92508	*PIEZO2*, Q9H5I5
Endogenous modulators	Cholesterol, 7-ketocholesterol, phosphatidylserine, phosphatidylinositol 4,5-bisphosphate, ceramide, docosahexaenoic acid, eicosapentaenoic acid, margaric acid, protons, amyloid beta (1-40) peptide	Phosphatidic acid, palmitoyl lysophosphatidic acid
Physical activators	Membrane stretch, cell indentation, fluid shear stress, cell traction force, substrate stiffening	Cell indentation
Selective activators	Yoda2b (pEC_{50} 6.9) [867] – Mouse, Yoda2 (pEC_{50} 6.8) [1081], Yaddle1 (pEC_{50} 6.4) [464], Yoda1 (pEC_{50} 4.6) [1349], Jedi1 (pEC_{50} 3.8) [1487] – Mouse, Jedi2 (pEC_{50} 3.8) [1487] – Mouse	–
Inhibitors	salvianolic acid B (pIC_{50} 5.9) [1070], Dooku1 (pIC_{50} 5.9) [379], Dooku1 (pIC_{50} 5.8) [379], escin (pIC_{50} 5.8) [1488], GsMTx-4 (pIC_{50} 5.4) [64], benzbromarone (pIC_{50} 5.4) [817], Gd^{3+} (@ 30 μM) [256], propofol (@ 50 μM) [1581], ruthenium red (@ 30 μM) [256]	GsMTx-4 (pIC_{50} 5.3) [29], Gd^{3+} (@ 30μM) [256], propofol (@ 50 μM) [1581], ruthenium red (@ 30 μM) [256]
Functional Characteristics	Activation and deactivation, a few milliseconds; Inactivation, time constant 15 ms at -80 mV ranging to seconds or minutes and slower at positive voltages; Unitary conductance, 29 pS; Ion selectivity, monovalent and divalent cations (PCa/PCs 1.21) - Mouse (Mm).	Activation and deactivation, a few milliseconds; Inactivation, time constant 7 ms at -80 mV and slower at positive voltages; Unitary conductance, 24 pS; Ion selectivity, monovalent and divalent cations (PCa/PCs 1.34) - Mouse (Mm).
Comments	No small molecule or toxin binding sites are confirmed on the channel, although an interaction site for Yoda1 has been suggested. The evidence for selective activation is greatest for Yoda1 [379, 1480], but none of the activators is guaranteed to be selective and the selectivity achieved will likely depend on the concentration of the activator and the biological context in which it is administered. Yoda1 has low aqueous solubility, which may be a factor behind the range of pEC_{50}s observed for it [1081]. Analogues such as Yoda2 have better aqueous solubility. Yoda1, Yoda2, Yoda2b, Yaddle1 and Dooku1 are chemically related molecules (Yoda1 analogues). OB-1 is thought to inhibit the channels *via* stomatin like 3 (*STOML3*; Q8TAV4), with its effect taking up to 3 hours to occur [1509].	No small molecule or toxin binding sites are confirmed on the channel.

Further reading on Piezo channels

Cheng CW *et al*. (2025) *PIEZO1* variant implications for biological understanding and human health. *Open Biol* **15**: 240345 [PMID:40628291]
Coste B *et al*. (2010) Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. *Science* **330**: 55-60 [PMID:20813920]
Douguet D *et al*. (2019) Mammalian Mechanoelectrical Transduction: Structure and Function of Force-Gated Ion Channels. *Cell* **179**: 340-354 [PMID:31585078]
Guo YR *et al*. (2017) Structure-based membrane dome mechanism for Piezo mechanosensitivity. *Elife* **6**: [PMID:29231809]
Kinsella JA *et al*. (2024) Pharmacology of PIEZO1 channels. *Br J Pharmacol* **181**: 4714-4732 [PMID:39402010]
Mulhall EM *et al*. (2023) Direct observation of the conformational states of PIEZO1. *Nature* **620**: 1117-1125 [PMID:37587339]
Smith KA *et al*. (2025) Regulation of PIEZO1 channel force sensitivity by interblade handshaking. *Sci Adv* **11**: eadt7046 [PMID:40512861]
Wang L *et al*. (2019) Structure and mechanogating of the mammalian tactile channel PIEZO2. *Nature***573**: 225-229 [PMID:31435011]
Xiao B. (2024) Mechanisms of mechanotransduction and physiological roles of PIEZO channels. *Nat Rev Mol Cell Biol* **25**: 886-903 [PMID:39251883]
Yang X *et al*. (2022) Structure deformation and curvature sensing of PIEZO1 in lipid membranes. *Nature***604**: 377-383 [PMID:35388220]
Zhou Z *et al*. (2023) Mechanisms of PIEZO Channel Inactivation. *Int J Mol Sci* **24**: [PMID:37762415]

Sodium leak channel, non-selective (NALCN)

Ion channels → Other ion channels → Sodium leak channel, non-selective (NALCN)

Overview: The sodium leak channel, non selective (NALCN) is a member of the family of four-domain voltage-gated cation channels that include voltage-gated sodium (Na_V) and calcium (Ca_V) channels [781, 1582]. It possesses distinctive ion selectivity and pharmacological properties compared to these latter ion channels [235, 1415]. NALCN, which is insensitive to tetrodotoxin (10 µM), has been proposed to mediate the tetrodotoxin-resistant and voltage-insensitive Na^+ leak current (I_L-Na) observed in many types of neurone [861]. However, whether NALCN is constitutively active has been challenged [139, 363, 1348]. NALCN is widely distributed within the central nervous system and is also expressed in the heart and pancreas specifically, in rodents, within the islets of Langerhans [781, 861]. There is now strong functional and structural evidence indicating that NALCN forms a channelosome with obligatory auxiliary subunits UNC79, UNC80 and FAM155A (also known as NALF1) [141, 235, 671, 753, 1624]. NALCN is the pore-forming α subunit, UNC79 and UNC80 are massive HEAT-repeat proteins that form an intertwined anti-parallel superhelical assembly that docks intracellularly onto NALCN. FAM155A forms an extracellular dome that shields extracellular access pathways to the selective filter of NALCN. There is also increasing evidence suggesting that the NALCN-UNC79-UNC80-FAM155A channelosome is modulated by additional auxiliary subunits including G proteins [1112] and neuronal SNARE complex proteins [1415]. However, there remain many areas of uncertainty surrounding NALCN function.
It is worth noting that there is currently no NALCN-specific pharmacology. Inhibitors include multivalent cations (Gd^{3+}, Ca^{2+}, Mg^{2+}, Ba^{2+}, Zn^{2+}) and small molecules (verapamil, 2-APB, DPBA, fluvastatin, L-703,606) [235, 501, 752, 1241].

Nomenclature	NALCN
HGNC, UniProt	*NALCN*, Q8IZF0
Activators	Constitutively active (Lu *et al*., 2007), or activated downstream of Src family tyrosine kinases (SFKs) (Lu *et al*.,2009; Swayne *et al*., 2009) [235, 861, 862, 863, 1348]
Channel blockers	Gd^{3+} (pIC_{50} 5.6), Ca^{2+} (pIC_{50} 3.9) [235], Cd^{2+} (pIC_{50} 3.8), Co^{2+} (pIC_{50} 3.6), verapamil (pIC_{50} 3.4)
Functional Characteristics	γ = 27 pS [753], P_{Na}/P_{Cs} = 2.5, P_{Na}/P_{Li} = 1.0, P_{Na}/P_K = 1.7 [235], activation $V_{1/2}$ of around +60 mV [1415]

Comments: It has been previously suggested that NALCN function is modulated by different signaling molecules/proteins including NK1, neurotensin, M3R, G proteins, Src tyrosine kinases and CaSR [862, 862, 862, 863, 1348, 1348, 1469]. There is an expansive body of evidence indicating that NALCN forms a complex with UNC79, UNC80 and FAM155 [969]. Clinical reports indicate that NALCN variants cause severe neurodevelopmental disorders including CLIFAHDD (congenital contractures of the limbs and face, hypotonia, and developmental delay), and IHPRF1 (infantile hypotonia with psychomotor retardation and characteristic facies-1) and -2 [24, 230, 657].

Further reading on Sodium leak channel, non-selective (NALCN)

Lu TZ *et al.* (2012) NALCN: a regulator of pacemaker activity. *Mol Neurobiol* **45**: 415-23 [PMID:22476981]

Monteil A *et al.* (2024) New insights into the physiology and pathophysiology of the atypical sodium leak channel NALCN. *Physiol Rev* **104**: 399-472 [PMID:37615954]

Philippart F *et al.* (2018) $G_{i/o}$ protein-coupled receptors in dopamine neurons inhibit the sodium leak channel NALCN. *Elife* **7**: [PMID:30556810]

Orai channels

Ion channels → Other ion channels → Store-operated ion channels → Orai channels

Overview: Orai channels are pore forming proteins which underlie calcium release-activated calcium (CRAC) channels. In numerous cell types, calcium influx is predominantly governed by store-operated calcium channels (SOCs). The process of store-operated calcium entry (SOCE) is orchestrated through the concerted interaction of two essential molecular components: the pore-forming Orai proteins (Orai1-3) and the endoplasmic reticulum calcium-sensing stromal interaction molecules (STIM1 and STIM2) [1196].

Nomenclature	Orai1	Orai2	Orai3
HGNC, UniProt	*ORAI1*, Q96D31	*ORAI2*, Q96SN7	*ORAI3*, Q9BRQ5
Selective channel blockers	zegocractin (pIC_{50} 6.9) [157, 1425], JPIII [89], compound 4k [821]	–	–
Comments	*ORAI1* is the gene that encodes the prototypical CRAC store-operated Ca^{2+} entry (SOCE) channel. CRAC channels are activated by depletion of Ca^{2+} in the endoplasmic reticulum that results from antigen-induced activation of a range of immunoreceptors (including TCRs, BCRs, Fcγ and Fcε receptors, chemokine GPCRs and some innate pattern-recognition receptors). A constitutively active Orai1 G98S mutant has been identified in patients with tubular aggregate myopathy.	–	–

Comments: The pathophysiological effect of functional CRAC channel deficiency can be caused by loss-of-function mutations in *ORAI1* or STIM molecules. Such CRAC channelopathies are characterised by impaired immune cell function and have been identified as an underlying cause of primary immunodeficiency with predominant features that resemble severe combined immunodeficiency disease.
ORAI1 and ORAI2 proteins form heteromeric complexes that constitute the pore of Ca^{2+} release-activated Ca^{2+} (CRAC) channels. Mice with double *Orai1/Orai2* knockout have severely impaired T cell function.
NCT04195347 is a phase I/II trial evaluating CM4620 (Auxora™), a CRAC channel inhibitor, for treating asparaginase-associated pancreatitis in pediatric and young adult leukemia/lymphoma patients. The study focuses on determining CM4620's safety, tolerability, and optimal dosing, while exploring its ability to prevent severe complications such as pancreatic necrosis, pseudocyst formation, and SIRS. Administered intravenously over four days soon after symptom onset, CM4620 is being tested as a targeted approach to limit calcium overload-driven pancreatic injury and inflammation, with results expected after 2026 [157].

Further reading on Orai channels

Lewis RS. (2020) Store-Operated Calcium Channels: From Function to Structure and Back Again. *Cold Spring Harb Perspect Biol* **12**: [PMID:31570335]

Rubaiy HN. (2023) ORAI Calcium Channels: Regulation, Function, Pharmacology, and Therapeutic Targets. *Pharmaceuticals (Basel)* **16**: [PMID:37259313]

