THE CONCISE GUIDE TO PHARMACOLOGY 2013/14: ION CHANNELS

Stephen P.H. Alexander*[1], Helen E. Benson[2], Elena Faccenda[2], Adam J. Pawson[2], Joanna L. Sharman[2], William A. Catterall[3], Michael Spedding[4], John A. Peters[5], Anthony J. Harmar[2] and CGTP Collaborators

*Author for correspondence; steve.alexander@guidetopharmacology.org
[1]*School of Life Sciences, University of Nottingham Medical School, Nottingham NG7 2UH, UK*
[2]*The University/BHF Centre for Cardiovascular Science, University of Edinburgh, Edinburgh EH16 4TJ, UK*
[3]*University of Washington, School of Medicine, Department of Pharmacology, Box 357280, Seattle, WA 98195-7280, USA*
[4]*Spedding Research Solutions SARL, Le Vésinet 78110, France*
[5]*Neuroscience Division, Medical Education Institute, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK*

BRITISH PHARMACOLOGICAL SOCIETY

IUPHAR
International Union of Basic and Clinical Pharmacology
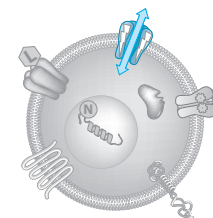
Abstract

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

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

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

An Introduction to Ion Channels

Overview: Ion channels are pore-forming proteins that allow the flow of ions across membranes, either plasma membranes or the membranes of intracellular organelles (Hille, 2001). 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 Concise Guide to PHARMACOLOGY 2013/14.

Resolution of ion channel structures, beginning with K channels (Doyle *et al.*, 1998) then Cl channels (Dutzler *et al.*, 2002) and most recently Na channels (Payandeh *et al.*, 2011) 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 Yu *et al.*, 2005). 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 (Overington *et al.*, 2006). However, the advent of novel, faster screening techniques for compounds acting on ion channels (Dunlop *et al.*, 2008) suggests that these proteins represent promising targets for the development of additional, novel therapeutic agents in the near future.

Conflict of interest

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

Further reading

Doyle D, Morais Cabral J, Pfuetzner RA, Kuo A, Gulbis JM, Cohen SL, Chait B, MacKinnon R. (1998) The structure of the potassium channel : molecular basis of potassium conduction and selectivity. *Science* **280**: 69–77.

Dunlop J, Bowlby M, Peri R, Vasilyev D, Arias R. (2008) High-throughput electrophysiology: an emerging paradigm for ion channel screening and physiology. *Nat Rev Drug Discov* **7**: 358–368.

Dutzler R, Campbell EB, Cadene M, Chait B, MacKinnon R. (2002) X-ray structure of a ClC chloride channel at 3.0A reveals the molecular basis of ion selectivity. *Nature* **415**: 287–294.

Hille B. (2001) Ion channel of excitable membranes. 3rd Edition. (Sunderland MA: Sinauer Associates).

Overington JP, Al-Lazikani B, Hopkins AL. (2006) How many drug targets are there? *Nat Rev Drug Discov* **5**: 993–996.

Payandeh J, Scheuer T, Zheng N, Catterall WA. (2011) The crystal structure of a voltage-gated sodium channel. *Nature* **475**: 353–358.

Yu FH, Yarov-Yarovoy V, Gutman GA, Catterall WA. (2005) Overview of molecular relationships in the voltage-gated ion channel superfamily. *Pharmacol Rev* **57**: 387–395.

List of records presented

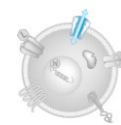# Acid-sensing (proton-gated) ion channels (ASICs)

Overview: Acid-sensing ion channels (ASICs, provisional nomenclature; [27,47]) 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 *Caenorhabitis elegans*, channels in *Drosophila melanogaster* and 'orphan' channels that include BLINaC [34] and INaC [35]. ASIC subunits contain two TM domains and assemble as homo- or hetero-trimers [22,26] to form proton-gated, voltage-insensitive, Na$^+$ permeable, channels (reviewed in [23]). Splice variants of ASIC1 [provisionally termed ASIC1a (ASIC, ASICα, BNaC2α) [43], ASIC1b (ASICβ, BNaC2β) [8] and ASIC1b2 (ASICβ2) [39]; note that ASIC1a is also permeable to Ca^{2+}] and ASIC2 [provisionally termed ASIC2a (MDEG1, BNaC1α, BNC1α) [21,33,44] and ASIC2b (MDEG2, BNaC1β) [28]] have been cloned. Unlike ASIC2a (listed in table), heterologous expression

of ASIC2b alone does not support H$^+$-gated currents. A third member, ASIC3 (DRASIC, TNaC1) [42], has been identified. A fourth mammalian member of the family (ASIC4/SPASIC) does not support a proton-gated channel in heterologous expression systems and is reported to down regulate the expression of ASIC1a and ASIC3 [1,16,24]. ASIC channels are primarily expressed in central and peripheral neurons including nociceptors where they participate in neuronal sensitivity to acidosis. They have also been detected in taste receptor cells (ASIC1-3), photoreceptors and retinal cells (ASIC1-3), cochlear hair cells (ASIC1b), testis (hASIC3), pituitary gland (ASIC4), lung epithelial cells (ASIC1a and -3), urothelial cells, adipose cells (ASIC3), vascular smooth muscle cells (ASIC1-3), immune cells (ASIC1,-3 and -4) and bone (ASIC1-3). The activation of ASIC1a within the central nervous system contributes to neuronal injury caused by

focal ischemia [48] and to axonal degeneration in autoimmune inflammation in a mouse model of multiple sclerosis [20]. However, activation of ASIC1a can terminate seizures [51]. Peripheral ASIC3-containing channels play a role in post-operative pain [12]. Further proposed roles for centrally and peripherally located ASICs are reviewed in [47] and [27]. The relationship of the cloned ASICs to endogenously expressed proton-gated ion channels is becoming established [14–15,19,25,27,29,38,45–47]. Heterologously expressed heteromultimers form ion channels with altered kinetics, ion selectivity, pH- sensitivity and sensitivity to blockers that resemble some of the native proton activated currents recorded from neurones [3,6,19,28].

Subunits

Nomenclature	ASIC1	ASIC2	ASIC3
HGNC, UniProt	*ASIC1*, P78348	*ASIC2*, Q16515	*ASIC3*, Q9UHC3
Endogenous activators (EC$_{50}$)	Extracellular H$^+$ (ASIC1a) (~1.6×10^{-7} – 6.3×10^{-7} M), Extracellular H$^+$ (ASIC1b) (~6.3×10^{-7} – 8×10^{-6} M)	Extracellular H$^+$ (~1×10^{-5} – 8×10^{-5} M)	Extracellular H$^+$ (transient component) (~2×10^{-7} – 6.3×10^{-7} M), Extracellular H$^+$ (sustained component) (~5×10^{-5} – 3.5×10^{-4} M)
Activators (EC$_{50}$)	–	–	GMQ (largely non-desensitizing; at pH 7.4) (~1×10^{-3} M), arcaine (at pH 7.4) (~1.2×10^{-3} M), agmatine (at pH 7.4) (~9.8×10^{-3} M)
Channel Blockers (IC$_{50}$)	psalmotoxin 1 (ASIC1a) (9×10^{-10} M), Zn^{2+} (ASIC1a) (~7×10^{-9} M), Pb^{2+} (ASIC1b) (~1.5×10^{-6} M), A317567 (ASIC1a) (~2×10^{-6} M), Pb^{2+} (ASIC1a) (~4×10^{-6} M), amiloride (ASIC1a) (1×10^{-5} M), benzamil (ASIC1a) (1×10^{-5} M), EIPA (ASIC1a) (1×10^{-5} M), nafamostat (ASIC1a) (~1.3×10^{-5} M), amiloride (ASIC1b) (2.1×10^{-5} – 2.3×10^{-5} M), flurbiprofen (ASIC1a) (3.5×10^{-4} M), ibuprofen (ASIC1a) (~3.5×10^{-4} M), Ni^{2+} (ASIC1a) (~6×10^{-4} M)	amiloride (2.8×10^{-5} M), A317567 (~3×10^{-5} M), nafamostat (~7×10^{-5} M), Cd^{2+} (~1×10^{-3} M)	APETx2 (transient component only) (6.3×10^{-8} M), nafamostat (transient component) (~2.5×10^{-6} M), A317567 (~1×10^{-5} M), amiloride (transient component only - sustained component enhanced by 200μM amiloride at pH 4) (1.6×10^{-5} – 6.3×10^{-5} M), Gd^{3+} (4×10^{-5} M), Zn^{2+} (6.1×10^{-5} M), aspirin (sustained component) (9.2×10^{-5} M), diclofenac (sustained component) (9.2×10^{-5} M), salicylic acid (sustained component) (2.6×10^{-4} M)
Radioligands (K$_d$)	[^{125}I]psalmotoxin 1 (ASIC1a) (2.13×10^{-10} M)	–	–
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$_{Na}$ ≫ 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	γ~ 13–15 pS; biphasic response consisting of rapidly inactivating transient and sustained components; very rapid activation (<5 ms) and inactivation (0.4s); fast recovery (0.4–0.6 s) @ pH 7.4, transient component partially inactivated at pH 7.2
Comment	ASIC1a and ASIC1b are also blocked by diarylamidines (IC$_{50}$ ~3 μM for ASIC1a)	ASIC2 is also blocked by diarylamidines	ASIC3 is also blocked by diarylamidines

Comments: psalmotoxin 1 (PcTx1) inhibits ASIC1a by modifying activation and desensitization by H^{+}, but promotes ASIC1b opening. PcTx1 has little effect upon ASIC2a, ASIC3, or ASIC1a expressed as a heteromultimer with either ASIC2a, or ASIC3 [15,19] but does block ASIC1a expressed as a heteromultimer with ASIC2b [36]. spermine, which apparently competes with PcTx1 for binding to ASIC1a, selectively enhances the function of the channel [17]. Blockade of ASIC1a by PcTx1 activates the endogenous enkephalin pathway and has very potent analgesic effects in rodents [31]. 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, ASIC1b, ASIC2a, or ASIC2a+ASIC3 [14–15]. IC$_{50}$ values for A317567 are inferred from blockade of ASIC channels native to dorsal root ganglion neurones [18]. 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 [29]). 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 [4,11,42]. The transient and sustained current components mediated by rASIC3 are selective for Na$^+$ [42]; for hASIC3 the transient component is Na$^+$ selective (PNa/PK > 10) whereas the sustained current appears non-selective (PNa/PK = 1.6) [4,11]. 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 [2,9] whereas oxidation, through the formation of intersubunit disulphide bonds, reduces currents mediated by ASIC1a [50]. ASIC1a is also irreversibly modulated by extracellular serine proteases, such as trypsin, through proteolytic cleavage [41]. Non-steroidal anti-inflammatory drugs (NSAIDs) are direct blockers of ASIC currents at therapeutic concentrations (reviewed in [40]). Extracellular Zn^{2+} potentiates proton activation of homomeric and heteromeric channels incorporating ASIC2a, but not homomeric ASIC1a or ASIC3 channels [5]. 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 [10]. NO potentiates submaximal currents activated by H^{+} mediated by ASIC1a, ASIC1b, ASIC2a and ASIC3 [7]. Ammonium activates ASIC channels (most likely ASIC1a) in midbrain dopaminergic neurones: that may be relevant to neuronal disorders associated with hyperammonemia [32]. 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 [29]. Inflammatory conditions and particular pro-inflammatory mediators induce overexpression of ASIC-encoding genes, enhance ASIC currents [30], and in the case of arachidonic acid directly activate the channel [13,37]. The sustained current component mediated by ASIC3 is potentiated by hypertonic solutions in a manner that is synergistic with the effect of arachidonic acid [13]. Selective activation of ASIC3 by GMQ at a site separate from the proton binding site is potentiated by mild acidosis and reduced extracellular Ca^{2+} [49].