References

1. Abbott GW. (2020) [32655402]
2. Abbott GW *et al.* (2024) [39390220]
3. Abdelsayed M *et al.* (2013) [24065921]
4. Abela AR *et al.* (2018) Patent number: WO2018107100A1.
5. Abi-Dargham A *et al.* (1993) [8419547]
6. Abiria SA *et al.* (2017) [28696294]
7. Abramowitz J *et al.* (2009) [18940894]
8. Abrams CJ *et al.* (1996) [8799888]
9. Accardi A *et al.* (2004) [14985752]
10. Accardi A *et al.* (2010) [20188062]
11. Acker BA *et al.* (2008) [18490160]
12. Adams ME *et al.* (1993) [8232218]
13. Agostinelli E *et al.* (2022) [35163502]
14. Ahern GP. (2003) [12761211]
15. Ahrens J *et al.* (2009) [19204413]
16. Ai C *et al.* (2023) [36696767]
17. Aierken A *et al.* (2021) [34658162]
18. Akbulut Y *et al.* (2015) [25707820]
19. Akopian AN *et al.* (2000) [10923674]
20. Akopian AN *et al.* (1996) [8538791]
21. Al-Hosni R *et al.* (2025) *BJP*
22. Al-Hosni R *et al.* (2025) [39829151]
23. Al-Hosni R *et al.* (2022) [35811176]
24. Al-Sayed MD *et al.* (2013) [24075186]
25. Alagem N *et al.* (2001) [11454958]
26. Alarcón-Alarcón D *et al.* (2022) [36272975]
27. Albaugh PA *et al.* (2002) [12408715]
28. Albuquerque EX *et al.* (2009) [19126755]
29. Alcaino C *et al.* (2017) [28085630]
30. Alekov AK *et al.* (2009) [19364886]
31. Alekov AK *et al.* (2008) [19036336]
32. Alexander SP *et al.* (2015) [26650442]
33. Alexander SP *et al.* (2017) [29055039]
34. Alexandrou AJ *et al.* (2016) [27050761]
35. Altomare C *et al.* (2003) [12702747]
36. Ambudkar IS *et al.* (2007) [17486362]
37. Anand D *et al.* (2022) [35276025]
38. Anand P *et al.* (2020) [32452762]
39. Anderson DJ *et al.* (2008) [17959745]
40. Andersson DA *et al.* (2004) [15190109]
41. Andersson DA *et al.* (2008) [18322093]
42. Andersson DA *et al.* (2009) [19416844]
43. André E *et al.* (2008) [18568077]
44. Andrews MD *et al.* (2015) [25893043]
45. Andrey F *et al.* (2005) [16085050]
46. Antunes FTT *et al.* (2024) [38342359]
47. Appendino G *et al.* (2005) [15356216]
48. Araud T *et al.* (2010) [20346921]
49. Arcas JM *et al.* (2019) [30545944]
50. Arif Pavel M *et al.* (2016) [27071085]
51. Asakawa M *et al.* (2006) [16858425]
52. Asano S *et al.* (2012) [22580348]
53. AstraZeneca. astrazeneca.com. Accessed on 12/09/2014.
54. Atack JR. (2008) [18482097]
55. Atack JR. (2010) [21309116]
56. Atlason PT *et al.* (2010) [20837679]
57. Atobe M *et al.* (2019) [30629441]
58. Auberson YP *et al.* (2002) [11909726]
59. Auer-Grumbach M *et al.* (2010) [20037588]
60. Babinski K *et al.* (2000) [10842183]
61. Babinski K *et al.* (1999) [9886053]
62. Baconguis I *et al.* (2014) [24507937]
63. Badheka D *et al.* (2017) [28829742]
64. Bae C *et al.* (2011) [21696149]
65. Bahamonde MI *et al.* (2003) [12794078]
66. Bai D *et al.* (2006) [16985167]
67. Bai X *et al.* (2023) [36574498]
68. Bai Y *et al.* (2020) [32149605]
69. Bai Z *et al.* (2021) [34928937]
70. Bal M *et al.* (2008) [18786918]
71. Balestrini A *et al.* (2021) [33620419]
72. Bandell M *et al.* (2004) [15046718]
73. Bang S *et al.* (2007) [17850966]
74. Bang-Andersen B *et al.* (2011) [21486038]
75. Baraldi PG *et al.* (2010) [20356305]
76. Barbet G *et al.* (2008) [18758465]
77. Barel O *et al.* (2008) [18678320]
78. Barfod ET *et al.* (2001) [11245600]
79. Barnard EA *et al.* (1998) [9647870]
80. Barnes NM *et al.* (2009) [18761359]
81. Baron A *et al.* (2013) [23624383]
82. Baron A *et al.* (2015) [25613302]
83. Baron A *et al.* (2001) [11457851]
84. Baron A *et al.* (2008) [18256271]
85. Barrera NP *et al.* (2005) [16116092]
86. Barrere C *et al.* (2020) *Archives of Cardiovascular Diseases Supplements* **12**: 259
87. Barret DCA *et al.* (2022) [34969975]
88. Bartok A *et al.* (2014) [24878374]
89. Bartoli F *et al.* (2020) [31906693]
90. Baukrowitz T *et al.* (1998) [9804555]
91. Baumann L *et al.* (2004) [14744918]
92. Bautista DM *et al.* (2006) [16564016]
93. Bautista DM *et al.* (2005) [16103371]
94. Bautista DM *et al.* (2007) [17538622]
95. Bavencoffe A *et al.* (2017) [28900918]
96. Beck A *et al.* (2006) [16585058]
97. Becker V *et al.* (2021) [33655414]
98. Beckmann H *et al.* (2017) [28807145]
99. Beech DJ. (2012) [21624095]
100. Beech DJ. (2013) [23412755]
101. Behrendt HJ *et al.* (2004) [14757700]
102. Beigi RD *et al.* (2003) [14522842]
103. Belelli D *et al.* (1995) [8848005]
104. Belelli D *et al.* (2009) [19828786]
105. Belelli D *et al.* (2005) [15959466]
106. Bell PD *et al.* (2003) [12655045]
107. Belrose JC *et al.* (2018) [29671419]
108. Bentzen BH *et al.* (2020) [32477117]
109. Bentzen BH *et al.* (2007) [17636045]
110. Bessac BF *et al.* (2008) [18398506]
111. Best L *et al.* (2010) [21099297]
112. Bettini E *et al.* (2010) [20810618]
113. Beumer J *et al.* (2021) [32958874]
114. Bezençon O *et al.* (2017) [29116786]
115. Bhattacharjee A *et al.* (2003) [14684870]
116. Bhattacharya A *et al.* (2013) [23889535]
117. Bianchi BR *et al.* (2007) [17660385]
118. Bianchi MT *et al.* (2003) [14645489]
119. Bienert GP *et al.* (2014) [24060746]
120. Birnbaumer L. (2009) [19281310]
121. Bitner RS *et al.* (2007) [17898229]
122. Biton B *et al.* (2012) [22171093]
123. Bize V *et al.* (2007) [17670907]
124. Blanc E *et al.* (1998) [9730813]
125. Blanchard MG *et al.* (2012) [21943094]
126. Blin S *et al.* (2016) [27035965]
127. Blin S *et al.* (2014) [25148687]
128. Blum CA *et al.* (2010) [20307063]
129. Bodnar AL *et al.* (2005) [15715459]
130. Boedtkjer DM *et al.* (2015) [26013995]
131. Bogdanović R *et al.* (2012) [21956615]
132. Boggula VR *et al.* (2018) [29885352]
133. Bohannon BM *et al.* (2020) [32207683]
134. Bohlen CJ *et al.* (2011) [22094702]
135. Bohlen CJ *et al.* (2010) [20510930]
136. Bon RS *et al.* (2013) [23763262]
137. Bon RS *et al.* (2022) [34499525]
138. Bonin RP *et al.* (2008) [18201756]
139. Boone AN *et al.* (2014) [24945283]
140. BoSmith RE *et al.* (1993) [7693281]
141. Bouasse M *et al.* (2019) [31409833]
142. Bourinet E *et al.* (1999) [10321243]
143. Bourque CW. (2008) [18509340]
144. Bowen CV *et al.* (2013) [23554944]
145. Bowie D. (2010) [19822544]
146. Boyer R *et al.* (2025) [40427633]
147. Brady CA *et al.* (2001) [11489465]
148. Brams M *et al.* (2020) [31990273]
149. Brenker C *et al.* (2012) [22354039]
150. Bricelj VM *et al.* (2005) [15815630]
151. Broad LM *et al.* (2006) [16738207]
152. Broertjes J *et al.* (2019) [30615643]
153. Brône B *et al.* (2008) [18501939]
154. Brooks CA *et al.* (2019) [31532662]
155. Brooks CA *et al.* (2019) [31413810]
156. Brown N *et al.* (2002) [12145096]
157. Bruen C *et al.* (2021) [33939666]
158. Brunner FS *et al.* (2017) [28320947]
159. Brüss M *et al.* (2000) [11111833]
160. Bruzzone R *et al.* (2005) [15715654]
161. Bruzzone R *et al.* (2003) [14597722]
162. Bucchi A *et al.* (2002) [12084770]
163. Buell G *et al.* (1996) [8598206]
164. Buisson B *et al.* (1996) [8987816]
165. Buta A *et al.* (2015) [25974655]
166. Butterworth MB *et al.* (2008) [18713729]
167. Cabanas H *et al.* (2018) [30134818]
168. Cadiou H *et al.* (2007) [18045919]
169. Cai W *et al.* (2024) [38467901]
170. Calcraft PJ *et al.* (2009) [19387438]
171. Canessa CM *et al.* (1994) [7810611]
172. Canessa CM *et al.* (1994) [8107805]
173. Cang C *et al.* (2014) [25256615]
174. Cang C *et al.* (2014) [24776928]
175. Cang C *et al.* (2013) [23394946]
176. Cantrell BE *et al.* (1996) [8809152]
177. Cao E *et al.* (2013) [24305161]
178. Capasso M *et al.* (2011) [20961760]
179. Capogna M *et al.* (2011) [21145601]
180. Carlos Dos Reis D *et al.* (2023) [36967909]
181. Carlson AE *et al.* (2009) [19718436]
182. Carlson AE *et al.* (2005) [16036917]
183. Carstens E *et al.* (2014) [24830011]
184. Castle NA *et al.* (2003) [12527813]
185. Catterall WA *et al.* (2005) [16382098]
186. Catterall WA *et al.* (2020) [31537174]
187. Catterall WA *et al.* (1981) [6114956]
188. Catterall WA *et al.* (2005) [16382099]
189. Cavara NA *et al.* (2008) [18654865]

190. Cazals Y *et al.* (2015) [26549439]
191. Celie PH *et al.* (2004) [15046723]
192. Chahine M *et al.* (1994) [8058462]
193. Chai H *et al.* (2019) [30620187]
194. Chang SS *et al.* (1996) [8589714]
195. Changeux JP. (2010) [20055696]
196. Changeux JP *et al.* (2008) [18262468]
197. Chappe V *et al.* (2003) [12588899]
198. Chassagnon IR *et al.* (2017) [28320941]
199. Chatterton JE *et al.* (2002) [11823786]
200. Chaudhari SS *et al.* (2013) [24055075]
201. Chaumont S *et al.* (2008) [18689682]
202. Chaves G *et al.* (2016) [26866814]
203. Chavez-Noriega LE *et al.* (1997) [8996215]
204. Chazot PL *et al.* (1998) [9721050]
205. Chebib M. (2004) [15566397]
206. Chen CC *et al.* (2017) [28732201]
207. Chen CC *et al.* (1998) [9707631]
208. Chen CC *et al.* (2014) [25119295]
209. Chen J *et al.* (2011) [21402443]
210. Chen PE *et al.* (2008) [17962328]
211. Chen PE *et al.* (2006) [16474411]
212. Chen TY. (2005) [15709979]
213. Chen TY *et al.* (1993) [7682292]
214. Chen X *et al.* (2005) [15955877]
215. Chen X *et al.* (2006) [16505147]
216. Chen X *et al.* (2010) [20114056]
217. Chen X *et al.* (2020) [32872338]
218. Chen XZ *et al.* (1999) [10517637]
219. Chen Y *et al.* (2003) [12871651]
220. Chen YH *et al.* (2000) [11122339]
221. Chen Z *et al.* (2023) [36973510]
222. Chen ZW *et al.* (2007) [17083446]
223. Cheng KT *et al.* (2011) [21290310]
224. Cheng KT *et al.* (2013) [23890115]
225. Cheng YR *et al.* (2018) [29793480]
226. Cherian OL *et al.* (2015) [25620774]
227. Cherny VV *et al.* (1999) [10578017]
228. Chien YC *et al.* (2025) [40264173]
229. Choe H *et al.* (2000) [10736307]
230. Chong JX *et al.* (2015) [25683120]
231. Chopra B *et al.* (2000) [10780999]
232. Chow PH *et al.* (2020) [32434851]
233. Chu XP *et al.* (2006) [16707785]
234. Chu XP *et al.* (2004) [15470133]
235. Chua HC *et al.* (2020) [32494638]
236. Chuang RS *et al.* (1998) [10196582]
237. Chung JJ *et al.* (2011) [21224844]
238. Chung JJ *et al.* (2014) [24813608]
239. Chung MK *et al.* (2005) [15722340]
240. Chung MK *et al.* (2004) [15175387]
241. Chung S *et al.* (2022) [34817438]
242. Church TW *et al.* (2015) [25421315]
243. Cil O *et al.* (2019) [31299174]
244. Cil O *et al.* (2021) [33836171]
245. Clapham DE. (2003) [14654832]
246. Clapham DE *et al.* (2005) [16382101]
247. Clapham DE *et al.* (2003) [14657417]
248. Coe JW *et al.* (2005) [16171993]
249. Colburn RW *et al.* (2007) [17481392]
250. Coleman N *et al.* (2014) [24958817]
251. Coleman SK *et al.* (1999) [10428084]
252. Collier DM *et al.* (2011) [21149458]
253. Collingridge GL *et al.* (2009) [18655795]
254. Compan V *et al.* (2012) [22442090]
255. Connors BW *et al.* (2004) [15217338]
256. Coste B *et al.* (2010) [20813920]
257. Cottrell GS *et al.* (2018) [30181139]
258. Crack BE *et al.* (1994) [7889301]
259. Crest M *et al.* (1992) [1730708]
260. Cribbs LL *et al.* (1990) [2175715]
261. Csanády L *et al.* (2019) [31205003]
262. Csanády L *et al.* (2019) [30516439]
263. Csanády L *et al.* (2010) [19966305]
264. Cuajungco MP *et al.* (2016) [26336837]
265. Cull-Candy S *et al.* (2006) [16713244]
266. Cull-Candy SG *et al.* (2004) [15494561]
267. Cummins TR *et al.* (1999) [10594087]
268. Curcic S *et al.* (2019) [30974125]
269. Czirják G *et al.* (2002) [11733509]
270. Díaz-Franulic I *et al.* (2020) [32747539]
271. Dai L *et al.* (2010) [20176855]
272. Dai XQ *et al.* (2007) [17804601]
273. Danahay H *et al.* (2020) [32821878]
274. Danahay H *et al.* (2020) [32235608]
275. Danahay H *et al.* (2025) [39561495]
276. Danahay H *et al.* (2023) [36950016]
277. Danahay H *et al.* (2025) [38851923]
278. Danahay HL *et al.* (2020) [31898911]
279. Daniel C *et al.* (2009) [19909284]
280. Das P *et al.* (2003) [14625088]
281. Dascal N *et al.* (1993) [8234283]
282. Davenport AJ *et al.* (2021) [34615939]
283. Davies PA *et al.* (1999) [9950429]
284. Davies PA *et al.* (2003) [12381728]
285. Day RE *et al.* (2014) [24090884]
286. De Clercq K *et al.* (2021) [33884443]
287. de Groot T *et al.* (2008) [18596722]
288. de Jonge HR *et al.* (2020) [33113586]
289. De La Fuente R *et al.* (2008) [18083779]
290. de Weille JR *et al.* (1998) [9744806]
291. de Weille JR *et al.* (1991) [1848702]
292. DeCaen PG *et al.* (2016) [27348301]
293. Decher N *et al.* (2011) [21865850]
294. DeCoursey TE. (2008) [18463791]
295. DeCoursey TE. (2008) [18801839]
296. Decoursey TE. (2003) [12663866]
297. DeCoursey TE. (2017) [29023793]
298. DeCoursey TE. (2010) [20134026]
299. DeCoursey TE *et al.* (2000) [10823889]
300. DeCoursey TE *et al.* (2003) [12673252]
301. Deeb TZ *et al.* (2009) [19131665]
302. del Camino D *et al.* (2010) [21068322]
303. Del Lungo M *et al.* (2012) [22091830]
304. Delaunay A *et al.* (2012) [22829666]
305. Dellisanti CD *et al.* (2007) [17643119]
306. Delmas P. (2005) [15889307]
307. Delmas P *et al.* (2004) [14766803]
308. Delmas P *et al.* (2004) [15336986]
309. Dembla S *et al.* (2017) [28826482]
310. Demir R *et al.* (2009) [19307742]
311. Deng HX *et al.* (2010) [20037587]
312. Deval E *et al.* (2015) [25724084]
313. Deval E *et al.* (2011) [21508231]
314. Deval E *et al.* (2008) [18923424]
315. Dhaka A *et al.* (2007) [17481391]
316. Di Virgilio F. (2003) [14522840]
317. Di Virgilio F *et al.* (2018) [29439897]
318. Diaz M *et al.* (2001) [11579158]
319. Dibattista M *et al.* (2024) [38677213]
320. Dietrich A *et al.* (2014) [25268281]
321. Dietrich PS *et al.* (1998) [9603190]
322. DiFrancesco D. (1993) [7682045]
323. Diness JG *et al.* (2017) [29018164]
324. Ding M *et al.* (2018) [29859875]
325. Dinklo T *et al.* (2011) [21084390]
326. Diochot S *et al.* (2004) [15044953]
327. Diochot S *et al.* (2012) [23034652]
328. Diochot S *et al.* (2007) [17113616]
329. Diochot S *et al.* (1998) [9506974]
330. Do HQ *et al.* (2023) [37026993]
331. Doñate-Macian P *et al.* (2022) [32959389]
332. Dogruer D *et al.* (2004) [14698195]
333. Dong XP *et al.* (2008) [18794901]
334. Dong XP *et al.* (2010) [20802798]
335. Donier E *et al.* (2008) [18662336]
336. Donnelly-Roberts DL *et al.* (2007) [17471177]
337. Donnelly-Roberts DL *et al.* (2004) [14634045]
338. Donnelly-Roberts DL *et al.* (2009) [19558545]
339. Döring F *et al.* (1998) [9786970]
340. Doyle DA *et al.* (1998) [9525859]
341. Dravid SM *et al.* (2007) [17303642]
342. Dryer SE *et al.* (1991) [1719422]
343. Du J *et al.* (2015) [26344198]
344. Du J *et al.* (2014) [24889629]
345. Du J *et al.* (2009) [19372375]
346. Dubé GR *et al.* (2005) [16061325]
347. Dubin AE *et al.* (1999) [10521471]
348. Duc C *et al.* (1994) [7806569]
349. Dudev T *et al.* (2015) [25955978]
350. Dumani A *et al.* (2025) [40635742]
351. Dunlop J *et al.* (2008) [18356919]
352. Duprat F *et al.* (2000) [10779373]
353. Dupuis DS *et al.* (2002) [11890900]
354. Duran C *et al.* (2010) [19827947]
355. Dutta AK *et al.* (2002) [12154180]
356. Dutta Banik D *et al.* (2018) [29311301]
357. Dutzler R. (2007) [17452037]
358. Dutzler R *et al.* (2002) [11796999]
359. Edelheit O *et al.* (2014) [24571549]
360. Edman S *et al.* (2012) [22579927]
361. Edwards E *et al.* (1996) [8891244]
362. Edwards JC *et al.* (2010) [20100480]
363. Egan JM *et al.* (2018) [29892559]
364. Eichler SA *et al.* (2008) [19210758]
365. El Chemaly A *et al.* (2010) [20026664]
366. El Kouhen R *et al.* (2005) [15837819]
367. Emir TLR. (2017) *In Neurobiology of TRP Channels (2nd Ed.)* Edited by Emir TLR: CRC Press/Taylor & Francis: [PMID:29356469]
368. Enuka Y *et al.* (2012) [22207244]
369. Er SY *et al.* (2017) [28327374]
370. Erreger K *et al.* (2004) [15701057]
371. Erreger K *et al.* (2007) [17622578]
372. Ertel EA *et al.* (2000) [10774722]
373. Esarte Palomero O *et al.* (2023) [36763973]
374. Escalera J *et al.* (2008) [18550530]
375. Escoubas P *et al.* (2000) [10829030]
376. Esteban JA. (2008) [18026130]
377. Esteva-Font C *et al.* (2016) [26993802]
378. Estévez R *et al.* (2001) [11734858]
379. Evans EL *et al.* (2018) [29498036]
380. Evans IA *et al.* (2024) [38646935]
381. Evans WH *et al.* (2002) [12126230]
382. Everaerts W *et al.* (2010) [20956320]
383. Fabjan J *et al.* (2020) [33519364]
384. Fahlke C *et al.* (2010) [21423394]

385. Fan J *et al.* (2023) [36302896]
386. Fanger CM *et al.* (2001) [11278890]
387. Fantoni ER *et al.* (2017) [28374288]
388. Farrant M *et al.* (2005) [15738957]
389. Fecher-Trost C *et al.* (2014) [24756713]
390. Fedida D *et al.* (1993) [8508531]
391. Fedigan S *et al.* (2017) [28733893]
392. Felix JP *et al.* (1999) [10213593]
393. Feng B *et al.* (2004) [14718249]
394. Feng L *et al.* (2010) [20929736]
395. Feng Z *et al.* (2024) [38749289]
396. Ferber M *et al.* (2004) [15208025]
397. Fernández Á *et al.* (2024) [38908487]
398. Ferrari D *et al.* (2004) [15383600]
399. Ferrera L *et al.* (2009) [19819874]
400. Fesenko EE *et al.* (1985) [2578616]
401. Fiedorczuk K *et al.* (2022) [36264792]
402. Fink M *et al.* (1998) [9628867]
403. Finol-Urdaneta RK *et al.* (2023) [37260417]
404. Fischer M *et al.* (2010) [20538786]
405. Fisher JL. (2009) [18585399]
406. Fisher JL. (2002) [12021393]
407. Flannery RJ *et al.* (2015) [26290373]
408. Fleig A *et al.* (2004) [15530641]
409. Fliegert R *et al.* (2017) [28671679]
410. Fonfria E *et al.* (2004) [15302683]
411. Ford AP *et al.* (2006) [16465177]
412. Fouda MA *et al.* (2022) [35436004]
413. Francois A *et al.* (2013) [23257507]
414. Freichel M *et al.* (2005) [15975974]
415. Friese MA *et al.* (2007) [17994101]
416. Frizelle PA *et al.* (2006) [16778008]
417. Frølund B *et al.* (2002) [12171573]
418. Fucile S *et al.* (2000) [11144365]
419. Fuller MD *et al.* (2007) [17951250]
420. Furukawa H *et al.* (2005) [16281028]
421. Galietta LJV. (2022) [35364521]
422. Galvez A *et al.* (1990) [1694175]
423. Gao L *et al.* (2000) [10920015]
424. Gao P *et al.* (2020) [31735085]
425. Gao X *et al.* (2024) [39107303]
426. Gao YY *et al.* (2021) [33763843]
427. Garceau D *et al.* (2019) [30902655]
428. Garcia ML *et al.* (1995) [7543240]
429. García-Añoveros J *et al.* (1997) [9037075]
430. García-Añoveros J *et al.* (2007) [17217068]
431. Garcia-Calvo M *et al.* (1993) [8360176]
432. Garcia-Valdes J *et al.* (2001) [11576530]
433. Garg P *et al.* (2012) [22851714]
434. Gargett CE *et al.* (1997) [9113369]
435. Garneau AP *et al.* (2015) [26313002]
436. Gaunt HJ *et al.* (2016) [27289383]
437. Gavva NR *et al.* (2005) [15615864]
438. Genovese M *et al.* (2019) [31622498]
439. Genovese M *et al.* (2023) [36444690]
440. Genovese M *et al.* (2024) [38788257]
441. Gentzsch M *et al.* (2020) [33201937]
442. Gerndt S *et al.* (2020) [32167471]
443. Gerstner A *et al.* (2000) [10662822]
444. Geyer RR *et al.* (2013) [23485707]
445. Ghanshani S *et al.* (2000) [10961988]
446. Ghovanloo MR *et al.* (2021) [33836525]
447. Ghovanloo MR *et al.* (2024) [38263462]
448. Ghovanloo MR *et al.* (2022) [35297036]
449. Ghovanloo MR *et al.* (2018) [30219789]
450. Ghovanloo MR *et al.* (2025) [40090585]
451. Ghovanloo MR *et al.* (2025) [39835903]
452. Giamarchi A *et al.* (2006) [16880824]
453. Giangiacomo KM *et al.* (1998) [9758866]
454. Gielen M *et al.* (2009) [19404260]
455. Gilchrist JM *et al.* (2024) [38195157]
456. Gill JK *et al.* (2011) [21436053]
457. Giraldez T *et al.* (2012) [22573384]
458. Gochman A *et al.* (2023) [36747846]
459. Goldin AL *et al.* (2000) [11144347]
460. Goldstein SA *et al.* (2005) [16382106]
461. Gonzales EB *et al.* (2009) [19641589]
462. Gonzalez C *et al.* (2010) [20023639]
463. Goodchild SJ *et al.* (2024) [38359277]
464. Goon S *et al.* (2024) [38716967]
465. Gordon JC *et al.* (2010) [20674564]
466. Gornati D *et al.* (2021) [34097384]
467. Gotti C *et al.* (2009) [19481063]
468. Gotti C *et al.* (2006) [16876883]
469. Gründer S *et al.* (2023) [36479972]
470. Grace MS *et al.* (2014) [24286227]
471. Grand T *et al.* (2008) [18297105]
472. Graves AR *et al.* (2008) [18449189]
473. Greenwood IA *et al.* (2007) [17150263]
474. Griffin AM *et al.* (2021) [33859800]
475. Grimm C *et al.* (2007) [18048323]
476. Grimm C *et al.* (2014) [25144390]
477. Grimm C *et al.* (2012) [22753890]
478. Grimm C *et al.* (2010) [20189104]
479. Grimm C *et al.* (2003) [12672799]
480. Grimm C *et al.* (2005) [15550678]
481. Grissmer S *et al.* (1994) [7517498]
482. Gründer S. (2020) *In The Oxford Handbook of Neuronal Ion Channels* Oxford University Press:
483. Gründer S *et al.* (2000) [10852210]
484. Gründer S *et al.* (2015) [25585135]
485. Grupe A *et al.* (1990) [2347305]
486. Guan YY *et al.* (2006) [16697056]
487. Guilbault C *et al.* (2007) [16888286]
488. Guinamard R *et al.* (2011) [21290294]
489. Guler AD *et al.* (2002) [12151520]
490. Gunthorpe MJ *et al.* (2009) [19063991]
491. Gunthorpe MJ *et al.* (2007) [17392405]
492. Gunthorpe MJ *et al.* (2004) [14654105]
493. Gururaja Rao S *et al.* (2018) [30040212]
494. Gutman GA *et al.* (2005) [16382104]
495. Ha K *et al.* (2020) [33164752]
496. Hadida S *et al.* (2014) [25441013]
497. Hadingham KL *et al.* (1996) [8632757]
498. Hadingham KL *et al.* (1995) [8719414]
499. Hadley JK *et al.* (2000) [10711337]
500. Häfner S *et al.* (2018) [29522264]
501. Hahn S *et al.* (2020) [32436268]
502. Halaszovich CR *et al.* (2000) [10970899]
503. Haloi N *et al.* (2025) [40215320]
504. Han Q *et al.* (2018) [30033153]
505. Han Y *et al.* (2021) [33501656]
506. Hanna MC *et al.* (2000) [10854267]
507. Hansen KB *et al.* (2012) [22553026]
508. Hansen KB *et al.* (2021) [34753794]
509. Hanukoglu A. (1991) [1939532]
510. Hanukoglu A *et al.* (2008) [18634878]
511. Hanukoglu A *et al.* (2018) [29702750]
512. Hanukoglu I *et al.* (2017) [28130590]
513. Hanukoglu I *et al.* (2016) [26772908]
514. Hara Y *et al.* (2002) [11804595]
515. Harbeson SL *et al.* (2017) [28611092]
516. Harding SD *et al.* (2018) [29149325]
517. Harteneck C. (2005) [15843919]
518. Harteneck C *et al.* (2011) [20932261]
519. Hartzell C *et al.* (2005) [15709976]
520. Hattori M *et al.* (2012) [22535247]
521. Hauser TA *et al.* (2009) [19482012]
522. Hawn MB *et al.* (2021) [34488544]
523. He LP *et al.* (2005) [15647288]
524. He Y *et al.* (2006) [16478442]
525. Heckel A *et al.* (2017) Patent number: WO2017028927A1.
526. Heitzmann D *et al.* (2008) [18034154]
527. Hejazi N *et al.* (2006) [16332990]
528. Held K *et al.* (2022) [32780479]
529. Held K *et al.* (2015) [25733887]
530. Hemmings HC *et al.* (2005) [16126282]
531. Henderson LM *et al.* (1987) [2825632]
532. Henson MA *et al.* (2010) [20097255]
533. Herd MB *et al.* (2007) [17531325]
534. Hernandez-Olmos V *et al.* (2012) [23075067]
535. Herrington J *et al.* (2011) [21948463]
536. Herrington J *et al.* (2006) [16567526]
537. Hervé JC *et al.* (2007) [17507078]
538. Hibbs RE *et al.* (2011) [21572436]
539. Higham J *et al.* (2019) [31048549]
540. Hildebrand MS *et al.* (2010) [20648059]
541. Hilf RJ *et al.* (2009) [19646860]
542. Hilgemann DW *et al.* (1996) [8688080]
543. Hill K *et al.* (2004) [15275834]
544. Hill K *et al.* (2004) [15549272]
545. Hille B. (1986) [2452140]
546. Hillyard DR *et al.* (1992) [1352986]
547. Hinman A *et al.* (2006) [17164327]
548. Hirata T *et al.* (2007) [17652911]
549. Hirzel K *et al.* (2006) [17114051]
550. Ho IHT *et al.* (2025) [39542827]
551. Ho K *et al.* (1993) [7680431]
552. Ho K *et al.* (2009) [19210926]
553. Ho MW *et al.* (1997) [9142840]
554. Hoenderop JG *et al.* (2001) [11744752]
555. Hofherr A *et al.* (2011) [21290302]
556. Hofmann F *et al.* (2005) [16382102]
557. Hofmann T *et al.* (2003) [12842017]
558. Hofmann T *et al.* (2014) [24633576]
559. Holbrook JD *et al.* (2009) [19012743]
560. Holm LM *et al.* (2005) [15988592]
561. Holm LM *et al.* (2004) [14985982]
562. Holst AG *et al.* (2024) [38092897]
563. Honore P *et al.* (2009) [19464323]
564. Honore P *et al.* (2006) [16982702]
565. Hope AG *et al.* (1993) [7683998]
566. Hope AG *et al.* (1996) [8818349]
567. Horak M *et al.* (2006) [16257494]
568. Horisberger JD *et al.* (2004) [14988660]
569. Hosie AM *et al.* (2007) [17560657]
570. Hosseini R *et al.* (2001) [11533126]
571. Hougaard C *et al.* (2007) [17486140]
572. Hougaard C *et al.* (2012) [22046005]
573. Houser A *et al.* (2025) [39667931]
574. Houtani T *et al.* (2005) [16083862]
575. Howard RJ *et al.* (2011) [21730162]
576. Hoyer D *et al.* (1994) [7938165]
577. Hu H *et al.* (2009) [19202543]
578. Hu HZ *et al.* (2004) [15194687]
579. Hu XQ *et al.* (2008) [18187416]
580. Hu Y *et al.* (2025) [40356890]
581. Huang CL *et al.* (1998) [9486652]