Further reading

Chen X, Orser BA, MacDonald JF. (2010) Design and screening of ASIC inhibitors based on aromatic diamidines for combating neurological disorders. *Eur J Pharmacol* **648**: 15–23. [PMID:20854810]

Deval E, Gasull X, Noël J, Salinas M, Baron A, Diochot S, Lingueglia E. (2010) Acid-sensing ion channels (ASICs): pharmacology and implication in pain. *Pharmacol Ther* **128**: 549–558. [PMID:20807551]

Waldmann R, Lazdunski M. (1998) H(+)-gated cation channels: neuronal acid sensors in the NaC/DEG family of ion channels. *Curr Opin Neurobiol* **8**: 418–424. [PMID:9687356]

Wemmie JA, Price MP, Welsh MJ. (2006) Acid-sensing ion channels: advances, questions and therapeutic opportunities. *Trends Neurosci* **29**: 578–586. [PMID:16891000]

Xiong ZG, Pignataro G, Li M, Chang SY, Simon RP. (2008) Acid-sensing ion channels (ASICs) as pharmacological targets for neurodegenerative diseases. *Curr Opin Pharmacol* **8**: 25–32. [PMID:17945532]

Xu TL, Duan B. (2009) Calcium-permeable acid-sensing ion channel in nociceptive plasticity: a new target for pain control. *Prog Neurobiol* **87**: 171–180. [PMID:19388206]

Aquaporins

Overview: Aquaporins and aquaglyceroporins (provisional nomenclature) are membrane channels that allow the permeation of water and certain other small solutes across the cell membrane. Since the isolation and cloning of the first aquaporin (AQP1) [54], 12 additional members of the family have been identified, although little is known about the functional properties of two of these (*AQP11*; Q8NBQ7 and *AQP12A*; Q8IXF9). The other 11 aquaporins can be divided into two families (aquaporins and aquaglyceroporins) depending on whether they are permeable to glycerol [53]. One or more members of this family of proteins have been found to be expressed in almost all tissues of the body. Individual AQP subunits have six transmembrane domains with an inverted symmetry between the first three and last three domains [52]. Functional AQPs exist as tetramers but, unusually, each subunit contains a separate pore, so each channel has four pores.

Subunits

Nomenclature	AQP0	AQP1	AQP2	AQP3	AQP4	AQP5	AQP6	AQP7	AQP8	AQP9	AQP10
HGNC, UniProt	*MIP*, P30301	*AQP1*, P29972	*AQP2*, P41181	*AQP3*, Q92482	*AQP4*, P55087	*AQP5*, P55064	*AQP6*, Q13520	*AQP7*, O14520	*AQP8*, O94778	*AQP9*, O43315	*AQP10*, Q96PS8
Permeability	water (low)	water (high)	water (high)	water (high), glycerol	water (high)	water (high)	water (low), anions	water (high), glycerol	water (high)	water (low), glycerol	water (low), glycerol
Endogenous activators	–	cGMP	–	–	–	–	–	–	–	–	–
Inhibitors	Hg^{2+}	Ag^+, Hg^{2+}, tetraethylammonium	Hg^{2+}	Hg^{2+} (also inhibited by acid pH)	–	Hg^{2+}	Hg^{2+}	Hg^{2+}	Hg^{2+}	Hg^{2+}, phloretin	Hg^{2+}
Comment	–	–	–	AQP3 is also inhibited by acid pH	AQP4 is inhibited by PKC activation	–	AQP6 is an intracellular channel permeable to anions as well as water [55]	–	–	–	–

Further reading

Amiry-Moghaddam M, Ottersen OP. (2003) The molecular basis of water transport in the brain. *Nat Rev Neurosci* **4**: 991–1001. [PMID:14682361]

Carbrey JM, Agre P. (2009) Discovery of the aquaporins and development of the field. *Handb Exp Pharmacol* **190**: 3–28. [PMID:19096770]

Castle NA. (2005) Aquaporins as targets for drug discovery. *Drug Discov Today* **10**: 485–493. [PMID:15809194]

Kimelberg HK. (2004) Water homeostasis in the brain: basic concepts. *Neuroscience* **129**: 851–860. [PMID:15561403]

King LS, Kozono D, Agre P. (2004) From structure to disease: the evolving tale of aquaporin biology. *Nat Rev Mol Cell Biol* **5**: 687–698. [PMID:15340377]

Rojek A, Praetorius J, Frøkiaer J, Nielsen S, Fenton RA. (2008) A current view of the mammalian aquaglyceroporins. *Annu Rev Physiol* **70**: 301–327. [PMID:17961083]

Verkman AS. (2009) Aquaporins: translating bench research to human disease. *J Exp Biol* **212** (Pt 11): 1707–1715. [PMID:19448080]
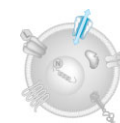
CatSper and Two-Pore channels

Overview: CatSper channels (CatSper1–4; nomenclature as agreed by NC-IUPHAR, [59]) are putative 6TM, voltage-gated, calcium permeant channels that are presumed to assemble as a tetramer of α-like subunits and mediate the current $I_{CatSper}$. In mammals, CatSper subunits are structurally most closely related to individual domains of voltage-activated calcium channels (Ca_v) [71]. CatSper1 [71], CatSper2 [70] and CatSpers 3 and 4 [61,66,69], in common with a recently identified putative 2TM auxiliary CatSperβ protein [65] and two putative 1TM associated CatSperγ and CatSperδ proteins [58,73], are restricted to the testis and localised to the principle piece of sperm tail.

Subunits

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, spermatozoa progesterone ($EC_{50} \sim 8$ nM) also potentiates the CatSper current ($I_{CatSper}$).	–	–	–
Channel Blockers (IC_{50})	NNC55-0396 ($2 \times 10^{-6} - 1 \times 10^{-5}$ M), ruthenium red (1×10^{-5} M), HC056456 (2×10^{-5} M), mibefradil (3×10^{-5} M), Cd^{2+} (2×10^{-4} M), Ni^{2+} (3×10^{-4} M)	–	–	–
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 [$V_{1/2}$ @ pH 6.0 = +87 mV (mouse); $V_{1/2}$ @ pH 7.5 = +11mV (mouse) or pH 7.4 = +85 mV (human)]	Required for $I_{CatSper}$	Required for $I_{CatSper}$	Required for $I_{CatSper}$

Comments: CatSper channel subunits expressed singly, or in combination, fail to functionally express in heterologous expression systems [70–71]. 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 [62] and also mature human sperm [63,72]. $I_{CatSper}$ is also undetectable in the spermatozoa of *Catsper2*(-/-), *Catsper3*(-/-), or *Catsper4*(-/-) mice and CatSper 1 associates with CatSper 2, 3, or 4 in heterologous expression systems [69]. Moreover, targeted disruption of *Catsper1, 2, 3,* or *4* 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 [56–57,69]. Thus, it is likely that the CatSper pore is formed by a heterotetramer of CatSpers1–4 [69] in association with the auxiliary subunits (β, γ, δ) that are also essential for function [58]. CatSper channels are required for the increase in intracellular Ca^{2+} concentration in sperm evoked by egg *zona pellucida* glycoproteins [74]. 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 [68]. Mouse KSper is encoded by *mSlo3*, a protein detected only in testis [67–68,75]. In human sperm, such alkalinization may result from the activation of H_v1, a proton channel [64]. Mutations in CatSpers are associated with syndromic and non-syndromic male infertility [60]. In human ejaculated spermatozoa, progesterone (8,17). In addition, certain prostaglandins (*e.g.* $PGF_{1\alpha}$, PGE_1) also potentiate CatSper mediated currents [63,72].

Further reading

Clapham DE, Garbers DL. (2005) International Union of Pharmacology. L. Nomenclature and structure-function relationships of CatSper and two-pore channels. *Pharmacol Rev* **57**: 451–454. [PMID:16382101]

Hildebrand MS, Avenarius MR, Fellous M, Zhang Y, Meyer NC, Auer J, Serres C, Kahrizi K, Najmabadi H, Beckmann JS *et al.* (2010) Genetic male infertility and mutation of CATSPER ion channels. *Eur J Hum Genet* **18**: 1178–1184. [PMID:20648059]

Kirichok Y, Lishko PV. (2011) Rediscovering sperm ion channels with the patch-clamp technique. *Mol Hum Reprod* **17**: 478–499. [PMID:21642646]

Lishko PV, Kirichok Y. (2010) The role of Hv1 and CatSper channels in sperm activation. *J Physiol (Lond)* **588** (Pt 23): 4667–4672. [PMID:20679352]

Ren D, Xia J. (2010) Calcium signaling through CatSper channels in mammalian fertilization. *Physiology (Bethesda)* **25**: 165–175. [PMID:20551230]
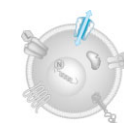
Chloride channels

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 [92]).

Excluding the transmitter-gated $GABA_A$ 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 [155]. 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 [96].

ClC family

Overview: The mammalian ClC family (reviewed in [77,87,92,94,108]) 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 [97]. 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 [103,114,125,134,146]; reviewed in [77,139]). It has recently been reported that the activity of ClC-5 as a Cl^-/H^+ exchanger is important for renal endocytosis [127]. Alternative splicing increases the structural diversity within the ClC family. The crystal structure of two bacterial ClC proteins has been described [95] and a eukaryotic ClC transporter (CmCLC) has recently been described at 3.5 Å resolution [99]. 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 [87,94,108,139]). 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 [76,99]. 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 [141].

Subunits

Nomenclature	ClC-1	ClC-2	ClC-Ka	ClC-Kb
HGNC, UniProt	*CLCN1*, P35523	*CLCN2*, P51788	*CLCNKA*, P51800	*CLCNKB*, P51801
Endogenous activators	–	arachidonic acid	–	–
Activators (EC$_{50}$)	–	lubiprostone, omeprazole	niflumic acid ($1 \times 10^{-5} - 1 \times 10^{-3}$ M)	niflumic acid ($1 \times 10^{-5} - 1 \times 10^{-3}$ M)
Channel Blockers (IC$_{50}$)	9-A-C, Cd^{2+}, fenofibric acid, *S*-(-)CPB, *S*-(-)CPP, niflumic acid, Zn^{2+}	Cd^{2+}, DPC, NPPB, Zn^{2+}, GaTx2 (K_d 1.5×10^{-11} M) [*voltage dependent*-100.0 mV]	3-phenyl-CPP, DIDS, niflumic acid (>1×10^{-3} M)	3-phenyl-CPP, DIDS
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-synthetase 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	γ = 26 pS; linear current-voltage relationship except at very negative potentials; no time dependence; inhibited by extracellular protons (pK = 7.1); potentiated by extracellular Ca^{2+}	Bidirectional rectification; no time dependence; inhibited by extracellular protons; potentiated by extracellular Ca^{2+}
Comment	ClC-1 is constitutively active	ClC-2 is also activated by amidation	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

Nomenclature	ClC-3	ClC-4	ClC-5	ClC-6	ClC-7
HGNC, UniProt	*CLCN3*, P51790	*CLCN4*, P51793	*CLCN5*, P51795	*CLCN6*, P51797	*CLCN7*, P51798
Channel Blockers (IC_{50})	phloretin (3×10^{-5} M)	Zn^{2+} (5×10^{-5} M) [131], Cd^{2+} (6.8×10^{-5} M) [131]	–	DIDS (1×10^{-3} M)	DIDS (4×10^{-5} M) [149], NS5818 (5.2×10^{-5} M) [149], NPPB (1.56×10^{-4} M) [149]
Functional characteristics	Cl^-/H^+ antiporter [121]; 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 ($2Cl^-$:$1H^+$) [79,134,146]; extreme outward rectification; voltage-dependent gating with midpoint of activation at +73 mV [130]; rapid activation and deactivation; inhibited by extracellular acidosis; non-hydrolytic nucleotide binding required for full activity	Cl^-/H^+ antiporter ($2Cl^-$:$1H^+$) [134,146,151,159]; 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-synthetase related (CBS) domains activates ClC-5	Cl^-/H^+ antiporter ($2Cl^-$:$1H^+$) [125]; outward rectification, rapid activation and deactivation	Cl^-/H^+ antiporter ($2Cl^-$:$1H^+$) [103,114,149]; strong outward rectification; voltage-dependent gating with a threshold more positive than ~ + 20 mV; very slow activation and deactivation
Comment	insensitive to the channel blockers DIDS, NPPB and tamoxifen (10 μM)	–	insensitive to the channel blockers DIDS (1 mM), DPC (1 mM), 9-A-C (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-A-C 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 ([115] and reviewed in [138]). 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 [153]. 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 [137]. Functional expression of human ClC-Ka and ClC-Kb requires the presence of barttin [97,147] reviewed in [98]. 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 [97,101,147] reviewed in [98]). 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 [116]. The biophysical and pharmacological properties of ClC-3, and the relationship of the protein to the endogenous volume-regulated anion channel(s) VRAC [78,105] are controversial and further complicated by the possibility that ClC-3 may function as both a Cl^-/H^+ exchanger and an ion channel [78,134,156]. 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^-), ClC-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 [79]. Similar findings have been made for ClC-5 [158]. ClC-7 associates with a β subunit, Ostm1, which increases the stability of the former [112] and is essential for its function [114].