582. Huang F *et al.* (2012) [22090471]
583. Huang J *et al.* (2023) [37330538]
584. Huang X *et al.* (2015) [26416729]
585. Huang X *et al.* (2017) [28479061]
586. Huang X *et al.* (2017) [27991902]
587. Huang Y *et al.* (2023) [37976835]
588. Huang Y *et al.* (2019) [31513012]
589. Hughes AD *et al.* (1993) [8388295]
590. Hughes BA *et al.* (2000) [10942728]
591. Hurle B *et al.* (2003) [12651873]
592. Hurst RS *et al.* (1991) [1921987]
593. Hurst RS *et al.* (2005) [15858066]
594. Hurth K *et al.* ACS Med Chem Meeting Abstracts, March 2014. Accessed on 06/04/2014.
595. Hwang SW *et al.* (2000) [10823958]
596. Illes P *et al.* (2021) [33125712]
597. Inagaki N *et al.* (1995) [7502040]
598. Inagaki N *et al.* (1996) [8630239]
599. Inoue R *et al.* (2001) [11179201]
600. Introini B *et al.* (2024) [39232129]
601. Iraci N *et al.* (2024) [38782404]
602. Irie S *et al.* (2014) [24756714]
603. Isaac JT *et al.* (2007) [17582328]
604. Isbrandt D *et al.* (2000) [10729221]
605. Isenberg KE *et al.* (1993) [7509203]
606. Ishibashi K *et al.* (1997) [9252401]
607. Ishibashi K *et al.* (2002) [12084581]
608. Ishibashi K *et al.* (2014) [24189537]
609. Ishihara K *et al.* (1996) [8866861]
610. Islam MS. (2011) [21290328]
611. Isom LL. (2001) [11486343]
612. Jackson AC *et al.* (2011) [21521608]
613. Jacob TC *et al.* (2008) [18382465]
614. Jacobs G *et al.* (2015) [25600961]
615. Jacobson KA *et al.* (2009) [18600475]
616. Jacobson KA *et al.* (2002) [12213051]
617. Jacobson KA *et al.* (1998) [9632352]
618. Jacobson KA *et al.* (2016) [26686393]
619. Jäger H *et al.* (2000) [10713270]
620. Jane DE *et al.* (2009) [18793656]
621. Jane DE *et al.* (2000) *In Handbook of Experimental Pharmacology, Pharmacology of Ionic Channel Function: Activators and Inhibitors* Edited by Endo M, Kurachi Y, Mishina M: Springer: 415-478
622. Janssens A *et al.* (2018) [30170189]
623. Jarvis MF *et al.* (2002) [12482951]
624. Jarvis MF *et al.* (2009) [18657557]
625. Jarvis MF *et al.* (2014) [24726441]
626. Jasti J *et al.* (2007) [17882215]
627. Jensen AA *et al.* (2008) [18597859]
628. Jensen AA *et al.* (2005) [16033252]
629. Jensen BS. (2002) [12481191]
630. Jensen BS *et al.* (1998) [9730970]
631. Jensen TN *et al.* (2006) [16647053]
632. Jentsch TJ. (2008) [18307107]
633. Jeon J *et al.* (2020) [33490083]
634. Jiang J *et al.* (2005) [16009728]
635. Jiang LH *et al.* (2003) [14523092]
636. Jiang LH *et al.* (2000) [10860929]
637. Jiang Q *et al.* (2010) [20580786]
638. Jin J *et al.* (2008) [18974357]
639. Jin JL *et al.* (2005) [16107607]
640. Jin W *et al.* (1999) [10572004]
641. Jin W *et al.* (1999) [10572003]
642. Jo S *et al.* (2020) [32193331]
643. Jo S *et al.* (2025) [40136042]
644. Joeres N *et al.* (2016) [27277303]
645. Johnson BD *et al.* (1996) [8913371]
646. Johnson JP *et al.* (2022) [35234610]
647. Johnston GA. (2005) [15974965]
648. Johnston GA *et al.* (2010) [20963487]
649. Joiner WJ *et al.* (1997) [9380751]
650. Jones AK *et al.* (2010) [20674046]
651. Jones F *et al.* (2021) [33860384]
652. Jones J *et al.* (2023) [37530822]
653. Jordt SE *et al.* (2004) [14712238]
654. Jung S *et al.* (2003) [12456670]
655. Just S *et al.* (2018) [29385160]
656. Juvin V *et al.* (2007) [17673572]
657. Köroğlu Ç *et al.* (2013) [23749988]
658. Kaczmarek LK *et al.* (2017) [28267675]
659. Kaczor AA *et al.* (2010) [20491632]
660. Kahler JP *et al.* (2023) [36762958]
661. Kai H *et al.* (2021) [34587541]
662. Kalamida D *et al.* (2007) [17651090]
663. Kaldenhoff R *et al.* (2014) [24141139]
664. Kalman K *et al.* (1998) [9488722]
665. Kamei T *et al.* (2024) [38776832]
666. Kanaya S *et al.* (1984) [6694106]
667. Kang D *et al.* (2005) [15677687]
668. Kang D *et al.* (2004) [14985088]
669. Kang J *et al.* (2012) [22353878]
670. Kang J *et al.* (2005) [15548764]
671. Kang Y *et al.* (2022) [35550517]
672. Kapeller J *et al.* (2011) [21192076]
673. Kapus A *et al.* (1993) [8270911]
674. Karakas E *et al.* (2011) [21677647]
675. Karashima Y *et al.* (2007) [17855602]
676. Karashima Y *et al.* (2009) [19144922]
677. Karim N *et al.* (2013) [23385381]
678. Karnovsky AM *et al.* (2003) [14597179]
679. Kasanami Y *et al.* (2022) [36075145]
680. Kashlan OB *et al.* (2012) [22405998]
681. Kassack MU *et al.* (2004) [15072843]
682. Kasumu AW *et al.* (2012) [23102227]
683. Kaszas K *et al.* (2012) [22005042]
684. Katoh TA *et al.* (2023) [36603091]
685. Kaupp UB *et al.* (1989) [2481236]
686. Kawate T *et al.* (2009) [19641588]
687. Kaye R *et al.* (2025) [40491382]
688. Keating C *et al.* (2025) [39756424]
689. Keating D *et al.* (2018) [30334692]
690. Kelemen B *et al.* (2020) [31987857]
691. Kellenberger S *et al.* (2003) [14500741]
692. Kellenberger S *et al.* (2015) [25287517]
693. Kelley SP *et al.* (2003) [12867984]
694. Kennard LE *et al.* (2005) [15685212]
695. Keserü GM. (2003) [12873512]
696. Kew JN *et al.* (2005) [15731895]
697. Khairatkar-Joshi N *et al.* (2015) [26030081]
698. Khakh BS *et al.* (2001) [11171941]
699. Khakh BS *et al.* (1999) [10460235]
700. Khom S *et al.* (2006) [16272224]
701. Khom S *et al.* (2010) [20718740]
702. Kim HJ *et al.* (2007) [17962195]
703. Kim HJ *et al.* (2008) [18369318]
704. King BF. (2023) [36279087]
705. King BF *et al.* (1999) [10556935]
706. King BF *et al.* (2005) [15778739]
707. Kirichok Y *et al.* (2006) [16467839]
708. Kirsch J. (2006) [16807723]
709. Kiselyov K *et al.* (2009) [19273053]
710. Kiselyov K *et al.* (2007) [17217079]
711. Kiselyov K *et al.* (2007) [17138610]
712. Kitchen P *et al.* (2015) [26365508]
713. Kitchen P *et al.* (2020) [32413299]
714. Kittaka H *et al.* (2017) [28612138]
715. Kiyonaka S *et al.* (2009) [19289841]
716. Klausen TK *et al.* (2009) [19361196]
717. Kleene SJ *et al.* (2019) [30883612]
718. Kleyman TR *et al.* (2020) [31721612]
719. Kleyman TR *et al.* (2018) [29120692]
720. Klugbauer N *et al.* (1995) [7720699]
721. Knaus A *et al.* (2007) [17261653]
722. Knepper MA *et al.* (2015) [25830425]
723. Knowlton WM *et al.* (2011) [20932257]
724. Kobayashi T *et al.* (2000) [10780978]
725. Kobayashi T *et al.* (2004) [15150531]
726. Koch HP *et al.* (2008) [18583477]
727. Koivisto AP *et al.* (2022) [34526696]
728. Kojima R *et al.* (2014) [24291101]
729. Kolisek M *et al.* (2005) [15808509]
730. Kollewe A *et al.* (2021) [34766907]
731. Konstas AA *et al.* (2003) [12456399]
732. Korpi ER *et al.* (2007) [17591542]
733. Korpi ER *et al.* (2002) [12126658]
734. Kotnis S *et al.* (2010) [20223879]
735. Kozak JA *et al.* (2002) [12149283]
736. Kraft R. (2007) [17658472]
737. Kraft R *et al.* (2006) [16604090]
738. Kraft R *et al.* (2004) [14512294]
739. Krakow D *et al.* (2009) [19232556]
740. Krapivinsky G *et al.* (2014) [24855944]
741. Krapivinsky G *et al.* (2017) [28784805]
742. Krapivinsky G *et al.* (1998) [9620703]
743. Krauson AJ *et al.* (2018) [29782492]
744. Krehan D *et al.* (2003) [14604650]
745. Kreida S *et al.* (2015) [26342685]
746. Kremeyer B *et al.* (2010) [20547126]
747. Kreple CJ *et al.* (2014) [24952644]
748. Krishek BJ *et al.* (1998) [9508826]
749. Kristensson C *et al.* (2022) [35227647]
750. Krogsgaard-Larsen P *et al.* (2002) [12469353]
751. Krügel U *et al.* (2017) [28106668]
752. Kschonsak M *et al.* (2020) [32698188]
753. Kschonsak M *et al.* (2022) [34929720]
754. Kubo Y *et al.* (2005) [16382105]
755. Kuduk SD *et al.* (2010) [22778804]
756. Kulagowski JJ *et al.* (1994) [8182696]
757. Kumar J *et al.* (2013) [22974439]
758. Kuner T *et al.* (1996) [8642401]
759. Kusaka S *et al.* (2001) [11179389]
760. Kuzmenkov AI *et al.* (2022) [36188602]
761. Kwok CHT *et al.* (2024) [39048565]
762. Ladefoged LK *et al.* (2018) [30257860]
763. Lafreniére RG *et al.* (2010) [20871611]
764. Lalo U *et al.* (2008) [18495881]
765. Lamb GD *et al.* (1987) [2451745]
766. Lambert S *et al.* (2011) [21278253]
767. Lambert S *et al.* (2005) [15961423]
768. Landouré G *et al.* (2010) [20037586]
769. Lang R *et al.* (2000) [10836990]
770. Lange PF *et al.* (2006) [16525474]
771. Lankiewicz S *et al.* (1998) [9463477]
772. Larsson JE *et al.* (2020) [32595524]
773. Laube B *et al.* (2002) [12413807]
774. Lazarenko RM *et al.* (2010) [20519544]
775. Leacock S *et al.* (2018) [29445326]
776. Leblanc N *et al.* (2015) [26064450]