CFTR

Overview: CFTR, a 12TM, ABC transporter-type protein, is a cAMP-regulated epithelial cell membrane Cl⁻ channel involved in normal fluid transport across various epithelia. Of the 1700 mutations identified in CFTR, the most common is the deletion mutant ΔF508 (a class 2 mutation) which results in impaired trafficking of CFTR and reduces its incorporation into the plasma membrane causing cystic fibrosis (reviewed in [88]). Channels carrying the ΔF508 mutation that do traffic to the plasma membrane demonstrate gating defects. Thus, pharmacological resto-ration the function of the ΔF508 mutant would require a compound that embodies 'corrector' (*i.e.* facilitates folding and trafficking to the cell surface) and 'potentiator' (*i.e.* promotes opening of channels at the cell surface) activities [88]. In addition to acting as an anion channel *per se*, CFTR may act as a regulator of several other conductances including inhibition of the epithelial Na channel (ENaC), calcium activated chloride channels (CaCC) and volume regulated anion channel (VRAC), activation of the outwardly rectifying chloride channel (ORCC), and enhancement of the sulphonylurea sensitivity of the renal outer medullary potassium channel (ROMK2), (reviewed in [126]). CFTR also regulates TRPV4, which provides the Ca^{2+} signal for regulatory volume decrease in airway epithelia [81]. The activities of CFTR and the chloride-bicarbonate exchangers SLC26A3 (DRA) and SLC26A6 (PAT1) are mutually enhanced by a physical association between the regulatory (R) domain of CFTR and the STAS domain of the SCL26 transporters, an effect facilitated by PKA-mediated phosphorylation of the R domain of CFTR [109].

Channels

Nomenclature	HGNC, UniProt	Activators (EC_{50})	Channel Blockers (IC_{50})	Functional characteristics	Comment
CFTR	*CFTR*, P13569	apigenin (Potentiation), capsaicin (Potentiation), CBIQ (Potentiation), felodipine (Potentiation), genistein (Potentiation), nimodipine (Potentiation), NS004 (Potentiation), phenylglycine-01 (Potentiation), SF-01 (Potentiation), UCCF-029 (Potentiation), UCCF-339 (Potentiation), UCCF-853 (Potentiation), VX-770 (Potentiation)	intracellular CFTR$_{inh}$-172 (intracellular application prolongs mean closed time), GaTx1, glibenclamide, extracellular GlyH-101	γ = 6–10 pS; permeability sequence = $Br^- \geq Cl^- > I^- > F^-$, ($P_I/P_{Cl}$ = 0.1–0.85); slight outward rectification; phosphorylation necessary for activation by ATP binding at binding nucleotide binding domains (NBD)1 and 2; positively regulated by PKC and PKGII (tissue specific); regulated by several interacting proteins including syntaxin 1A, Munc18 and PDZ domain proteins such as NHERF (EBP50) and CAP70	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. SF-01 is an example of a sulfonamide. Malonic acid hydrazide conjugates are also CFTR channel blockers (see Verkman and Galietta, 2009 [155])

Comments: In addition to the agents listed in the table, the novel small molecule, ataluren, induces translational read through of nonsense mutations in CFTR (reviewed in [150]). Corrector compounds that aid the folding of DF508CFTR to increase the amount of protein expressed and potentially delivered to the cell surface include VX-532 (which is also a potentiator), VRT-325, KM11060, Corr-3a and Corr-4a see [155] for details and structures of Corr-3a and Corr-4a). Inhibition of CFTR by intracellular application of the peptide GaTx1, from *Leiurus quinquestriatus herbareus* venom, occurs preferentially for the closed state of the channel [102]. CFTR contains two cytoplasmic nucleotide binding domains (NBDs) that bind ATP. A single open-closing cycle is hypothesised to involve, in sequence: binding of ATP at the N-terminal NBD1, ATP binding to the C-terminal NBD2 leading to the formation of an intramolecular NBD1-NBD2 dimer associated with the open state, and subsequent ATP hydrolysis at NBD2 facilitating dissociation of the dimer and channel closing, and the initiation of a new gating cycle [80,122]. Phosphorylation by PKA at sites within a cytoplasmic regulatory (R) domain facilitates the interaction of two NBD domains. PKC (and PKGII within intestinal epithelial cells via guanylinstimulated cGMP formation) positively regulate CFTR activity.

Calcium activated chloride channel

Overview: Chloride channels activated by intracellular calcium (CaCC) are widely expressed in excitable and non-excitable cells where they perform diverse functions [106]. The molecular nature of CaCC has been uncertain with both *CLCA, TWEETY* and *BEST* genes having been considered as likely candidates [92,107,117]. It is now accepted that CLCA expression products are unlikely to form channels *per se* and probably function as cell adhesion proteins, or are secreted [133]. Similarly, *TWEETY* gene products do not recapitulate the properties of endogenous CaCC. The bestrophins encoded by genes *BEST1-4* have a topology more consistent with ion channels [107] and form chloride channels that are activated by physiological concentrations of Ca^{2+}, but whether such activation is direct is not known [107]. However, currents generated by bestrophin over-expression do not resemble native CaCC currents. The evidence for and against bestrophin proteins forming CaCC is critically reviewed by Duran *et al*. in their 2010 paper [92]. Recently, a new gene family, TMEM16 (anoctamin) consisting of 10 members (TMEM16A-K; anoctamin 1–10) has been identified and there is firm evidence that some of these members form chloride channels [91,110]. TMEM16A (anoctamin 1; Ano 1) produces Ca^{2+}-activated Cl^- currents with kinetics similar to native CaCC currents recorded from different cell types [86,142,148,157]. Knockdown of TMEM16A greatly reduces currents mediated by calcium-activated chloride channels in submandibular gland cells [157] and smooth muscle cells from pulmonary artery [118]. In TMEM16A[(-/-)] mice secretion of Ca^{2+}-dependent Cl^- secretion by several epithelia is reduced [132,142]. Alternative splicing regulates the voltage- and Ca^{2+}- dependence of TMEM16A and such processing may be tissue-specific manner and thus contribute to functional diversity [100]. There are also reports that TMEM16B (anoctamin 2; Ano 2) supports CaCC activity (*e.g.* [135]) and in TMEM16B[(-/-)] mice Ca-activated Cl^- currents in the main olfactory epithelium (MOE) and in the vomeronasal organ are virtually absent [85].

Subunits

Nomenclature	HGNC, UniProt	Endogenous activators (EC_{50})	Endogenous channel blockers (IC_{50})	Channel Blockers (IC_{50})	Functional characteristics
CaCC	*ANO1*, Q5XXA6	intracellular Ca^{2+}	Ins(3,4,5,6)P_4	9-A-C, DCDPC, DIDS, flufenamic acid, fluoxetine, mibefradil, niflumic acid, NPPB, SITS, tannic acid	$\gamma = 0.5$–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: Blockade of $I_{Cl(Ca)}$ by niflumic acid, DIDS and 9-A-C is voltage-dependent whereas block by NPPB is voltage-independent [106]. Extracellular niflumic acid; DCDPC and 9-A-C (but not DIDS) exert a complex effect upon $I_{Cl(Ca)}$ in vascular smooth muscle, enhancing and inhibiting inwardly and outwardly directed currents in a manner dependent upon $[Ca^{2+}]_i$ (see [113] for summary). Considerable crossover in pharmacology with large conductance Ca^{2+}-activated K^+ channels also exists (see [104] for overview). Two novel compounds, CaCC$_{inh}$-A01 and CaCC$_{inh}$-B01 have recently been identified as blockers of calcium-activated chloride channels in T84 human intestinal epithelial cells [89] for structures). Significantly, other novel compounds totally block currents mediated by TMEM116A, but have only a modest effect upon total current mediated by CaCC native to T84 cells or human bronchial epithelial cells, suggesting that TMEM16A is not the predominant CaCC in such cells [124]. CaMKII modulates CaCC in a tissue dependent manner (reviewed by [106,113]). CaMKII inhibitors block activation of $I_{Cl(Ca)}$ in T84 cells but have no effect in parotid acinar cells. In tracheal and arterial smooth muscle cells, but not portal vein myocytes, inhibition of CaMKII reduces inactivation of $I_{Cl(Ca)}$. Intracellular Ins(3,4,5,6)P_4 may act as an endogenous negative regulator of CaCC channels activated by Ca^{2+}, or CaMKII. Smooth muscle CaCC are also regulated positively by Ca^{2+}-dependent phosphatase, calcineurin (see [113] for summary).

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 [144]. 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 [93,143]. 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 [83]. A family of human high conductance Cl$^-$ channels (TTYH1-3) that resemble Maxi Cl$^-$ channels has been cloned [152], but alternatively, Maxi Cl$^-$ channels have also been suggested to correspond to the voltage-dependent anion channel, VDAC, expressed at the plasma membrane [82,128].

Channels

Nomenclature	Activators (EC$_{50}$)	Endogenous channel blockers (IC$_{50}$)	Channel Blockers (IC$_{50}$)	Functional characteristics	Comment
Maxi Cl$^-$	extracellular chlorpromazine, cytosolic GTPγS, extracellular tamoxifen, extracellular toremifene, extracellular triflupromazine	intracellular arachidonic acid	DPC, extracellular Gd^{3+}, SITS, DIDS (4x10^{-5} M) [149], extracellular Zn^{2+} (5x10^{-5} M) [131], NPPB (1.56x10^{-4} M) [149]	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	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 [93,143]. Channel activation by anti-oestrogens in whole cell recordings requires the presence of intracellular nucleotides and is prevented by pre-treatment with 17β-estradiol, dibutyryl cAMP, or intracellular dialysis with GDPβS [90]. 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 [90]. 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 [140].

Volume regulated chloride channels

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 [84,123,126,129]). 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* P-glycoprotein, Icln, Band 3 anion exchanger and phospholemman are also no longer considered likely to fulfil this function (see reviews [126,145]).

Channels

Nomenclature	Activators (EC$_{50}$)	Endogenous channel blockers (IC$_{50}$)	Channel Blockers (IC$_{50}$)	Functional characteristics	Comment
VRAC	GTPγS	arachidonic acid, extracellular Mg^{2+}	1,9-dideoxyforskolin, 9-A-C, carbenoxolone, clomiphene, DCPIB, diBA-(5)-C4, DIDS, gossypol, IAA-94, mefloquine, mibefradil, nafoxidine, NDGA, NPPB, NS3728, quinidine, quinine, tamoxifen	$\gamma = 10$–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$_2$O$_2$ and Src-PLCγ-Ca^{2+} pathways; regulation by PKCα required for optimal activity; cholesterol depletion enhances activity; activated by direct stretch of β1-integrin	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.

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 cAMP-activated Cl⁻ channel that does not correspond to CFTR has been described in intestinal Paneth cells [154]. A Cl channel activated by cGMP 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 [119,136]. It has been proposed that bestrophin-3 (*BEST3*, Q8N1M1) is an essential component of the cGMP-activated channel [120]. A proton-activated, outwardly rectifying anion channel has also been described [111].

Further reading

Accardi A, Picollo A. (2010) CLC channels and transporters: proteins with borderline personalities. *Biochim Biophys Acta* **1798**: 1457–1464. [PMID:20188062]

Alekov AK, Fahlke C. (2008) Anion channels: regulation of ClC-3 by an orphan second messenger. *Curr Biol* **18**: R1061–R1064. [PMID:19036336]

Aleksandrov AA, Aleksandrov LA, Riordan JR. (2007) CFTR (ABCC7) is a hydrolyzable-ligand-gated channel. *Pflugers Arch* **453**: 693–702. [PMID:17021796]

Amaral MD, Kunzelmann K. (2007) Molecular targeting of CFTR as a therapeutic approach to cystic fibrosis. *Trends Pharmacol Sci* **28**: 334–341. [PMID:17573123]

Aromataris EC, Rychkov GY. (2006) ClC-1 chloride channel: Matching its properties to a role in skeletal muscle. *Clin Exp Pharmacol Physiol* **33**: 1118–1123. [PMID:17042925]

Ashlock MA, Olson ER. (2011) Therapeutics development for cystic fibrosis: a successful model for a multisystem genetic disease. *Annu Rev Med* **62**: 107–125. [PMID:21226613]

Best L, Brown PD, Sener A, Malaisse WJ. (2010) Electrical activity in pancreatic islet cells: The VRAC hypothesis. *Islets* **2**: 59–64. [PMID:21099297]

Chen TY. (2005) Structure and function of clc channels. *Annu Rev Physiol* **67**: 809–839. [PMID:15709979]

Chen TY, Hwang TC. (2008) CLC-0 and CFTR: chloride channels evolved from transporters. *Physiol Rev* **88**: 351–387. [PMID:18391167]

Cuthbert AW. (2011) New horizons in the treatment of cystic fibrosis. *Br J Pharmacol* **163**: 173–183. [PMID:21108631]

Duan D. (2009) Phenomics of cardiac chloride channels: the systematic study of chloride channel function in the heart. *J Physiol (Lond)* **587** (Pt 10): 2163–2177. [PMID:19171656]

Duan DD. (2011) The ClC-3 chloride channels in cardiovascular disease. *Acta Pharmacol Sin* **32**: 675–684. [PMID:21602838]

Duran C, Hartzell HC. (2011) Physiological roles and diseases of Tmem16/Anoctamin proteins: are they all chloride channels?. *Acta Pharmacol Sin* **32**: 685–692. [PMID:21642943]

Duran C, Thompson CH, Xiao Q, Hartzell HC. (2010) Chloride channels: often enigmatic, rarely predictable. *Annu Rev Physiol* **72**: 95–121. [PMID:19827947]

Dutzler R. (2007) A structural perspective on ClC channel and transporter function. *FEBS Lett* **581**: 2839–2844. [PMID:17452037]

Edwards JC, Kahl CR. (2010) Chloride channels of intracellular membranes. *FEBS Lett* **584**: 2102–2111. [PMID:20100480]

Fahlke C, Fischer M. (2010) Physiology and pathophysiology of ClC-K/barttin channels. *Front Physiol* **1**: 155. [PMID:21423394]

Ferrera L, Caputo A, Galietta LJ. (2010) TMEM16A protein: a new identity for Ca(2+)-dependent Cl⁻ channels. *Physiology (Bethesda)* **25**: 357–363. [PMID:21186280]

Gadsby DC, Vergani P, Csanády L. (2006) The ABC protein turned chloride channel whose failure causes cystic fibrosis. *Nature* **440**: 477–483. [PMID:16554808]

Galietta LJ. (2009) The TMEM16 protein family: a new class of chloride channels?. *Biophys J* **97**: 3047–3053. [PMID:20006941]

Greenwood IA, Leblanc N. (2007) Overlapping pharmacology of Ca2+-activated Cl⁻ and K+ channels. *Trends Pharmacol Sci* **28**: 1–5. [PMID:17150263]

Guan YY, Wang GL, Zhou JG. (2006) The ClC-3 Cl⁻ channel in cell volume regulation, proliferation and apoptosis in vascular smooth muscle cells. *Trends Pharmacol Sci* **27**: 290–296. [PMID:16697056]

Hartzell C, Putzier I, Arreola J. (2005) Calcium-activated chloride channels. *Annu Rev Physiol* **67**: 719–758. [PMID:15709976]

Hartzell HC, Qu Z, Yu K, Xiao Q, Chien LT. (2008) Molecular physiology of bestrophins: multi-functional membrane proteins linked to best disease and other retinopathies. *Physiol Rev* **88**: 639–672. [PMID:18391176]

Jentsch TJ. (2008) CLC chloride channels and transporters: from genes to protein structure, pathology and physiology. *Crit Rev Biochem Mol Biol* **43**: 3–36. [PMID:18307107]

Kirk KL, Wang W. (2011) A unified view of cystic fibrosis transmembrane conductance regulator (CFTR) gating: combining the allosterism of a ligand-gated channel with the enzymatic activity of an ATP-binding cassette (ABC) transporter. *J Biol Chem* **286**: 12813–12819. [PMID:21296873]

Krämer BK, Bergler T, Stoelcker B, Waldegger S. (2008) Mechanisms of Disease: the kidney-specific chloride channels ClCKA and ClCKB, the Barttin subunit, and their clinical relevance. *Nat Clin Pract Nephrol* **4**: 38–46. [PMID:18094726]

Kunzelmann K, Tian Y, Martins JR, Faria D, Kongsuphol P, Ousingsawat J, Thevenod F, Roussa E, Rock J, Schreiber R. (2011) Anoctamins. *Pflugers Arch* **462**: 195–208. [PMID:21607626]

Leblanc N, Ledoux J, Saleh S, Sanguinetti A, Angermann J, O'Driscoll K, Britton F, Perrino BA, Greenwood IA. (2005) Regulation of calcium-activated chloride channels in smooth muscle cells: a complex picture is emerging. *Can J Physiol Pharmacol* **83**: 541–556. [PMID:16091780]

Muallem D, Vergani P. (2009) Review. ATP hydrolysis-driven gating in cystic fibrosis transmembrane conductance regulator. *Philos Trans R Soc Lond, B, Biol Sci* **364**: 247–255. [PMID:18957373]

Mulligan SJ, MacVicar BA. (2006) VRACs CARVe a path for novel mechanisms of communication in the CNS. *Sci STKE* **2006**: pe42. [PMID:17047222]

Noy E, Senderowitz H. (2011) Combating cystic fibrosis: in search for CF transmembrane conductance regulator (CFTR) modulators. *ChemMedChem* **6**: 243–251. [PMID:21275046]

Okada Y. (2006) Cell volume-sensitive chloride channels: phenotypic properties and molecular identity. *Contrib Nephrol* **152**: 9–24. [PMID:17065805]

Okada Y, Sato K, Numata T. (2009) Pathophysiology and puzzles of the volume-sensitive outwardly rectifying anion channel. *J Physiol (Lond)* **587** (Pt 10): 2141–2149. [PMID:19171657]

Patel AC, Brett TJ, Holtzman MJ. (2009) The role of CLCA proteins in inflammatory airway disease. *Annu Rev Physiol* **71**: 425–449. [PMID:18954282]

Planells-Cases R, Jentsch TJ. (2009) Chloride channelopathies. *Biochim Biophys Acta* **1792**: 173–189. [PMID:19708126]

Plans V, Rickheit G, Jentsch TJ. (2009) Physiological roles of CLC Cl(-)/H (+) exchangers in renal proximal tubules. *Pflugers Arch* **458**: 23–37. [PMID:18853181]

Puljak L, Kilic G. (2006) Emerging roles of chloride channels in human diseases. *Biochim Biophys Acta* **1762**: 404–413. [PMID:16457993]

Pusch M, Zifarelli G, Murgia AR, Picollo A, Babini E. (2006) Channel or transporter? The CLC saga continues. *Exp Physiol* **91**: 149–152. [PMID:16179405]

Riordan JR. (2005) Assembly of functional CFTR chloride channels. *Annu Rev Physiol* **67**: 701–718. [PMID:15709975]

Riquelme G. (2009) Placental chloride channels: a review. *Placenta* **30**: 659–669. [PMID:19604577]

Sabirov RZ, Okada Y. (2009) The maxi-anion channel: a classical channel playing novel roles through an unidentified molecular entity. *J Physiol Sci* **59**: 3–21. [PMID:19340557]

Sloane PA, Rowe SM. (2010) Cystic fibrosis transmembrane conductance regulator protein repair as a therapeutic strategy in cystic fibrosis. *Curr Opin Pulm Med* **16**: 591–597. [PMID:20829696]

Verkman AS, Galietta LJ. (2009) Chloride channels as drug targets. *Nat Rev Drug Discov* **8**: 153–171. [PMID:19153558]

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 [162–164]. 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 (Cx23, Cx25, Cx26, Cx30, Cx30.2, Cx30.3, Cx31, Cx31.1, Cx31.9, Cx32, Cx36, Cx37, Cx40, Cx40.1, Cx43, Cx45, Cx46, Cx47, Cx50, Cx59, Cx62) and 3 pannexin genes (Px1, Px2, Px3; which are structur-ally related to the invertebrate innexin genes) code for gap junction proteins (provisional nomenclature) 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 [165]. 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 [168]. 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 [169]. Like the connexins, at least some of the pannexins can form hemichannels [162,166].

Subunits

Nomenclature	Cx23, Cx25, Cx26, Cx30, Cx30.2, Cx30.3, Cx31, Cx31.1, Cx31.9, Cx32, Cx36, Cx37, Cx40, Cx40.1, Cx43, Cx45, Cx46, Cx47, Cx50, Cx59, Cx62	Px1, Px2, Px3
HGNC, UniProt	*GJE1*, A6NN92; *GJB7*, Q6PEY0; *GJB2*, P29033; *GJB6*, O95452; *GJC3*, Q8NFK1; *GJB4*, Q9NTQ9; *GJB3*, O75712; *GJB5*, O95377; *GJD3*, Q8N144; *GJB1*, P08034; *GJD2*, Q9UKL4; *GJA4*, P35212; *GJA5*, P36382; *GJD4*, Q96KN9; *GJA1*, P17302; *GJC1*, P36383; *GJA3*, Q9Y6H8; *GJC2*, Q5T442; *GJA8*, P48165; *GJA9*, P57773; *GJA10*, Q969M2	*PANX1*, Q96RD7; *PANX2*, Q96RD6; *PANX3*, Q96QZ0
Endogenous inhibitors	extracellular Ca^{2+} (blocked by raising external Ca^{2+})	–
Inhibitors	carbenoxolone, flufenamic acid, octanol	carbenoxolone, flufenamic acid (little block by flufenamic acid)
Comment	–	The pannexins are 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 [167]. At least some pannexin hemichannels are more sensitive to carbenoxolone than connexins but much less sensitive to flufenamic acid [161]. 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, [160]).

Further reading

Cruciani V, Mikalsen SO. (2006) The vertebrate connexin family. *Cell Mol Life Sci* **63**: 1125–1140. [PMID:16568237]

Evans WH, De Vuyst E, Leybaert L. (2006) The gap junction cellular internet: connexin hemichannels enter the signalling limelight. *Biochem J* **397**: 1–14. [PMID:16761954]

Kandouz M, Batist G. (2010) Gap junctions and connexins as therapeutic targets in cancer. *Expert Opin Ther Targets* **14**: 681–692. [PMID:20446866]

MacVicar BA, Thompson RJ. (2010) Non-junction functions of pannexin-1 channels. *Trends Neurosci* **33**: 93–102. [PMID:20022389]

Meşe G, Richard G, White TW. (2007) Gap junctions: basic structure and function. *J Invest Dermatol* **127**: 2516–2524. [PMID:17934503]

Shestopalov VI, Panchin Y. (2008) Pannexins and gap junction protein diversity. *Cell Mol Life Sci* **65**: 376–394. [PMID:17982731]

Söhl G, Maxeiner S, Willecke K. (2005) Expression and functions of neuronal gap junctions. *Nat Rev Neurosci* **6**: 191–200. [PMID:15738956]

Zoidl G, Dermietzel R. (2010) Gap junctions in inherited human disease. *Pflugers Arch* **460**: 451–466. [PMID:20140684]

Cyclic nucleotide-regulated channels

Overview: Cyclic nucleotide-gated (CNG) channels are responsible for signalling in the primary sensory cells of the vertebrate visual and olfactory systems. A standardised nomenclature for CNG channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels [176].

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 [175,177], where light signals through rhodopsin and transducin to stimulate phosphodiesterase and reduce intracellular cGMP level. This results in a closure of CNG channels and a reduced 'dark current'. Similar channels were found in the cilia of olfactory neurons [178] and the pineal gland [174]. The cyclic nucleotides bind to a domain in the C terminus of the subunit protein: other channels directly binding cyclic nucleotides include HCN, eag and certain plant potassium channels.