777. Leblanc N *et al.* (2005) [16091780]
778. Lee CH *et al.* (2017) [28086084]
779. Lee CH *et al.* (2019) [31787376]
780. Lee CH *et al.* (2011) [21763685]
781. Lee JH *et al.* (1999) [10094463]
782. Lee JH *et al.* (1999) [10585925]
783. Lee JYP *et al.* (2018) [29134638]
784. Lee K *et al.* (1995) [7589189]
785. Lee N *et al.* (2003) [12672827]
786. Lee SP *et al.* (2008) [18334983]
787. Lee SY *et al.* (2008) [18509058]
788. Lee TS *et al.* (2006) [16899990]
789. Leeson PD *et al.* (1992) [1534584]
790. Leffler A *et al.* (2011) [21861907]
791. Lei X *et al.* (2022) [36526620]
792. Lei YT *et al.* (2014) [25237295]
793. Leisle L *et al.* (2011) [21527911]
794. Lemmens-Gruber R *et al.* (2023) [37175488]
795. Lerche C *et al.* (2000) [10787416]
796. Lerma J. (2006) [16361114]
797. Lerma J. (2011) [21709676]
798. Lesage F *et al.* (2000) [10880510]
799. Leslie TK *et al.* (2023) [36183245]
800. Leuner K *et al.* (2010) [20008516]
801. Leuner K *et al.* (2007) [17666455]
802. Levitz J *et al.* (2016) [27035963]
803. Lewis RJ *et al.* (2000) [10938268]
804. Li GD *et al.* (2009) [19282280]
805. Li GD *et al.* (2006) [17093081]
806. Li J *et al.* (2025) [39814994]
807. Li M *et al.* (2006) [16636202]
808. Li M *et al.* (2017) [28099415]
809. Li N *et al.* (2025) [40808385]
810. Li S *et al.* (2025) [39739807]
811. Li SJ *et al.* (2010) [20147290]
812. Li T *et al.* (2021) [33238160]
813. Li WG *et al.* (2010) [21143836]
814. Li X *et al.* (2021) [32884139]
815. Li Z *et al.* (2024) [38443561]
816. Liang P *et al.* (2024) [38814250]
817. Liang P *et al.* (2024) [38033286]
818. Liantonio A *et al.* (2007) [17128287]
819. Liantonio A *et al.* (2008) [18216243]
820. Liao M *et al.* (2013) [24305160]
821. Liardo E *et al.* (2024) [39232360]
822. Lichtenegger M *et al.* (2018) [29556099]
823. Lien CC *et al.* (2002) [11790809]
824. Lievremont JP *et al.* (2005) [15933213]
825. Liman ER. (2007) [17217064]
826. Liman *et al.* (2007) Edited by W. B. Liedtke and S. Heller:
827. Lin BL *et al.* (2019) [31028142]
828. Lin SH *et al.* (2015) [25828470]
829. Lin SH *et al.* (2015) [25582292]
830. Lin Z *et al.* (2012) [22405088]
831. Linford NJ *et al.* (1998) [9811906]
832. Linguegia E *et al.* (1997) [9368048]
833. Linguegia E *et al.* (1993) [8382172]
834. Link TM *et al.* (2010) [20118928]
835. Linsdell P. (2017) [27699452]
836. Lishko PV *et al.* (2011) [21412339]
837. Lishko PV *et al.* (2010) [20679352]
838. Liu B *et al.* (2010) [20335661]
839. Liu B *et al.* (2011) [22006988]
840. Liu D *et al.* (2003) [14657398]
841. Liu J *et al.* (2007) [17478420]
842. Liu K *et al.* (2025) [40040241]
843. Liu L *et al.* (2003) [12842134]
844. Liu Q *et al.* (2022) [35525986]
845. Liu S *et al.* (2016) [26756551]
846. Liu SJ *et al.* (2007) [17275103]
847. Liu X *et al.* (2018) [29443690]
848. Liu X *et al.* (2020) [31936014]
849. Liu Y *et al.* (2021) [33564124]
850. Liu Y *et al.* (2011) [21290296]
851. Lobley A *et al.* (2003) [12932298]
852. Lochner M *et al.* (2010) [20409468]
853. Lodge D. (2009) [18765242]
854. Lopatin AN *et al.* (1994) [7969496]
855. Lopes CM *et al.* (2000) [10748056]
856. Lopez IA *et al.* (2019) [31092032]
857. Lord B *et al.* (2015) [26386289]
858. Lou J *et al.* (2022) [35221714]
859. Loucif AJC *et al.* (2018) [29150838]
860. Lozovaya N *et al.* (2005) [16107637]
861. Lu B *et al.* (2007) [17448995]
862. Lu B *et al.* (2009) [19092807]
863. Lu B *et al.* (2010) [21040849]
864. Lu M *et al.* (2008) [18326490]
865. Lucas P *et al.* (2003) [14642279]
866. Lucchesi K *et al.* (1989) [2477548]
867. Ludlow MJ *et al.* (2025) *iScience*
868. Lukas RJ *et al.* (1999) [10353988]
869. Lummis SC *et al.* (2011) [21775477]
870. Luscher B *et al.* (2011) [21555068]
871. Lynagh T *et al.* (2018) [30061402]
872. Lynagh T *et al.* (2017) [28949138]
873. Lynch JW. (2009) [18721822]
874. Lynch JW. (2004) [15383648]
875. Lyon M *et al.* (2023) [36649421]
876. Müller ME *et al.* (2024) [38891889]
877. Ma D *et al.* (2023) [37857637]
878. Ma D *et al.* (2022) [36763058]
879. Ma S *et al.* (2008) [18930858]
880. Ma T *et al.* (1997) [9388476]
881. Ma Z *et al.* (2016) [26603282]
882. Macpherson LJ *et al.* (2007) [17237762]
883. Macpherson LJ *et al.* (2005) [15916949]
884. Macpherson LJ *et al.* (2006) [16829128]
885. Macpherson LJ *et al.* (2007) [17942735]
886. Madjroh N *et al.* (2021) [34560054]
887. Madry C *et al.* (2008) [18711142]
888. Magrì A *et al.* (2018) [29682501]
889. Mahieu F *et al.* (2007) [17142461]
890. Maier M *et al.* (2022) [35916168]
891. Maier T *et al.* (2015) [25847402]
892. Maingret F *et al.* (1999) [9880510]
893. Maingret F *et al.* (2000) [10835347]
894. Maingret F *et al.* (2001) [11226154]
895. Maingret F *et al.* (1999) [10480871]
896. Majeed Y *et al.* (2010) [20735426]
897. Majeed Y *et al.* (2011) [21406603]
898. Makhina EN *et al.* (1994) [8051145]
899. Maksay G *et al.* (2009) [19383091]
900. Malayev A *et al.* (2002) [11861317]
901. Mälkiä A *et al.* (2007) [17317754]
902. Mälkiä A *et al.* (2011) [20932258]
903. Mall MA. (2020) [32732328]
904. Mall MA *et al.* (2024) [39117676]
905. Malosio ML *et al.* (1991) [1651228]
906. Malysz J *et al.* (2009) [19389923]
907. Mamet J *et al.* (2002) [12486159]
908. Mansoor SE *et al.* (2016) [27626375]
909. Manville RW *et al.* (2018) [30021858]
910. Maricq AV *et al.* (1991) [1718042]
911. Markham A. (2022) [35347635]
912. Marra S *et al.* (2016) [26772186]
913. Marshall DL *et al.* (1994) [7533951]
914. Martin RL *et al.* (2000) [10991994]
915. Martínez-López P *et al.* (2009) [19338774]
916. Martins AP *et al.* (2012) [22624030]
917. Mascia MP *et al.* (2000) [10908659]
918. Masiulis S *et al.* (2019) [30602790]
919. Matalon S *et al.* (2015) [26432872]
920. Matchkov VV *et al.* (2004) [14718479]
921. Matchkov VV *et al.* (2008) [18776041]
922. Mathar I *et al.* (2014) [24226423]
923. Matsuda JJ *et al.* (2008) [17977943]
924. Mattmann ME *et al.* (2012) [22910039]
925. Mayer ML. (2006) [16554805]
926. Mazurov AA *et al.* (2011) [21919481]
927. McCarthy AE *et al.* (2019) [31587896]
928. McCormack K *et al.* (2013) [23818614]
929. McDonough SI *et al.* (1996) [8786437]
930. McIntyre P *et al.* (2001) [11226139]
931. McKay S *et al.* (2012) [22022974]
932. McNamara CR *et al.* (2007) [17686976]
933. McNamara FN *et al.* (2005) [15685214]
934. McRory JE *et al.* (2004) [14973233]
935. Meena AS *et al.* (2022) [35705057]
936. Meier JC *et al.* (2005) [15895087]
937. Meissner G. (2017) [29122978]
938. Meseguer V *et al.* (2014) [24445575]
939. Mesirca P *et al.* (2024) [38167790]
940. Miao Y *et al.* (2015) [26027738]
941. Michel AD *et al.* (2008) [18071294]
942. Michel AD *et al.* (1995) [8548175]
943. Michel AD *et al.* (2008) [18660826]
944. Michel AD *et al.* (2009) [19309360]
945. Michel AD *et al.* (2006) [17031382]
946. Michel AD *et al.* (2006) [16487507]
947. Miehe S *et al.* (2012) [22530015]
948. Mihályi C *et al.* (2024) [39495914]
949. Miki K *et al.* (2013) [23453951]
950. Millar NS. (2008) [18246096]
951. Millar NS *et al.* (2009) [18723036]
952. Miller M *et al.* (2011) [21795696]
953. Miller PS *et al.* (2005) [15905212]
954. Miller PS *et al.* (2005) [16144831]
955. Miller PS *et al.* (2010) [20096941]
956. Milstein AD *et al.* (2008) [18514334]
957. Minard A *et al.* (2019) [31277085]
958. Minard A *et al.* (2018) [29865154]
959. Miner K *et al.* (2019) [30837866]
960. Mintz IM *et al.* (1992) [1311418]
961. Mittermeier L *et al.* (2019) [30770447]
962. Miu P *et al.* (2001) [11406188]
963. Miyake A *et al.* (1995) [7565620]
964. Mochizuki S *et al.* (1999) [10204690]
965. Mochizuki S *et al.* (2000) [10884508]
966. Mody I *et al.* (2004) [15331240]
967. Möhler H. (2007) [17394533]
968. Molinari EJ *et al.* (2000) [10666507]
969. Monteil A *et al.* (2024) [37615954]
970. Moqrich A *et al.* (2005) [15746429]
971. Moran MM *et al.* (2018) [28924972]
972. Morgan AJ *et al.* (2014) [24277557]
973. Morgan D *et al.* (2009) [19805063]
974. Morley RM *et al.* (2005) [15801853]
975. Moss SJ *et al.* (2001) [11283747]