Subunits

Nomenclature	CNGA1	CNGA2	CNGA3	CNGA4	CNGB1	CNGB3
HGNC, UniProt	*CNGA1*, P29973	*CNGA2*, Q16280	*CNGA3*, Q16281	*CNGA4*, Q8IV77	*CNGB1*, Q14028	*CNGB3*, Q9NQW8
Activators	cGMP (EC$_{50}$ ~ 30 μM) >> cAMP	cGMP ~ cAMP (EC$_{50}$ ~ 1 μM)	cGMP (EC$_{50}$ ~ 30 μM) >> cAMP	–	–	–
Inhibitors	L-(cis)-diltiazem	–	L-(cis)-diltiazem	–	–	–
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: 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; Cone: CNGA3$_2$/CNGB3$_2$; Olfactory neurons: CNGA2$_2$/CNGA4/CNGB1b [180–184].

Hyperpolarisation-activated, cyclic nucleotide-gated (HCN) The hyperpolarisation-activated, cyclic nucleotide-gated (HCN) channels are cation channels that are activated by hyperpolarisation at voltages negative to ~-50 mV. The cyclic nucleotides cAMP and cGMP directly activate the channels and shift the activation curves of HCN channels to more positive voltages, thereby enhancing channel activity. HCN channels underlie pacemaker currents found in many excitable cells including cardiac cells and neurons [173,179]. 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 [170]. A standardised nomenclature for HCN channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels [176].

Nomenclature	HCN1	HCN2	HCN3	HCN4
HGNC, UniProt	*HCN1*, O60741	*HCN2*, Q9UL51	*HCN3*, Q9P1Z3	*HCN4*, Q9Y3Q4
Activators	cAMP > cGMP (both weak)	cAMP > cGMP	–	cAMP > cGMP
Inhibitors	Cs$^+$, ivabradine, ZD7288	Cs$^+$, ivabradine, ZD7288	Cs$^+$, ivabradine, ZD7288	Cs$^+$, ivabradine, ZD7288

Comments: 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 [171] and ivabradine [172] have proven useful in identifying and studying functional HCN channels in native cells. zatebradine and cilobradine are also useful blocking agents.
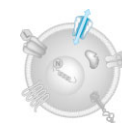
Further reading

Baruscotti M, Bottelli G, Milanesi R, DiFrancesco JC, DiFrancesco D. (2010) HCN-related channelopathies. *Pflugers Arch* **460**: 405–415. [PMID:20213494]

Baruscotti M, Bucchi A, Difrancesco D. (2005) Physiology and pharmacology of the cardiac pacemaker ("funny") current. *Pharmacol Ther* **107**: 59–79. [PMID:15963351]

Biel M, Michalakis S. (2009) Cyclic nucleotide-gated channels. *Handb Exp Pharmacol* **191**: 111–136. [PMID:19089328]

Biel M, Wahl-Schott C, Michalakis S, Zong X. (2009) Hyperpolarization-activated cation channels: from genes to function. *Physiol Rev* **89**: 847–885. [PMID:19584315]

Bois P, Guinamard R, Chemaly AE, Faivre JF, Bescond J. (2007) Molecular regulation and pharmacology of pacemaker channels. *Curr Pharm Des* **13**: 2338–2349. [PMID:17692005]

Bradley J, Reisert J, Frings S. (2005) Regulation of cyclic nucleotide-gated channels. *Curr Opin Neurobiol* **15**: 343–349. [PMID:15922582]

Brown RL, Strassmaier T, Brady JD, Karpen JW. (2006) The pharmacology of cyclic nucleotide-gated channels: emerging from the darkness. *Curr Pharm Des* **12**: 3597–3613. [PMID:17073662]

Craven KB, Zagotta WN. (2006) CNG and HCN channels: two peas, one pod. *Annu Rev Physiol* **68**: 375–401. [PMID:16460277]

Cukkemane A, Seifert R, Kaupp UB. (2011) Cooperative and uncooperative cyclic-nucleotide-gated ion channels. *Trends Biochem Sci* **36**: 55–64. [PMID:20729090]

DiFrancesco D. (2010) The role of the funny current in pacemaker activity. *Circ Res* **106**: 434–446. [PMID:20167941]

Dunlop J, Vasilyev D, Lu P, Cummons T, Bowlby MR. (2009) Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and pain. *Curr Pharm Des* **15**: 1767–1772. [PMID:19442189]

Hofmann F, Biel M, Kaupp UB. (2005) International Union of Pharmacology. LI. Nomenclature and structure-function relationships of cyclic nucleotide-regulated channels. *Pharmacol Rev* **57**: 455–462. [PMID:16382102]

Maher MP, Wu NT, Guo HQ, Dubin AE, Chaplan SR, Wickenden AD. (2009) HCN channels as targets for drug discovery. *Comb Chem High Throughput Screen* **12**: 64–72. [PMID:19149492]

Mazzolini M, Marchesi A, Giorgetti A, Torre V. (2010) Gating in CNGA1 channels. *Pflugers Arch* **459**: 547–555. [PMID:19898862]

Meldrum BS, Rogawski MA. (2007) Molecular targets for antiepileptic drug development. *Neurotherapeutics* **4**: 18–61. [PMID:17199015]

Tardif JC. (2008) Ivabradine: I(f) inhibition in the management of stable angina pectoris and other cardiovascular diseases. *Drugs Today* **44**: 171–181. [PMID:18536779]

Wahl-Schott C, Biel M. (2009) HCN channels: structure, cellular regulation and physiological function. *Cell Mol Life Sci* **66**: 470–494. [PMID:18953682]
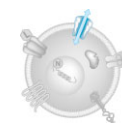
Epithelial sodium channels (ENaC)

Overview: The epithelial sodium channels (ENaC) mediates sodium reabsorption in the aldosterone-sensitive distal part of the nephron and the collecting duct of the kidney. ENaC is found on other tight epithelial tissues such as the airways, distal colon and exocrine glands. ENaC activity is tightly regulated in the kidney by aldosterone, angiotensin II (*AGT*, P01019), vasopressin, insulin (*INS*, P01308) and glucocorticoids; this fine regulation of ENaC is essential to maintain sodium balance between daily intake and urinary excretion of sodium, circulating volume and blood pressure. ENaC expression is also vital for clearance of foetal lung fluid, and to maintain air-surface-liquid [195,199]. Sodium reabsorption is suppressed by the 'potassium-sparing' diuretics amiloride and triamterene. ENaC is a heteromultimeric channel made of homologous α β and γ subunits. The primary structure of αENaC subunit was identified by expression cloning [188]; β and γ ENaC were identified by functional complementation of the α subunit [189]. Each ENaC subunit contains 2 TM α helices connected by a large extracellular loop and short cytoplasmic amino- and carboxy-termini. The stoichiometry of the epithelial sodium channel in the kidney and related epithelia is, by homology with the structurally related channel ASIC1a, thought to be a heterotrimer of 1α:1β:1γ subunits [193].

Channels

Nomenclature	Subunits	Activators (EC$_{50}$)	Channel Blockers (IC$_{50}$)	Functional characteristics
ENaCαβγ	ENaC α, ENaC β, ENaC γ	S3969 (1.2x10^{-6} M) [200]	P552-02 (7.6x10^{-9} M), benzamil (~1x10^{-8} M), amiloride (1x10^{-7} – 2x10^{-7} M), triamterene (~5x10^{-6} M) [189,196]	γ ≈ 4–5 pS, P$_{Na}$/P$_K$ > 20; tonically open at rest; expression and ion flux regulated by circulating aldosterone-mediated changes in gene transcription. The action of aldosterone, which occurs in 'early' (1.5–3 h) and 'late' (6–24 hr) phases is competitively antagonised by spironolactone, its active metabolites and eplerenone. Glucocorticoids are important functional regulators in lung/airways and this control is potentiated by thyroid hormone; but the mechanism underlying such potentiation is unclear [185,206,209]. The density of channels in the apical membrane, and hence G$_{Na}$, can be controlled *via* both serum and glucocorticoid-regulated kinases (SGK1, 2 and 3) [190–191] and *via* cAMP/PKA [203]; and these protein kinases appear to act by inactivating Nedd-4/2, a ubiquitin ligase that normally targets the ENaC channel complex for internalization and degradation [186,190]. ENaC is constitutively activated by soluble and membrane-bound serine proteases, such as furin, prostasin (CAP1), plasmin and elastase [197–198,204,207–208]. The activation of ENaC by proteases is blocked by a protein, SPLUNC1, secreted by the airways and which binds specifically to ENaC to prevent its cleavage [192]. Pharmacological inhibitors of proteases (*e.g.* camostat acting upon prostasin) reduce the activity of ENaC [202]. Phosphatidylinositides such as PtIns(4,5)P$_2$ and PtIns(3,4,5)P$_3$) stabilise channel gating probably by binding to the β and γ ENaC subunits, respectively [201,205], whilst C terminal phosphorylation of β and γ-ENaC by ERK1/2 has been reported to inhibit the withdrawal of the channel complex from the apical membrane [212]. This effect may contribute to the cAMP-mediated increase in sodium conductance.

Comments: Data in the table refer to the αβγ heteromer. There are several human diseases resulting from mutations in ENaC subunits. Liddle's syndrome (including features of salt-sensitive hypertension and hypokalemia), is associated with gain of function mutations in the β and γ subunits leading to defective ENaC ubiquitylation and increased stability of active ENaC at the cell surface [208,210–211]. Enzymes that deubiquitylate ENaC increase its function *in vivo*. Pseudohypoaldosteronism type 1 (PHA-1) can occur through either mutations in the gene encoding the mineralocorticoid receptor, or loss of function mutations in genes encoding ENaC subunits [187]. Regulation of ENaC by phosphoinositides may underlie insulin (*INS*, P01308)-evoked renal Na$^+$ retention that can complicate the clinical management of type 2 diabetes using insulin-sensitizing thiazolidinedione drugs [194].

Further reading

Bhalla V, Hallows KR. (2008) Mechanisms of ENaC regulation and clinical implications. *J Am Soc Nephrol* **19**: 1845–1854. [PMID:18753254]

Bubien JK. (2010) Epithelial Na+ channel (ENaC), hormones, and hypertension. *J Biol Chem* **285**: 23527–23531. [PMID:20460373]

Butterworth MB. (2010) Regulation of the epithelial sodium channel (ENaC) by membrane trafficking. *Biochim Biophys Acta* **1802**: 1166–1177. [PMID:20347969]

Hamm LL, Feng Z, Hering-Smith KS. (2010) Regulation of sodium transport by ENaC in the kidney. *Curr Opin Nephrol Hypertens* **19**: 98–105. [PMID:19996890]
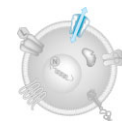
Kitamura K, Tomita K. (2010) Regulation of renal sodium handling through the interaction between serine proteases and serine protease inhibitors. *Clin Exp Nephrol* **14**: 405–410. [PMID:20535627]

Kleyman TR, Carattino MD, Hughey RP. (2009) ENaC at the cutting edge: regulation of epithelial sodium channels by proteases. *J Biol Chem* **284**: 20447–20451. [PMID:19401469]

Loffing J, Korbmacher C. (2009) Regulated sodium transport in the renal connecting tubule (CNT) via the epithelial sodium channel (ENaC). *Pflugers Arch* **458**: 111–135. [PMID:19277701]

Ma HP, Chou CF, Wei SP, Eaton DC. (2007) Regulation of the epithelial sodium channel by phosphatidylinositides: experiments, implications, and speculations. *Pflugers Arch* **455**: 169–180. [PMID:17605040]

Planès C, Caughey GH. (2007) Regulation of the epithelial Na+ channel by peptidases. *Curr Top Dev Biol* **78**: 23–46. [PMID:17338914]

Pochynyuk O, Bugaj V, Stockand JD. (2008) Physiologic regulation of the epithelial sodium channel by phosphatidylinositides. *Curr Opin Nephrol Hypertens* **17**: 533–540. [PMID:18695396]

Rossier BC, Stutts MJ. (2009) Activation of the epithelial sodium channel (ENaC) by serine proteases. *Annu Rev Physiol* **71**: 361–379. [PMID:18928407]

Rotin D, Schild L. (2008) ENaC and its regulatory proteins as drug targets for blood pressure control. *Curr Drug Targets* **9**: 709–716. [PMID:18691017]

Schild L. (2010) The epithelial sodium channel and the control of sodium balance. *Biochim Biophys Acta* **1802**: 1159–1165. [PMID:20600867]
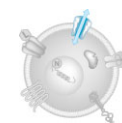
IP$_3$ receptor

Overview: The inositol 1,4,5-trisphosphate (IP$_3$) receptors (provisional nomenclature) 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$_3$ receptors are closely associated with certain proteins: calmodulin (*CALM2*, *CALM3*, *CALM1*, P62158) and FKBP (and calcineurin via FKBP). They are phosphorylated by PKA, PKC, PKG and CaMKII.