976. Motoyama K *et al.* (2018) [29752182]
977. Moura Barbosa AJ *et al.* (2010) [20724042]
978. Moussaieff A *et al.* (2008) [18492727]
979. Muanprasat C *et al.* (2004) [15277574]
980. Mukhopadhyay I *et al.* (2014) [24819048]
981. Mulligan SJ *et al.* (2006) [17047222]
982. Munro G *et al.* (2016) [26663905]
983. Murrell-Lagnado RD *et al.* (2022) [35776329]
984. Musset B *et al.* (2010) [20037153]
985. Musset B *et al.* (2010) [20231140]
986. Musset B *et al.* (2011) [22020278]
987. Na T *et al.* (2014) [24756712]
988. Nadler MJ *et al.* (2001) [11385574]
989. Nagata K *et al.* (2005) [15843607]
990. Nagata K *et al.* (2008) [18162548]
991. Nagle JF *et al.* (1978) [272644]
992. Nakagawa F *et al.* (2020) [32051870]
993. Nakagawa T. (2010) [21080238]
994. Nakamura T *et al.* (1987) [3027574]
995. Nakanishi O *et al.* (2020) [32102918]
996. Nam YW *et al.* (2025) [40246884]
997. Namkung W *et al.* (2010) [20581223]
998. Naur P *et al.* (2007) [17715062]
999. Nausch B *et al.* (2014) [24951278]
1000. Navarro B *et al.* (2007) [17460039]
1001. Naylor J *et al.* (2016) [26565375]
1002. Nazirogˇlu M *et al.* (2012) [21964764]
1003. Neagoe I *et al.* (2010) [20466723]
1004. Neeper MP *et al.* (2007) [17395593]
1005. Newcomb R *et al.* (1998) [9799496]
1006. Newman AS *et al.* (2013) [23594147]
1007. Neyton J *et al.* (2006) [16452656]
1008. Ng CK *et al.* (2011) [21428815]
1009. Nicke A *et al.* (1998) [9606184]
1010. Nie L *et al.* (1997) [9292225]
1011. Niesler B. (2011) [21345729]
1012. Niesler B *et al.* (2003) [12801637]
1013. Niesler B *et al.* (2008) [18466097]
1014. Niesler B *et al.* (2007) [17392525]
1015. Niforatos W *et al.* (2007) [17314320]
1016. Nilius B. (2007) [17368864]
1017. Nilius B *et al.* (2003) [12558550]
1018. Nilius B *et al.* (2014) [25296415]
1019. Nilius B *et al.* (2006) [16424899]
1020. Nilius B *et al.* (2010) [20127491]
1021. Nilius B *et al.* (2008) [18923420]
1022. Nilius B *et al.* (2007) [17237345]
1023. Nilius B *et al.* (2004) [15331675]
1024. Nilius B *et al.* (2005) [15590641]
1025. Nilius B *et al.* (2004) [14758478]
1026. Nilius B *et al.* (2004) [14707014]
1027. Nina DUllrich. (2005) *In TRPM4 and TRPM5: Functional characterisation and comparison of two novel* Ca^{2+}*-activated cation channels of the TRPM subfamily* Faculteit Geneeskunde, Dept. Moleculaire Celbiologie, KU Leuven:
1028. No authors listed. (2004) [15293871]
1029. Nörenberg W *et al.* (2011) [21262970]
1030. Nörenberg W *et al.* (2012) [22506590]
1031. Noreng S *et al.* (2018) [30251954]
1032. Noreng S *et al.* (2020) [32729833]
1033. North RA *et al.* (2013) [23253448]
1034. Novarino G *et al.* (2010) [20430975]
1035. Novello JC *et al.* (1999) [10082164]
1036. Nury H *et al.* (2011) [21248852]
1037. Oancea E *et al.* (2009) [19436059]
1038. Oberwinkler J *et al.* (2005) [15824111]
1039. Oberwinkler J *et al.* (2014) [24756716]
1040. Oberwinkler J *et al.* (2007) [17217062]
1041. Oertel J *et al.* (2007) [17145751]
1042. Oh SJ *et al.* (2013) [23997117]
1043. Ohya S *et al.* (2003) [12690036]
1044. Okada SF *et al.* (2004) [15477379]
1045. Okada T *et al.* (1999) [10488066]
1046. Okada Y *et al.* (2009) [19171657]
1047. Oken AC *et al.* (2022) [35784697]
1048. Okuda K *et al.* (2021) [33321047]
1049. Olesen SP *et al.* (1994) [8137869]
1050. Olsen RW *et al.* (2011) [21194017]
1051. Olsen RW *et al.* (2008) [18790874]
1052. Olsen RW *et al.* (2009) [18760291]
1053. Omura M *et al.* (2014) [25001287]
1054. Omura M *et al.* (2015) [25701815]
1055. Ong HL *et al.* (2017) [28900914]
1056. Ong ST *et al.* (2025) [40294255]
1057. Orhan G *et al.* (2011) [21354396]
1058. Ormond SJ *et al.* (2006) [16452399]
1059. Ortner NJ *et al.* (2017) [28592699]
1060. Osmakov DI *et al.* (2020) [32733241]
1061. Osmakov DI *et al.* (2013) [23801332]
1062. Osteen JD *et al.* (2016) [27281198]
1063. Osteen JD *et al.* (2008) [18658230]
1064. Overington JP *et al.* (2006) [17139284]
1065. Owsianik G *et al.* (2006) [16460288]
1066. Ozhathil LC *et al.* (2018) [29579323]
1067. Pagano E *et al.* (2023) [36168728]
1068. Palacios-Prado N *et al.* (2022) [35486697]
1069. Palmer LG *et al.* (2012) [22038262]
1070. Pan X *et al.* (2022) [35194776]
1071. Paoletti P. (2011) [21395862]
1072. Paoletti P *et al.* (2013) [23686171]
1073. Paoletti P *et al.* (2007) [17088105]
1074. Pape HC. (1996) [8815797]
1075. Papke RL *et al.* (2008) [18448138]
1076. Papke RL *et al.* (2001) [11303054]
1077. Park U *et al.* (2011) [21832173]
1078. Parker RM *et al.* (1996) [8994113]
1079. Parker RM *et al.* (1996) [8936343]
1080. Parnas M *et al.* (2009) [19135721]
1081. Parsonage G *et al.* (2023) [36457143]
1082. Partiseti M *et al.* (1998) [9738472]
1083. Patel A *et al.* (2010) [20490539]
1084. Patel AJ *et al.* (1999) [10321245]
1085. Patel AJ *et al.* (1998) [9687497]
1086. Paul M *et al.* (2002) [11867382]
1087. Paulsen CE *et al.* (2015) [25855297]
1088. Payandeh J *et al.* (2011) [21743477]
1089. Payne CE *et al.* (2015) [25625641]
1090. Pearson WL *et al.* (1999) [9882736]
1091. Pedarzani P *et al.* (2005) [16239218]
1092. Pedarzani P *et al.* (2001) [11134030]
1093. Pedemonte N *et al.* (2007) [17452495]
1094. Pedersen SF *et al.* (2005) [16098585]
1095. Pedregal C *et al.* (2000) [10821708]
1096. Peier AM *et al.* (2002) [12016205]
1097. Peigneur S *et al.* (2012) [22972919]
1098. Pelegrin P *et al.* (2009) [19212823]
1099. Pelegrin P *et al.* (2007) [17121814]
1100. Peng C *et al.* (2004) [15134637]
1101. Penzotti JL *et al.* (2001) [11159437]
1102. Pérez-Vizcaíno F *et al.* (1993) [7506331]
1103. Perrais D *et al.* (2009) [18761361]
1104. Perrais D *et al.* (2010) [20850188]
1105. Perraud AL *et al.* (2001) [11385575]
1106. Perry M *et al.* (2004) [15266014]
1107. Peters JA *et al.* (2005) [16194573]
1108. Petheo GL *et al.* (2010) [21124855]
1109. Petrus M *et al.* (2007) [18086313]
1110. Peverini L *et al.* (2018) [30108481]
1111. Philippaert K *et al.* (2017) [28361903]
1112. Philippart F *et al.* (2018) [30556810]
1113. Picollo A *et al.* (2005) [16034421]
1114. Piechowicz KA *et al.* (2016) [26796863]
1115. Pierandrei S *et al.* (2021) [33916525]
1116. Pifferi S *et al.* (2009) [19475416]
1117. Pignier C *et al.* (2000) [11045961]
1118. Pingle SC *et al.* (2007) [17217056]
1119. Pinheiro P *et al.* (2006) [16847640]
1120. Pinto MC *et al.* (2021) [34326672]
1121. Piper AS *et al.* (2002) [11850506]
1122. Piper AS *et al.* (2004) [14724180]
1123. Pirahanchi Y *et al.* (2021) [30725773]
1124. Pitt SJ *et al.* (2008) [18987182]
1125. Piyasirananda W *et al.* (2021) [33334897]
1126. Planells-Cases R *et al.* (2009) [19708126]
1127. Plant LD *et al.* (2010) [20498050]
1128. Plant LD *et al.* (2012) [23169818]
1129. Plant TD *et al.* (2003) [12765689]
1130. Plasschaert LW *et al.* (2018) [30069046]
1131. Plesch E *et al.* (2018) [30479274]
1132. Plested AJ. (2011) [21713670]
1133. Polster A *et al.* (2015) [25548159]
1134. Pope L *et al.* (2018) [30089357]
1135. Potier M *et al.* (2008) [18536932]
1136. Preisig-Müller R *et al.* (2002) [12032359]
1137. Preston GM *et al.* (1992) [1373524]
1138. Price MP *et al.* (1996) [8626462]
1139. Pritchett DB *et al.* (1989) [2551039]
1140. Puertollano R *et al.* (2009) [19158345]
1141. Pusch M *et al.* (2002) [12512775]
1142. Pusch M *et al.* (2006) [16179405]
1143. Putney JW. (2005) [16133266]
1144. Qi H *et al.* (2007) [17227845]
1145. Qi H *et al.* (2022) [35256942]
1146. Qian F *et al.* (2005) [15971078]
1147. Qiang M *et al.* (2018) [30042215]
1148. Qin N *et al.* (2008) [18550765]
1149. Qin X *et al.* (2013) [23145923]
1150. Qu C *et al.* (2017) [28395140]
1151. Qu Z *et al.* (2014) [24639373]
1152. Quallo T *et al.* (2017) [28826490]
1153. Quill TA *et al.* (2001) [11675491]
1154. Qunies AM *et al.* (2023) [37812884]
1155. Qunies AM *et al.* (2024) [38893312]
1156. Rödström KEJ *et al.* (2024) [38755204]
1157. Rajan S *et al.* (2001) [11060316]
1158. Rajan S *et al.* (2000) [10747866]
1159. Rambow J *et al.* (2014) [25225485]
1160. Ramerstorfer J *et al.* (2010) [20303942]
1161. Ramerstorfer J *et al.* (2011) [21248110]
1162. Rampe D *et al.* (1997) [9395068]
1163. Ramsey IS *et al.* (2018) [29483132]
1164. Ramsey IS *et al.* (2010) [20543828]
1165. Ramsey IS *et al.* (2006) [16554753]
1166. Ramsey IS *et al.* (2009) [19372380]
1167. Rapedius M *et al.* (2005) [15980413]
1168. Rash LD. (2017) [28528673]
1169. Rauh R *et al.* (2017) [27941075]
1170. Rautenberg S *et al.* (2023) [35902436]

1171. Redd MA *et al.* (2021) [34264749]
1172. Ren D *et al.* (2001) [11595941]
1173. Rennhack A *et al.* (2018) [29723408]
1174. Rettig J *et al.* (1992) [1378392]
1175. Reyes R *et al.* (1998) [9812978]
1176. Richter JM *et al.* (2014) [25140002]
1177. Richter JM *et al.* (2014) [24117252]
1178. Riquelme G. (2009) [19604577]
1179. Roberts A *et al.* (2020) [32102919]
1180. Robertson JL *et al.* (2010) [21048711]
1181. Rochat H *et al.* (1998) [9792177]
1182. Rock MJ *et al.* (2008) [18587396]
1183. Rodríguez-Moreno A *et al.* (2007) [17981346]
1184. Rohacs T. (2009) [19376575]
1185. Romi-Lebrun R *et al.* (1997) [9354615]
1186. Romine JL *et al.* (2007) [17266205]
1187. Rook ML *et al.* (2021) [32306405]
1188. Rosenbaum T *et al.* (2004) [14981138]
1189. Rosenbaum T *et al.* (2003) [12508052]
1190. Rossier BC *et al.* (2015) [25540145]
1191. Rossier BC *et al.* (2009) [18928407]
1192. Rotin D *et al.* (2011) [20972579]
1193. Roy S *et al.* (2014) [24561672]
1194. Ruah SSH *et al.* (2009) Patent number: US20090131492A1.
1195. Rubaiy HN. (2019) [30656647]
1196. Rubaiy HN. (2023) [37259313]
1197. Rubaiy HN *et al.* (2017) [28325835]
1198. Rubaiy HN *et al.* (2018) [29859013]
1199. Rucktooa P *et al.* (2009) [19576182]
1200. Rühl P *et al.* (2021) [33859333]
1201. Rundström N *et al.* (1994) [8090751]
1202. Runnels LW *et al.* (2002) [11941371]
1203. Runnels LW *et al.* (2001) [11161216]
1204. Rüsch D *et al.* (2007) [17360702]
1205. Ryckmans T *et al.* (2011) [21741838]
1206. Sabat M *et al.* (2022) [36402081]
1207. Sabirov RZ *et al.* (2001) [11524456]
1208. Sabirov RZ *et al.* (2009) [19340557]
1209. Sabirova RKh *et al.* (1972) [4642630]
1210. Safa P *et al.* (2001) [11514547]
1211. Sagot E *et al.* (2008) [18578478]
1212. Said EA *et al.* (2024) [39362502]
1213. Sakai H *et al.* (1999) [10457052]
1214. Sakai R *et al.* (2001) [11160654]
1215. Sakurai Y *et al.* (2015) [25722412]
1216. Salameh A *et al.* (2005) [16216217]
1217. Salido GM *et al.* (2009) [19061922]
1218. Salinas M *et al.* (2006) [16284080]
1219. Samie M *et al.* (2013) [23993788]
1220. Samsó M. (2017) [27671094]
1221. Sanchez M *et al.* (1996) [8938726]
1222. Sanechika S *et al.* (2021) [33877504]
1223. Sano Y *et al.* (2003) [12754259]
1224. Sardini A *et al.* (2003) [14729152]
1225. Sasaki M *et al.* (2006) [16556803]
1226. Saul A *et al.* (2013) [24391538]
1227. Sawada Y *et al.* (2008) [18364033]
1228. Saxena A *et al.* (2002) [12107247]
1229. Saxena A *et al.* (1998) [9813171]
1230. Saxena NC *et al.* (1997) [9203639]
1231. Schaefer L *et al.* (2000) [10767424]
1232. Scheel O *et al.* (2005) [16034422]
1233. Schenkel LB *et al.* (2016) [26942860]
1234. Schiller IC *et al.* (2022) [35335209]
1235. Schleifer H *et al.* (2012) [22862290]
1236. Schmalz F *et al.* (1998) [9612272]
1237. Schmidt A *et al.* (2017) [29025967]
1238. Schmidt S *et al.* (2023) [36674884]
1239. Scholl U *et al.* (2006) [16849430]
1240. Scholze P *et al.* (1996) [8813598]
1241. Schott K *et al.* (2024) [38787877]
1242. Schreiber R *et al.* (2024) [38642428]
1243. Schrenzel J *et al.* (1998) [9565037]
1244. Schroeder BC *et al.* (2000) [10816588]
1245. Schröter KH *et al.* (1991) [1840526]
1246. Schulz P *et al.* (2010) [20830208]
1247. Schumacher MA *et al.* (2010) [20515731]
1248. Seeburg PH *et al.* (2003) [12850211]
1249. Seeliger D *et al.* (2013) [23113556]
1250. Seidler U *et al.* (1997) [9423183]
1251. Semyanov A *et al.* (2004) [15111008]
1252. Seo K *et al.* (2014) [24453217]
1253. Seo Y *et al.* (2016) [27219012]
1254. Sergeeva OA *et al.* (2010) [20511229]
1255. Shah M *et al.* (2000) [10683185]
1256. Shakkottai VG *et al.* (2001) [11527975]
1257. Shao J *et al.* (2019) [31664615]
1258. Sharma S *et al.* (2018) [29453757]
1259. Sharma S *et al.* (2019) [30943030]
1260. Sharma S *et al.* (2020) [31950584]
1261. Shei RJ *et al.* (2018) [30340955]
1262. Sheldon RS *et al.* (1986) [2431264]
1263. Shemon AN *et al.* (2004) [15210579]
1264. Shen D *et al.* (2012) [22415822]
1265. Sheng S *et al.* (2007) [17522058]
1266. Sheppard DN *et al.* (1992) [1281220]
1267. Sherkheli MA *et al.* (2010) [20816009]
1268. Shi S *et al.* (2021) [34329684]
1269. Shimizu T *et al.* (2009) [18663466]
1270. Shimkets RA *et al.* (1994) [7954808]
1271. Shoshan-Barmatz V *et al.* (2010) [20346371]
1272. Shteinberg M *et al.* (2021) [34090606]
1273. Sidach SS *et al.* (2002) [11896142]
1274. Sieghart W. (2006) [17175817]
1275. Sieghart W *et al.* (2022) [35017178]
1276. Sieghart W *et al.* (2018) [30275042]
1277. Sigel E *et al.* (2011) [21189125]
1278. Sigel E *et al.* (2012) [23038269]
1279. Simó-Vicens R *et al.* (2017) [28925012]
1280. Simonin C *et al.* (2015) [26457814]
1281. Sine SM *et al.* (2006) [16554804]
1282. Singleton DH *et al.* (2007) [17536794]
1283. Sinnegger-Brauns MJ *et al.* (2009) [19029287]
1284. Skolnick P *et al.* (1997) [9353361]
1285. Skov M *et al.* (2024) [38507469]
1286. Small B *et al.* (1998) [9849663]
1287. Smart D *et al.* (2001) [11301059]
1288. Smith AJ *et al.* (2010) [20501796]
1289. Smith ES *et al.* (2007) [17258862]
1290. Smith JF *et al.* (2013) [23530196]
1291. Smith MA *et al.* (2003) [12562896]
1292. Smith PL *et al.* (2006) [16899456]
1293. Smith RD *et al.* (1998) [9437003]
1294. Smith SM *et al.* (2011) [22006335]
1295. Smith SS. (2013) [24027497]
1296. Smothers CT *et al.* (2007) [17502428]
1297. Snyder DS *et al.* (2013) [23814642]
1298. Sobolevsky AI *et al.* (2009) [19946266]
1299. Søgaard R *et al.* (2001) [11245603]
1300. Söhl G *et al.* (2005) [15738956]
1301. Solt K *et al.* (2005) [16081679]
1302. Song C *et al.* (2022) [35210842]
1303. Soom M *et al.* (2001) [11172809]
1304. Soto F *et al.* (1999) [10193905]
1305. Spehr J *et al.* (2009) [19228965]
1306. Spix B *et al.* (2022) [35031603]
1307. Stallmeyer B *et al.* (2012) [21887725]
1308. Starowicz K *et al.* (2007) [17349697]
1309. Staruschenko A *et al.* (2007) [17443775]
1310. Stewart A *et al.* (2003) [12623220]
1311. Stewart CG *et al.* (2024) [39104314]
1312. Stiber JA *et al.* (2012) [23054893]
1313. Stieber J *et al.* (2005) [16043489]
1314. Stieber J *et al.* (2006) [16387796]
1315. Stocker JW *et al.* (2003) [12433690]
1316. Stocker M *et al.* (2004) [15208027]
1317. Stokłosa P *et al.* (2021) [34771564]
1318. Stokes L *et al.* (2006) [17031385]
1319. Stoltz DA *et al.* (2010) [20427821]
1320. Stórustovu SI *et al.* (2006) [16272218]
1321. Story GM *et al.* (2003) [12654248]
1322. Straub I *et al.* (2013) [24006495]
1323. Straub I *et al.* (2013) [23190005]
1324. Strøbæk D *et al.* (2013) [22891655]
1325. Strøbaek D *et al.* (2006) [16926279]
1326. Strøbaek D *et al.* (2000) [10696100]
1327. Strøbaek D *et al.* (2004) [15471565]
1328. Strømgaard K *et al.* (2002) [11934578]
1329. Strübing C *et al.* (2001) [11301024]
1330. Strünker T *et al.* (2011) [21412338]
1331. Stühmer W *et al.* (1989) [2555158]
1332. Su Q *et al.* (2021) [34381056]
1333. Su Q *et al.* (2018) [30093605]
1334. Sun D *et al.* (2020) [32915133]
1335. Sun H *et al.* (1999) [10381768]
1336. Sun J *et al.* (2017) [28575668]
1337. Sun J *et al.* (2020) [31883792]
1338. Sun X *et al.* (2020) [31983608]
1339. Sun X *et al.* (2019) [30918114]
1340. Sun XY *et al.* (2018) [30108138]
1341. Sun ZC *et al.* (2020) [32273889]
1342. Surprenant A *et al.* (2009) [18851707]
1343. Sutko JL *et al.* (1996) [8874493]
1344. Sutton KA *et al.* (2006) [16883570]
1345. Suzuki H *et al.* (2016) [27433342]
1346. Suzuki M *et al.* (2004) [15010458]
1347. Swanson DM *et al.* (2005) [15771431]
1348. Swayne LA *et al.* (2009) [19575010]
1349. Syeda R *et al.* (2015) [26001275]
1350. Syme CA *et al.* (2000) [10712246]
1351. Szallasi A *et al.* (2007) [17464295]
1352. Török F *et al.* (2025) [39370994]
1353. Ta CM *et al.* (2016) [26562072]
1354. Takahashi N *et al.* (1994) [8083233]
1355. Takaya J *et al.* (2015) [26630251]
1356. Takezawa R *et al.* (2006) [16407466]
1357. Takumi T *et al.* (1995) [7608203]
1358. Talavera K *et al.* (2009) [19749751]
1359. Talley EM *et al.* (2002) [11886861]
1360. Taly A *et al.* (2009) [19721446]
1361. Tan Q *et al.* (2021) [33179259]
1362. Tanaka M *et al.* (2025) [40365404]
1363. Tanemoto M *et al.* (2002) [11988170]
1364. Tanemoto M *et al.* (2000) [10856114]
1365. Tang C *et al.* (2024) [39656529]
1366. Tang Q *et al.* (2018) [29700422]