Subunits

Nomenclature	IP$_3$R1	IP$_3$R2	IP$_3$R3
HGNC, UniProt	*ITPR1*, Q14643	*ITPR2*, Q14571	*ITPR3*, Q14573
Endogenous activators (EC$_{50}$)	cytosolic ATP (< mM range), IP$_3$ (endogenous; nM - µM range), cytosolic Ca^{2+} (Concentration range = < 7.5x10^{-4} M)	cytosolic Ca^{2+} (nM range), IP$_3$ (endogenous; nM - µM range)	cytosolic Ca^{2+} (nM range), IP$_3$ (endogenous; nM - µM range)
Activators (EC$_{50}$)	adenophostin A (pharmacological; nM range), Ins(2,4,5)P$_3$ (pharmacological; also activated by other InsP$_3$ analogues)	adenophostin A (pharmacological; nM range), Ins(2,4,5)P$_3$ (pharmacological; also activated by other InsP$_3$ analogues)	–
Endogenous antagonists (IC$_{50}$)	heparin (µg/ml)	heparin (µg/ml)	heparin (µg/ml)
Antagonists (IC$_{50}$)	caffeine (mM range), decavanadate (µM range), PIP$_2$ (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+})
Comment	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

Barker CJ, Berggren PO. (2013) New horizons in cellular regulation by inositol polyphosphates: insights from the pancreatic β-cell. *Pharmacol Rev* **65**: 641–669. [PMID:23429059]

Decrock E, De Bock M, Wang N, Gadicherla AK, Bol M, Delvaeye T, Vandenabeele P, Vinken M, Bultynck G, Krysko DV *et al.* (2013) IP3, a small molecule with a powerful message. *Biochim Biophys Acta* **1833**: 1772–1786. [PMID:23291251]

Foskett JK. (2010) Inositol trisphosphate receptor Ca2+ release channels in neurological diseases. *Pflugers Arch* **460**: 481–494. [PMID:20383523]

Kiviluoto S, Vervliet T, Ivanova H, Decuypere JP, De Smedt H, Missiaen L, Bultynck G, Parys JB. (2013) Regulation of inositol 1,4,5-trisphosphate receptors during endoplasmic reticulum stress. *Biochim Biophys Acta* **1833**: 1612–1624. [PMID:23380704]

Rossi AM, Tovey SC, Rahman T, Prole DL, Taylor CW. (2012) Analysis of IP3 receptors in and out of cells. *Biochim Biophys Acta* **1820**: 1214–1227. [PMID:22033379]

Potassium channels

Overview: Potassium channels are fundamental regulators of excitability. They control the frequency and the shape of action potential waveform, the secretion of hormones and neurotransmitters and cell membrane potential. Their activity may be regulated by voltage, calcium and neurotransmitters (and the signalling pathways they stimulate). They consist of a primary pore-forming a subunit often associated with auxiliary regulatory subunits. Since there are over 70 different genes encoding K channels α subunits in the human genome, it is beyond the scope of this guide to treat each subunit individually. Instead, channels have been grouped into families and subfamilies based on their structural and functional properties. The three main families are the 2TM (two transmembrane domain), 4TM and 6TM families. A standardised nomenclature for potassium channels has been proposed by the NC-IUPHAR subcommittees on potassium channels [213–216].

Inwardly rectifying potassium channels

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 ($K_{IR}2.x$), 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 (SUR)). The pore-forming a subunits form tetramers, and heteromeric channels may be formed within subfamilies (*e.g.* $K_{IR}3.2$ with $K_{IR}3.3$).

Subunits

Nomenclature	$K_{ir}1.1$	$K_{ir}2.1$, $K_{ir}2.2$, $K_{ir}2.3$, $K_{ir}2.4$	$K_{ir}3.1$, $K_{ir}3.2$, $K_{ir}3.3$, $K_{ir}3.4$	$K_{ir}4.1$, $K_{ir}4.2$	$K_{ir}5.1$	$K_{ir}6.1$, $K_{ir}6.2$	$K_{ir}7.1$
HGNC, UniProt	*KCNJ1*, P48048	*KCNJ2*, P63252; *KCNJ12*, Q14500; *KCNJ4*, P48050; *KCNJ14*, Q9UNX9	*KCNJ3*, P48549; *KCNJ6*, P48051; *KCNJ9*, Q92806; *KCNJ5*, P48544	*KCNJ10*, P78508; *KCNJ15*, Q99712	*KCNJ16*, Q9NPI9	*KCNJ8*, Q15842; *KCNJ11*, Q14654	*KCNJ13*, O60928
Endogenous inhibitors	–	intracellular Mg^{2+}	–	–	–	–	–
Endogenous activators	–	–	PIP_2	–	–	–	–
Associated subunits	–	–	–	–	–	SUR1, SUR2A, SUR2B	–
Activators	–	–	–	–	–	cromakalim, diazoxide, minoxidil, nicorandil	–
Inhibitors	–	–	–	–	–	glibenclamide, tolbutamide	–
Functional characteristics	Inward-rectifier current	IK_1 in heart, 'strong' inward–rectifier current	G-protein-activated inward-rectifier current	Inward-rectifier current	Inward-rectifier current	ATP-sensitive, inward-rectifier current	Inward-rectifier current
Comment	–	$K_{IR}2.1$ 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	$K_{IR}3.1$ is also activated by $G_{\beta\gamma}$, $K_{IR}3.2$ is also activated by $G_{\beta\gamma}$, $K_{IR}3.3$ is also activated by $G_{\beta\gamma}$, $K_{IR}3.4$ is also activated by $G_{\beta\gamma}$	–	–	–	–
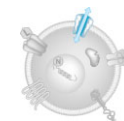
Two-P potassium channels

Overview: The 4TM family of K channels are thought to underlie many leak currents in native cells. They are open at all voltages and regulated by a wide array of neurotransmitters and biochemical mediators. The primary pore-forming αsubunit contains two pore domains (indeed, they are often referred to as two-pore domain K channels or K2P) and so it is envisaged that they form functional dimers rather than the usual K channel tetramers. There is some evidence that they can form heterodimers within subfamilies (*e.g.* $K_{2P}3.1$ with $K_{2P}9.1$). There is no current, clear, consensus on nomenclature of 4TM K channels, nor on the division into subfamilies [213]. The suggested division into subfamilies, below, is based on similarities in both structural and functional properties within subfamilies.

Subunits

Nomenclature	$K_{2P}1.1$, $K_{2P}6.1$, $K_{2P}7.1$	$K_{2P}2.1$, $K_{2P}10.1$, $K_{2P}4.1$	$K_{2P}3.1$, $K_{2P}9.1$, $K_{2P}15.1$	$K_{2P}16.1$, $K_{2P}5.1$, $K_{2P}17.1$	$K_{2P}13.1$, $K_{2P}12.1$	$K_{2P}18.1$
HGNC, UniProt	*KCNK1*, O00180; *KCNK6*, Q9Y257; *KCNK7*, Q9Y2U2	*KCNK2*, O95069; *KCNK10*, P57789; *KCNK4*, Q9NYG8	*KCNK3*, O14649; *KCNK9*, Q9NPC2; *KCNK15*, Q9H427	*KCNK16*, Q96T55; *KCNK5*, O95279; *KCNK17*, Q96T54	*KCNK13*, Q9HB14; *KCNK12*, Q9HB15	*KCNK18*, Q7Z418
Endogenous activators (EC_{50})	–	arachidonic acid	–	–	–	–
Activators (EC_{50})	–	halothane, riluzole	halothane	–	–	–
Inhibitors	–	–	anandamide, ruthenium red	–	halothane	–
Endogenous inhibitors	–	–	–	–	–	arachidonic acid
Functional characteristics	Background current	Background current	Background current	Background current	Background current	Background current
Comment	$K_{2P}1.1$ is inhibited by acid pH_i, $K_{2P}6.1$ is inhibited by acid pH_i, $K_{2P}7.1$ is inhibited by acid pH_i	$K_{2P}2.1$ is also activated by stretch, heat and acid pH_i, $K_{2P}10.1$ is also activated by stretch, heat and acid pH_i, $K_{2P}4.1$ is also activated by stretch, heat and acid pH_i	$K_{2P}3.1$ is also activated by alkakine pH_o and inhibited by acid pH_o, $K_{2P}9.1$ is also inhibited by acid pH_o, $K_{2P}15.1$ is inhibited by acid pH_o	$K_{2P}16.1$ is activated by alkaline pH_o, $K_{2P}5.1$ is activated by alkaline pH_o, $K_{2P}17.1$ is activated by alkaline pH_o	–	–

Comments: The $K_{2P}7.1$, $K_{2P}15.1$ 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 4-aminopyridine, but are blocked to varying degrees by Ba^{2+} ions.
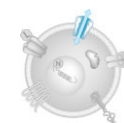
## Voltage-gated and calcium-activated potassium channels

Overview: The 6TM family of K channels comprises the voltage-gated K_V subfamilies, the KCNQ subfamily the EAG subfamily (which includes herg channels), the Ca^{2+}-activated Slo subfamily (actually with 7TM) and the Ca^{2+}-activated SK subfamily. 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).

Subunits

Nomenclature	$K_v1.1$, $K_v1.2$, $K_v1.3$, $K_v1.4$, $K_v1.5$, $K_v1.6$, $K_v1.7$, $K_v1.8$	$K_v2.1$, $K_v2.2$	$K_v3.1$, $K_v3.2$, $K_v3.3$, $K_v3.4$	$K_v4.1$, $K_v4.2$, $K_v4.3$	$K_v7.1$, $K_v7.2$, $K_v7.3$, $K_v7.4$, $K_v7.5$	$K_v10.1$, $K_v10.2$, $K_v11.1$, $K_v11.2$, $K_v11.3$, $K_v12.1$, $K_v12.2$, $K_v12.3$	$K_{Ca}1.1$, $K_{Ca}4.1$, $K_{Ca}4.2$, $K_{Ca}5.1$	$K_{Ca}2.1$, $K_{Ca}2.2$, $K_{Ca}2.3$, $K_{Ca}3.1$
HGNC, UniProt	*KCNA1*, Q09470; *KCNA2*, P16389; *KCNA3*, P22001; *KCNA4*, P22459; *KCNA5*, P22460; *KCNA6*, P17658; *KCNA7*, Q96RP8; *KCNA10*, Q16322	*KCNB1*, Q14721; *KCNB2*, Q92953	*KCNC1*, P48547; *KCNC2*, Q96PR1; *KCNC3*, Q14003; *KCNC4*, Q03721	*KCND1*, Q9NSA2; *KCND2*, Q9NZV8; *KCND3*, Q9UK17	*KCNQ1*, P51787; *KCNQ2*, O43526; *KCNQ3*, O43525; *KCNQ4*, P56696; *KCNQ5*, Q9NR82	*KCNH1*, O95259; *KCNH5*, Q8NCM2; *KCNH2*, Q12809; *KCNH6*, Q9H252; *KCNH7*, Q9NS40; *KCNH8*, Q96L42; *KCNH3*, Q9ULD8; *KCNH4*, Q9UQ05	*KCNMA1*, Q12791; *KCNT1*, Q5JUK3; *KCNT2*, Q6UVM3; *KCNU1*, A8MYU2	*KCNN1*, Q92952; *KCNN2*, Q9H2S1; *KCNN3*, Q9UGI6; *KCNN4*, O15554
Associated subunits	K_v β1 and K_v β2	$K_v5.1$, $K_v6.1$–6.4, $K_v8.1$–8.2 and $K_v9.1$–9.3	MiRP2 is an associated subunit for $K_v3.4$	KChIP and KChAP	minK and MiRP2	minK and MiRP1	–	–
Activators (EC$_{50}$)	–	–	–	–	retigabine	–	NS004, NS1619	–
Inhibitors	α-dendrotoxin, margatoxin, noxiustoxin, tetraethylammonium (potent)tetraethylammonium (moderate)4-aminopyridine (potent)	tetraethylammonium (moderate)	4-aminopyridine (potent), tetraethylammonium (potent)sea anemone toxin BDS-I	–	linopirdine, tetraethylammonium, XE991	astemizole, E4031, terfenadine	charybdotoxin, iberiotoxin, tetraethylammonium	apamin, charybdotoxin
Functional characteristics	K_V, K_A	K_V	K_V, K_A	K_A	cardiac IK_S, M current, M current	cardiac IK_R	Maxi K_{Ca} K_{Na} (slack & slick)	SK_{Ca}, IK_{Ca}