1367. Tang QY *et al.* (2010) [19934650]
1368. Tang W *et al.* (1994) [8034048]
1369. Tao J *et al.* (2014) [24759175]
1370. Tarabova B *et al.* (2007) [17651721]
1371. Tatulian L *et al.* (2001) [11466425]
1372. Teramoto N *et al.* (2003) [14623761]
1373. Territo PR *et al.* (2017) [27765863]
1374. Thiel G *et al.* (2013) [23511953]
1375. Thiel G *et al.* (2017) [28720517]
1376. Thompson AJ *et al.* (2011) [21505038]
1377. Thompson AJ *et al.* (2011) [21059362]
1378. Thompson AJ *et al.* (2010) [20849671]
1379. Thompson AJ *et al.* (2008) [18311193]
1380. Thompson AJ *et al.* (2006) [17073663]
1381. Thompson AJ *et al.* (2007) [17373882]
1382. Thompson AJ *et al.* (2011) [21708905]
1383. Thompson CH *et al.* (2009) [19574231]
1384. Thompson SA *et al.* (2002) [12367611]
1385. Thompson SA *et al.* (1999) [10455284]
1386. Thompson SA *et al.* (2004) [15100159]
1387. Thorneloe KS *et al.* (2008) [18499743]
1388. Tiapko O *et al.* (2019) [30997005]
1389. Timmermann DB *et al.* (2007) [17625074]
1390. Togashi K *et al.* (2006) [16601673]
1391. Togashi K *et al.* (2008) [18204483]
1392. Tomasinsig L *et al.* (2008) [18765670]
1393. Tombola F *et al.* (2008) [18498736]
1394. Tombola F *et al.* (2010) [20023640]
1395. Tomita S. (2010) [20134027]
1396. Toncheva D *et al.* (2014) [24949484]
1397. Tóth B *et al.* (2012) [22847436]
1398. Tóth B *et al.* (2015) [25918360]
1399. Towart R *et al.* (2009) [19439185]
1400. Tradtrantip L *et al.* (2017) [28258578]
1401. Tradtrantip L *et al.* (2010) [19808995]
1402. Trattnig SM *et al.* (2016) [26872532]
1403. Traynelis SF *et al.* (1998) [9698310]
1404. Traynelis SF *et al.* (2010) [20716669]
1405. Trebak M *et al.* (2007) [17217081]
1406. Tringham E *et al.* (2012) [22344687]
1407. Truong EC *et al.* (2017) [28493701]
1408. Tsumura T *et al.* (1998) [9769420]
1409. Tu YH *et al.* (2018) [29371428]
1410. Tzvetkov MV *et al.* (2007) [17010535]
1411. Ugawa S *et al.* (2007) [17826743]
1412. Ugawa S *et al.* (2001) [11588592]
1413. Ullrich ND *et al.* (2005) [15670874]
1414. Urban N *et al.* (2016) [26500253]
1415. Usher S *et al.* (2025) [40085699]
1416. Vaandrager AB *et al.* (1997) [9024297]
1417. Vaelli P *et al.* (2024) [39322410]
1418. Van den Eynde C *et al.* (2022) [35714693]
1419. van Megen WH *et al.* (2022) [35022312]
1420. Vandewauw I *et al.* (2018) [29539642]
1421. Vandewiele F *et al.* (2022) [35822895]
1422. Vega-Saenz de Miera E *et al.* (1992) [1381835]
1423. Veldhuis NA *et al.* (2015) [25361914]
1424. Veleiro AS *et al.* (2009) [19199916]
1425. Velicelebi G *et al.* (2016) Patent number: WO2016138472A1.
1426. Vennekens R *et al.* (2007) [17217063]
1427. Vennekens R *et al.* (2008) [18220815]
1428. Vergani P *et al.* (2005) [15729345]
1429. Verkman AS *et al.* (2014) [24625825]
1430. Verkman AS *et al.* (2009) [19153558]
1431. Verkman AS *et al.* (2017) Patent number: US9790218B2.
1432. Verstegen MMA *et al.* (2020) [33318612]
1433. Vick JS *et al.* (2015) [25592215]
1434. Vigil FA *et al.* (2020) [32636759]
1435. Vincent F *et al.* (2009) [19737537]
1436. Virginio C *et al.* (2022) [35058176]
1437. Virginio C *et al.* (1998) [9614197]
1438. Vithlani M *et al.* (2011) [21742794]
1439. Voets T *et al.* (2004) [15306801]
1440. Voets T *et al.* (2007) [17395625]
1441. Voets T *et al.* (2007) [17217067]
1442. Vogt A *et al.* (2005) [16143426]
1443. Vogt-Eisele AK *et al.* (2007) [17420775]
1444. Voilley N *et al.* (2001) [11588175]
1445. Vriens J *et al.* (2009) [19297520]
1446. Vriens J *et al.* (2014) [24390427]
1447. Vriens J *et al.* (2011) [21555074]
1448. Vriens J *et al.* (2018) [29305649]
1449. Vukicevic M *et al.* (2006) [16282326]
1450. Vulchanova L *et al.* (1997) [9364478]
1451. Wafford KA *et al.* (2009) [18762200]
1452. Wagner TF *et al.* (2008) [18978782]
1453. Wahl P *et al.* (2001) [11125018]
1454. Waldmann R *et al.* (1997) [9261094]
1455. Waldmann R *et al.* (1997) [9062189]
1456. Waldmann R *et al.* (1995) [7499195]
1457. Waldmann R *et al.* (1996) [8631835]
1458. Walker JR *et al.* (2012) [23077250]
1459. Walker RL *et al.* (2002) [12388058]
1460. Wallner M *et al.* (2006) [16814864]
1461. Walsh KB *et al.* (1986) [2418195]
1462. Walstab J *et al.* (2010) [20522555]
1463. Walstab J *et al.* (2010) [20621123]
1464. Wang B *et al.* (2019) [31636563]
1465. Wang G *et al.* (1990) [2154667]
1466. Wang G *et al.* (1992) [1331975]
1467. Wang H *et al.* (2020) [32004513]
1468. Wang H *et al.* (2009) [19516020]
1469. Wang H *et al.* (2009) [19535918]
1470. Wang HL *et al.* (2007) [17585751]
1471. Wang HS *et al.* (2000) [10825393]
1472. Wang HS *et al.* (1998) [9836639]
1473. Wang J *et al.* (2023) [37836658]
1474. Wang J *et al.* (2005) [16042391]
1475. Wang JJ *et al.* (2020) [31980622]
1476. Wang L *et al.* (2018) [30467180]
1477. Wang L *et al.* (2019) [30655942]
1478. Wang M *et al.* (2020) [32513195]
1479. Wang RX *et al.* (2011) [21187320]
1480. Wang S *et al.* (2016) [27797339]
1481. Wang SY *et al.* (1998) [9482942]
1482. Wang W *et al.* (2006) [16319075]
1483. Wang X *et al.* (2020) [32094294]
1484. Wang X *et al.* (2012) [23063126]
1485. Wang XQ *et al.* (2006) [17046694]
1486. Wang Y *et al.* (2017) [26648074]
1487. Wang Y *et al.* (2018) [29610524]
1488. Wang Y *et al.* (2023) [37541373]
1489. Wang Y *et al.* (2002) [12237342]
1490. Wang Y *et al.* (2010) [19842162]
1491. Wang YZ *et al.* (2015) [26523449]
1492. Wang Z *et al.* (2019) [31441214]
1493. Ware AW *et al.* (2021) [33630195]
1494. Warth R *et al.* (2004) [15141089]
1495. Washburn DG *et al.* (2013) [23886683]
1496. Watanabe H *et al.* (2003) [12879072]
1497. Watanabe S *et al.* (2016) [26837049]
1498. Watanabe TX *et al.* (1995) [7474554]
1499. Waxman SG. (2023) [37530829]
1500. Weatherall KL *et al.* (2010) [20359520]
1501. Webb TI *et al.* (2007) [17692006]
1502. Wehage E *et al.* (2002) [11960981]
1503. Wei AD *et al.* (2005) [16382103]
1504. Wei ZL *et al.* (2015) [26235950]
1505. Weitz D *et al.* (2002) [12467591]
1506. Wemmie JA *et al.* (2013) [23783197]
1507. Werner S *et al.* (2019) [31746599]
1508. Wescott SA *et al.* (2013) [22820171]
1509. Wetzel C *et al.* (2017) [27941788]
1510. Wickenden AD *et al.* (2000) [10953053]
1511. Wiemuth D *et al.* (2014) [24365967]
1512. Willegems K *et al.* (2022) [35768468]
1513. Williams DK *et al.* (2011) [21575610]
1514. Williams JA *et al.* (2008) [18518786]
1515. Williams ME *et al.* (1994) [8071363]
1516. Winter M *et al.* (2020) [33352987]
1517. Wishka DG *et al.* (2006) [16821801]
1518. Wissenbach U *et al.* (2007) [17217060]
1519. Wittekindt OH *et al.* (2004) [14978258]
1520. Witzgall R. (2007) [17217069]
1521. Won J *et al.* (2025) [39478185]
1522. Wong CO *et al.* (2010) [20233211]
1523. Wood ML *et al.* (2012) [21843503]
1524. Woudenberg-Vrenken TE *et al.* (2011) [20814221]
1525. Wray S *et al.* (2021) [34867456]
1526. Wrighton DC *et al.* (2015) [26045093]
1527. Wu J *et al.* (2006) [16825297]
1528. Wu J *et al.* (2011) [21787755]
1529. Wu LJ *et al.* (2010) [20716668]
1530. Wu SN *et al.* (2002) [11809993]
1531. Wu SN *et al.* (1999) [10428416]
1532. Wulff H *et al.* (2000) [10884437]
1533. Wyllie DJ *et al.* (2013) [23376022]
1534. Xia J *et al.* (2009) [19211808]
1535. Xiao B *et al.* (2008) [18815250]
1536. Xie J *et al.* (2011) [22180838]
1537. Xiong W *et al.* (2011) [21460829]
1538. Xiong ZG *et al.* (2007) [17127388]
1539. Xu F *et al.* (2003) [12970074]
1540. Xu H *et al.* (2005) [16192383]
1541. Xu H *et al.* (2006) [16617338]
1542. Xu H *et al.* (2007) [17989217]
1543. Xu H *et al.* (2002) [12077604]
1544. Xu H *et al.* (2015) [25668017]
1545. Xu L *et al.* (2020) [32728032]
1546. Xu SZ *et al.* (2005) [15806115]
1547. Xu W *et al.* (2001) [11487617]
1548. Xu X *et al.* (2013) *Biophys J* **104**: 454a
1549. Xu Y *et al.* (2020) [33584647]
1550. Yamada A *et al.* (2024) [39379156]
1551. Yamada A *et al.* (2024) [38359825]
1552. Yamada M *et al.* (1997) [9130167]
1553. Yamaguchi N *et al.* (2003) [12707260]
1554. Yamashita T *et al.* (1996) [8735700]
1555. Yan J *et al.* (2021) [34087722]
1556. Yang B. (2017) *In Advances in Experimental Medicine and Biology* Edited by Yang B: Springer: 1-276 [ISBN: 9789402410570]
1557. Yang B *et al.* (2006) [16876206]
1558. Yang B *et al.* (1997) [9195910]
1559. Yang J *et al.* (1995) [7748552]
1560. Yang KC *et al.* (2009) [19498417]

1561. Yang L *et al.* (2014) [25114023]
1562. Yang S *et al.* (2015) [26420335]
1563. Yang Z *et al.* (2008) [18755158]
1564. Yang Z *et al.* (2007) [17714449]
1565. Yang Z *et al.* (2025) [40172963]
1566. Yao J *et al.* (2005) [15695820]
1567. Yashiro K *et al.* (2025) [39981749]
1568. Ye L *et al.* (2021) [33352109]
1569. Yeh HI *et al.* (2017) [29079713]
1570. Yevenes GE *et al.* (2010) [20647311]
1571. Yevenes GE *et al.* (2006) [17040914]
1572. Yevenes GE *et al.* (2003) [12858180]
1573. Yevenes GE *et al.* (2011) [21557733]
1574. Yildirim E *et al.* (2003) [12601176]
1575. Yin Y *et al.* (2022) [36227998]
1576. Yoder N *et al.* (2020) [32496192]
1577. Yoder N *et al.* (2018) [29513651]
1578. You H *et al.* (2010) [20638393]
1579. Young GT *et al.* (2008) [18791069]
1580. Yu CR. (2015) [26157356]
1581. Yu D *et al.* (2025) [40485107]
1582. Yu FH *et al.* (2004) [15467096]
1583. Yu FH *et al.* (2005) [16382097]
1584. Yu J *et al.* (2021) [33567265]
1585. Yu L *et al.* (2010) [20142439]
1586. Yu L *et al.* (2020) [32128386]
1587. Yu M *et al.* (2019) [31749913]
1588. Yu P *et al.* (2019) [31216484]
1589. Yu X *et al.* (2021) [34788616]
1590. Yu Y *et al.* (2010) [20920791]
1591. Yuan JP *et al.* (2009) [19574740]
1592. Yue L *et al.* (2021) [34254641]
1593. Yuzaki M. (2003) [12725908]
1594. Zamponi GW *et al.* (2009) [19815411]
1595. Zdebik AA *et al.* (2008) [18063579]
1596. Zeevi DA *et al.* (2007) [17306511]
1597. Zeng D *et al.* (1996) [8967455]
1598. Zeng XH *et al.* (2011) [21427226]
1599. Zennaro MC *et al.* (2012) [21664233]
1600. Zezula J *et al.* (1996) [8773466]
1601. Zha XM *et al.* (2009) [19218436]
1602. Zhang D *et al.* (2001) [11239575]
1603. Zhang E *et al.* (2015) [25502473]
1604. Zhang G *et al.* (2022) [36351900]
1605. Zhang H *et al.* (2023) [36596769]
1606. Zhang H *et al.* (2018) [29723786]
1607. Zhang H *et al.* (2019) [30377214]
1608. Zhang H *et al.* (2021) [33784097]
1609. Zhang M *et al.* (2025) [40470184]
1610. Zhang S *et al.* (2024) [38167918]
1611. Zhang XF *et al.* (2010) [20566409]
1612. Zhang Y *et al.* (2022) [35563730]
1613. Zhao M *et al.* (1999) [10473538]
1614. Zhao Z *et al.* (2021) [34265294]
1615. Zheng J *et al.* (2002) [12467592]
1616. Zheng J *et al.* (2004) [15134638]
1617. Zheng QH. (2020) [32273217]
1618. Zheng X *et al.* (2022) [34969976]
1619. Zheng Y *et al.* (2022) [34767770]
1620. Zholos A. (2010) [20233227]
1621. Zhong G *et al.* (2021) [33786819]
1622. Zhong H *et al.* (2002) [12432397]
1623. Zhou H *et al.* (1996) [8997197]
1624. Zhou L *et al.* (2022) [35387979]
1625. Zhou LM *et al.* (1997) [8996224]
1626. Zhou T *et al.* (2020) [33155599]
1627. Zhou Y *et al.* (2017) [29217578]
1628. Zhou Z *et al.* (1998) [9449325]
1629. Zhou Z *et al.* (1999) [10376921]
1630. Zhu H *et al.* (2021) [34555840]
1631. Zhu MX. (2011) [22593967]
1632. Zhu Y *et al.* (2015) [25816897]
1633. Ziemann AE *et al.* (2009) [19945383]
1634. Zierler S *et al.* (2011) [21926172]
1635. Zifarelli G *et al.* (2009) [19131966]
1636. Zitt C *et al.* (1996) [8663995]
1637. Zong P *et al.* (2022) [35421327]
1638. Zong P *et al.* (2022) [35445217]
1639. Zufall F *et al.* (2005) [15971083]
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