Further reading

Ahern CA, Kobertz WR. (2009) Chemical tools for K(+) channel biology. *Biochemistry* **48**: 517–526. [PMID:19113860]

Bayliss DA, Barrett PQ. (2008) Emerging roles for two-pore-domain potassium channels and their potential therapeutic impact. *Trends Pharmacol Sci* **29**: 566–575. [PMID:18823665]

Bean BP. (2007) The action potential in mammalian central neurons. *Nat Rev Neurosci* **8**: 451–465. [PMID:17514198]

Dalby-Brown W, Hansen HH, Korsgaard MP, Mirza N, Olesen SP. (2006) K(v)7 channels: function, pharmacology and channel modulators. *Curr Top Med Chem* **6**: 999–1023. [PMID:16787276]

Enyedi P, Czirják G. (2010) Molecular background of leak K+ currents: two-pore domain potassium channels. *Physiol Rev* **90**: 559–605. [PMID:20393194]

Goldstein SA, Bayliss DA, Kim D, Lesage F, Plant LD, Rajan S. (2005) International Union of Pharmacology. LV. Nomenclature and molecular relationships of two-P potassium channels. *Pharmacol Rev* **57**: 527–540. [PMID:16382106]

Gutman GA, Chandy KG, Grissmer S, Lazdunski M, McKinnon D, Pardo LA, Robertson GA, Rudy B, Sanguinetti MC, Stühmer W, Wang X. (2005) International Union of Pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. *Pharmacol Rev* **57**: 473–508. [PMID:16382104]
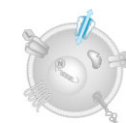
Hancox JC, McPate MJ, El Harchi A, Zhang YH. (2008) The hERG potassium channel and hERG screening for drug-induced torsades de pointes. *Pharmacol Ther* **119**: 118–132. [PMID:18616963]

Hansen JB. (2006) Towards selective Kir6.2/SUR1 potassium channel openers, medicinal chemistry and therapeutic perspectives. *Curr Med Chem* **13**: 361–376. [PMID:16475928]

Honoré E. (2007) The neuronal background K2P channels: focus on TREK1. *Nat Rev Neurosci* **8**: 251–261. [PMID:17375039]

Jenkinson DH. (2006) Potassium channels–multiplicity and challenges. *Br J Pharmacol* **147** Suppl 1: S63–S71. [PMID:16402122]

Judge SI, Bever CT. (2006) Potassium channel blockers in multiple sclerosis: neuronal Kv channels and effects of symptomatic treatment. *Pharmacol Ther* **111**: 224–259. [PMID:16472864]

Kannankeril P, Roden DM, Darbar D. (2010) Drug-induced long QT syndrome. *Pharmacol Rev* **62**: 760–781. [PMID:21079043]

Kobayashi T, Ikeda K. (2006) G protein-activated inwardly rectifying potassium channels as potential therapeutic targets. *Curr Pharm Des* **12**: 4513–4523. [PMID:17168757]

Kubo Y, Adelman JP, Clapham DE, Jan LY, Karschin A, Kurachi Y, Lazdunski M, Nichols CG, Seino S, Vandenberg CA. (2005) International Union of Pharmacology. LIV. Nomenclature and molecular relationships of inwardly rectifying potassium channels. *Pharmacol Rev* **57**: 509–526. [PMID:16382105]

Lawson K, McKay NG. (2006) Modulation of potassium channels as a therapeutic approach. *Curr Pharm Des* **12**: 459–470. [PMID:16472139]

Lüscher C, Slesinger PA. (2010) Emerging roles for G protein-gated inwardly rectifying potassium (GIRK) channels in health and disease. *Nat Rev Neurosci* **11**: 301–315. [PMID:20389305]

Mannhold R. (2006) Structure-activity relationships of K(ATP) channel openers. *Curr Top Med Chem* **6**: 1031–1047. [PMID:16787278]

Mathie A, Veale EL. (2007) Therapeutic potential of neuronal two-pore domain potassium-channel modulators. *Curr Opin Investig Drugs* **8**: 555–562. [PMID:17659475]

Nardi A, Olesen SP. (2008) BK channel modulators: a comprehensive overview. *Curr Med Chem* **15**: 1126–1146. [PMID:18473808]

Pongs O, Schwarz JR. (2010) Ancillary subunits associated with voltage-dependent K+ channels. *Physiol Rev* **90**: 755–796. [PMID:20393197]

Salkoff L, Butler A, Ferreira G, Santi C, Wei A. (2006) High-conductance potassium channels of the SLO family. *Nat Rev Neurosci* **7**: 921–931. [PMID:17115074]

Stocker M. (2004) Ca(2+)-activated K+ channels: molecular determinants and function of the SK family. *Nat Rev Neurosci* **5**: 758–770. [PMID:15378036]

Takeda M, Tsuboi Y, Kitagawa J, Nakagawa K, Iwata K, Matsumoto S. (2011) Potassium channels as a potential therapeutic target for trigeminal neuropathic and inflammatory pain. *Mol Pain* **7**: 5. [PMID:21219657]

Trimmer JS, Rhodes KJ. (2004) Localization of voltage-gated ion channels in mammalian brain. *Annu Rev Physiol* **66**: 477–519. [PMID:14977411]

Wang H, Tang Y, Wang L, Long CL, Zhang YL. (2007) ATP-sensitive potassium channel openers and 2,3-dimethyl-2-butylamine derivatives. *Curr Med Chem* **14**: 133–155. [PMID:17266574]

Weatherall KL, Goodchild SJ, Jane DE, Marrion NV. (2010) Small conductance calcium-activated potassium channels: from structure to function. *Prog Neurobiol* **91**: 242–255. [PMID:20359520]

Wei AD, Gutman GA, Aldrich R, Chandy KG, Grissmer S, Wulff H. (2005) International Union of Pharmacology. LII. Nomenclature and molecular relationships of calcium-activated potassium channels. *Pharmacol Rev* **57**: 463–472. [PMID:16382103]

Wickenden AD, McNaughton-Smith G. (2009) Kv7 channels as targets for the treatment of pain. *Curr Pharm Des* **15**: 1773–1798. [PMID:19442190]

Witchel HJ. (2007) The hERG potassium channel as a therapeutic target. *Expert Opin Ther Targets* **11**: 321–336. [PMID:17298291]

Wulff H, Castle NA, Pardo LA. (2009) Voltage-gated potassium channels as therapeutic targets. *Nat Rev Drug Discov* **8**: 982–1001. [PMID:19949402]
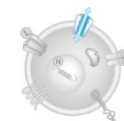
Ryanodine receptor

Overview: The ryanodine receptors (RyRs, provisional nomenclature) 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 [218]. The function of the ryanodine receptor channels may also be influenced by closely associated proteins such as the tacrolimus (FK506)-binding protein, calmodulin [219], triadin, calsequestrin, junctin and sorcin, and by protein kinases and phosphatases.

Subunits

Nomenclature	RyR1	RyR2	RyR3
HGNC, UniProt	*RYR1*, P21817	*RYR2*, Q92736	*RYR3*, Q15413
Endogenous activators (EC_{50})	cytosolic ATP (endogenous; mM range), luminal Ca^{2+} (endogenous), cytosolic Ca^{2+} (endogenous; µM range)	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)
Activators (EC_{50})	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 (IC_{50})	cytosolic Mg^{2+} (mM range), 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)
Antagonists (IC_{50})	dantrolene	–	dantrolene
Channel Blockers (IC_{50})	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+}: ($P_{Ca}/P_{K} \sim 6$) single-channel conductance: ~90 pS (50mM Ca^{2+}), 770 pS (200 mM K^{+})	Ca^{2+}: ($P_{Ca}/P_{K} \sim 6$) single-channel conductance: ~90 pS (50mM Ca^{2+}), 720 pS (210 mM K^{+})	Ca^{2+}: ($P_{Ca}/P_{K} \sim 6$) single-channel conductance: ~140 pS (50mM Ca^{2+}), 777 pS (250 mM K^{+})
Comment	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 [217,220].

Further reading

Betzenhauser MJ, Marks AR. (2010) Ryanodine receptor channelopathies. *Pflugers Arch* **460**: 467–480. [PMID:20179962]

Gaburjakova M, Bal NC, Gaburjakova J, Periasamy M. (2013) Functional interaction between calsequestrin and ryanodine receptor in the heart. *Cell Mol Life Sci* **70**: 2935–2945. [PMID:23109100]

Kushnir A, Betzenhauser MJ, Marks AR. (2010) Ryanodine receptor studies using genetically engineered mice. *FEBS Lett* **584**: 1956–1965. [PMID:20214899]

MacMillan D. (2013) FK506 binding proteins: cellular regulators of intracellular Ca2+ signalling. *Eur J Pharmacol* **700**: 181–193. [PMID:23305836]

McCauley MD, Wehrens XH. (2011) Ryanodine receptor phosphorylation, calcium/calmodulin-dependent protein kinase II, and life-threatening ventricular arrhythmias. *Trends Cardiovasc Med* **21**: 48–51. [PMID:22578240]

Niggli E, Ullrich ND, Gutierrez D, Kyrychenko S, Poláková E, Shirokova N. (2013) Posttranslational modifications of cardiac ryanodine receptors: Ca(2+) signaling and EC-coupling. *Biochim Biophys Acta* **1833**: 866–875. [PMID:22960642]

Van Petegem F. (2012) Ryanodine receptors: structure and function. *J Biol Chem* **287**: 31624–31632. [PMID:22822064]
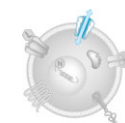
Sodium leak channel, non-selective

Overview: The sodium leak channel, non selective (NC-IUPHAR tentatively recommends the nomenclature $Na_{Vi}2.1$) is structurally a member of the family of voltage-gated sodium channel family ($Na_v1.1 - Na_v1.9$) [221,228]. In contrast to the latter, $Na_{Vi}2.1$, is voltage-insensitive (denoted in the subscript 'vi' in the tentative nomenclature) and possesses distinctive ion selectivity and pharmacological properties. $Na_{Vi}2.1$, 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 [222]. However, whether $Na_{Vi}2.1$ is constitutively active has been challenged [226]. $Na_{Vi}2.1$ 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 [221–222].

Subunits

Nomenclature	HGNC, UniProt	Activators	Channel Blockers (IC50)	Functional characteristics
$Na_{vi}2.1$	*NALCN*, Q8IZF0	Constitutively active (Lu *et al.*, 2007), or activated downstream of Src family tyrosine kinases (SFKs) (Lu *et al.*, 2009; Swayne *et al.*, 2009); positively modulated by decreased extracellular Ca^{2+} concentration (Lu *et al.*, 2010) [222–224,226]	Gd^{3+} (1.4×10^{-6} M), Cd^{2+} (1.5×10^{-4} M), Co^{2+} (2.6×10^{-4} M), verapamil (3.8×10^{-4} M)	γ = 27 pS (by fluctuation analysis), P_{Na}/P_{Cs} = 1.3, P_K/P_{Cs} = 1.2, P_{Ca}/P_{Cs} = 0.5, linear current voltage-relationship, voltage-independent and non-inactivating

Comments: In native and recombinant expression systems $Na_{Vi}2.1$ can be activated by stimulation of NK_1 (in hippocampal neurones), neurotensin (in ventral tegmental area neurones) and M3 muscarinic acetylcholine receptors (in MIN6 pancreatic β-cells) and in a manner that is independent of signalling through G-proteins [223,226]. Pharmacological and molecular biological evidence indicates such modulation to occur though a pathway that involves the activation of Src family tyrosine kinases. It is suggested that $Na_{Vi}2.1$ exists as a macromolecular complex with M3 receptors [226] and peptide receptors [223], in the latter instance in association with the protein UNC-80, which recruits Src to the channel complex [223,227]. By contrast, stimulation of $Na_{Vi}2.1$ by decreased extracellular Ca^{2+} concentration is G-protein dependent and involves a Ca^{2+}-sensing G protein-coupled receptor and UNC80 which links $Na_{Vi}2.1$ to the protein UNC79 in the same complex [224]. $Na_{Vi}2.1$ null mutant mice have severe disturbances in respiratory rhythm and die within 24 hours of birth [222]. $Na_{Vi}2.1$ heterozygous knockout mice display increased serum sodium concentrations in comparison to wildtype littermates and a role for the channel in osmoregulation has been postulated [225].

Further reading

Gilon P, Rorsman P. (2009) NALCN: a regulated leak channel. *EMBO Rep* **10**: 963–964. [PMID:19662077]

Swayne LA, Mezghrani A, Lory P, Nargeot J, Monteil A. (2010) The NALCN ion channel is a new actor in pancreatic β-cell physiology. *Islets* **2**: 54–56. [PMID:21099296]
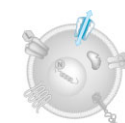
Transient receptor potential channels

Overview: The TRP superfamily of channels (nomenclature agreed by NC-IUPHAR; [244,351]), 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 transmembrane domains and assemble as homo- or hetero-tetramers to form cation selective channels with diverse modes of activation and varied permeation properties (reviewed by [314]). Established, or potential, physiological functions of the individual members of the TRP families are discussed in detail in the recommended reviews and a compilation edited by Islam [271]. The established, or potential, involvement of TRP channels in disease is reviewed in [279,307] and [308], together with a special edition of *Biochemica et Biophysica Acta* on the subject [307]. The pharmacology of most TRP channels is poorly developed [351]. 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. Most TRP channels are regulated by phosphoinostides such as PtIns(4,5)P_2 and IP_3 although the effects reported are often complex, occasionally contradictory, and likely be dependent upon experimental conditions (reviewed by [309,327,343]). Such regulation is generally not included in the tables.

TRPA (ankyrin) family TRPA1 is the sole mammalian member of this group (reviewed by [259]). In some [234,274,330,334], but not other [272,303], studies TRPA1 is activated by noxious cold. One study suggests that activation of TRPA1 is secondary to a cold-induced elevation of $[Ca^{2+}]_i$ [357], but this has been refuted [274]. Additionally, TRPA1 has been proposed to be a component of a mechanosensitive transduction channel of vertebrate hair cells [246,303], but TRPA1$^{(-/-)}$ mice demonstrate no impairment in hearing, or vestibular function [238,284]. There is consensus that TRPA1 acts as a nociceptor for environmental irritants [235].

TRPC (canonical) family Members of the TRPC subfamily (reviewed by [229-230,241-242,258,277,316,324]) fall into the subgroups outlined below. TRPC2 (not tabulated) is a pseudogene in man. It is generally accepted that all TRPC channels are activated downstream of $G_{q/11}$-coupled receptors, or receptor tyrosine kinases (reviewed by [321,337,351]). A comprehensive listing of G-protein coupled receptors that activate TRPC channels is given in [229]. Hetero-oligomeric complexes of TRPC channels and their association with proteins to form signalling complexes are detailed in [230] and [278]. TRPC channels have

frequently been proposed to act as store-operated channels (SOCs) (or compenents of mulimeric complexes that form SOCs), activated by depletion of intracellular calcium stores (reviewed by [230,243,317,322,329,354]), but this is controversial. All members of the TRPC family are blocked by 2-APB and SKF96356 [265-266]. Activation of TRPC channels by lipids is discussed by [241].

TRPC1/C4/C5 subgroup TRPC4/C5 may be distinguished from other TRP channels by their potentiation by micromolar concentrations of La^{3+}.

TRPC3/C6/C7 subgroup All members are activated by diacylglycerol independent of protein kinase C stimulation [266].

TRPM (melastatin) family Members of the TRPM subfamily (reviewed by [257,265,317,356]) fall into the five subgroups outlined below.

TRPM1/M3 subgroup TRPM1 exists as five splice variants and is involved in normal melanocyte pigmentation [312] and is also a visual transduction channel in retinal ON bipolar cells [283]. TRPM3 (reviewed by [313]) exists as multiple splice variants four of which (mTRPM3α1, mTRPM3α2, hTRPM3a and hTRPM3$_{1325}$) have been characterised and found to differ significantly in their biophysical properties. TRPM3 has recently been found to contribute to the detection of noxious heat [346].

TRPM2 TRPM2 functions as a sensor of redox status in cells and is also activated by heat (reviewed by [353]). Numerous splice variants of TRPM2 exist which differ in their activation mechanisms [254].

TRPM4/5 subgroup TRPM4 and TRPM5 are thermosensitive and have the distinction within all TRP channels of being impermeable to Ca^{2+} [351]. A splice variant of TRPM4 (*i.e.*TRPM4b) and TRPM5 are molecular candidates for endogenous calcium-activated cation (CAN) channels [262]. TRPM4 has been shown to be an important regulator of Ca^{2+} entry in to mast cells [339] and dendritic cell migration [236]. TRPM5 in taste receptor cells of the tongue appears essential for the transduction of sweet, amino acid and bitter stimuli [289].

TRPM6/7 subgroup TRPM6 and 7 combine channel and enzymatic activities ('chanzymes') and are involved in Mg^{2+} homeostasis (reviewed by [237,318,328]).

TRPM8 Is a channel activated by cooling and pharmacological agents evoking a 'cool' sensation and participates in the thermosensation of cold temperatures [240,245,252] reviewed by [282,291,302,344].

TRPML (mucolipin) family The TRPML family [323,325,355] 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) are the cause of 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 fusion between late endosome-lysosome hybrid vesicles. TRPML2 (MCLN2) remains to be functionally characterised in detail. TRPML3 is important for hair cell maturation, stereocilia maturation and intracellular vesicle transport. A naturally occurring gain of function mutation in TRPML3 (*i.e.* A419P) results in the varitint waddler (V*a*) mouse phenotype (reviewed by [310,325]).

TRPP (polycystin) family The TRPP family (reviewed by [249,251,260,268,349]) subsumes the polycystins that are divided into two structurally distinct groups, polycystic kidney disease 1-like (PKD1-like) and polycystic kidney disease 2-like (PKD2-like). Members of the PKD1-like group, in mammals, include PKD1 (reclassified as TRPP1), PDKREJ, PKD1L1, PKD1L2 and PKD1L3. The PKD2-like members comprise PKD2, PKD2L1 and PKD2L2, which have renamed TRPP2, TRPP3 and TRPP5, respectively [300]. *PKDREJ* (Q9NTG1), *PKD1L1* (Q8TDX9), mouse *PKD1L2* (Q7TN88), *PKD1L3* (Q7Z443) and TRPP5 (*PKD2L2*, Q9NZM6) are not listed in the table due to lack of functional data. Similarly, *TRPP1* (P98161) is also omitted because although one study [233] has reported the induction of a cation conductance in CHO cells transfected with TRPP1, there is no unequivocal evidence that TRPP1 is a channel *per se* and in other studies (*e.g.* [250,264]) TRPP1 is incapable of producing currents.

TRPV (vanilloid) family Members of the TRPV family (reviewed by [340]) can broadly be divided into the theromosensitive, non-selective cation channels, TRPV1-4 and the calcium selective channels TRPV5 and TRPV6.

TRPV1-V4 subfamily TRPV1 is involved in the development of thermal hyperalgesia following inflammation and may
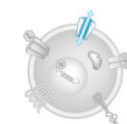
contribute to the detection of noxius heat (reviewed by [320,333,335]). Numerous splice variants of TRPV1 have been described, some of which modulate the activity of TRPV1, or act in a dominant negative manner when co-expressed with TRPV1 [331]. The pharmacology of TRPV1 channels is discussed in detail in [263] and [345]. TRPV2 is probably not a thermosensor in man
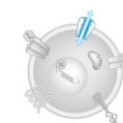
[315], but has recently been implicated in innate immunity [290]. TRPV3 and TRPV4 are both thermosensitive, with the latter also having a mechanosensing function [255].

TRPV5/V6 subfamily 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 [248,348]).

Subunits

Nomenclature	TRPC1	TRPC4	TRPC5
HGNC, UniProt	*TRPC1*, P48995	*TRPC4*, Q9UBN4	*TRPC5*, Q9UL62
Chemical activators	NO-mediated cysteine S-nitrosylation	–	–
Physical activators	membrane stretch (likely direct)	–	–
Other chemical activators	–	NO-mediated cysteine S-nitrosylation, potentiation by extracellular protons	NO-mediated cysteine S-nitrosylation (disputed), potentiation by extracellular protons
Physical activators	–	–	membrane stretch (likely indirect)
Endogenous activators (EC$_{50}$)	–	–	lysophosphatidylcholine, intracellular Ca^{2+} (at negative potentials) (6.35x10^{-7} M)
Activators (EC$_{50}$)	–	La^{3+} (µM range)	7,4'-dihydroxyisoflavone, genistein (independent of tyrosine kinase inhibition) [350], La^{3+} (µM range), Gd^{3+} (Concentration range = 1x10^{-4} M), Pb^{2+} (Concentration range = 5x10^{-6} M)
Channel Blockers (IC$_{50}$)	2-APB, Gd^{3+}, GsMTx-4, La^{3+}, SKF96365	2-APB, La^{3+} (mM range), niflumic acid, SKF96365, ML204 (2.9x10^{-6} M) [299]	2-APB, BTP2, chlorpromazine, flufenamic acid, GsMTx-4, KB-R7943, La^{3+} (mM range), SKF96365, ML204 (~1x10^{-5} M) [299]
Functional characteristics	γ = 16 pS (fluctuation analysis), conducts mono- and di-valent cations non-selectively; monovalent cation current suppressed by extracellular Ca^{2+}; non-rectifying, or mildly inwardly rectifying; non-inactivating	γ = 30 –41 pS, conducts mono and di-valent cations non-selectively (P$_{Ca}$/P$_{Na}$ = 1.1 – 7.7); dual (inward and outward) rectification	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

Nomenclature	TRPC3	TRPC6	TRPC7
HGNC, UniProt	*TRPC3*, Q13507	*TRPC6*, Q9Y210	*TRPC7*, Q9HCX4
Chemical activators	diacylglycerols	–	diacylglycerols
Other chemical activators	–	diacylglycerols	–
Physical activators	–	membrane stretch (likely indirect)	–
Endogenous activators (EC$_{50}$)	–	20-HETE, arachidonic acid, lysophosphatidylcholine	–
Activators (EC$_{50}$)	–	2,4 diahexanxoylphloroglucinol [287], flufenamate, hyperforin [288]	–
Channel Blockers (IC$_{50}$)	2-APB, ACAA, BTP2, Gd^{3+}, KB-R7943, La^{3+}, Ni^{2+}, Pyr3 [280], SKF96365	2-APB, ACAA, amiloride, Cd^{2+}, Gd^{3+}, GsMTx-4, Extracellular H$^+$, KB-R7943, ML9, SKF96365, La^{3+} (~6x10^{-6} M)	2-APB, amiloride, La^{3+}, SKF96365
Functional characteristics	γ = 66 pS; conducts mono and di-valent cations non-selectively (P$_{Ca}$/P$_{Na}$ = 1.6); monovalent cation current suppressed by extracellular Ca^{2+}; dual (inward and outward) rectification	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+}

Nomenclature	TRPM1	TRPM3
HGNC, UniProt	*TRPM1*, Q7Z4N2	*TRPM3*, Q9HCF6
Physical activators	–	heat (Q$_{10}$ = 7.2 between 15 - 25°C; Vriens *et al.*, 2011), hypotonic cell swelling [346]
Endogenous activators (EC$_{50}$)	pregnenolone sulphate [285]	epipregnanolone sulphate [294], pregnenolone sulphate [347]
Activators (EC$_{50}$)	–	dihydro-D-erythrosphingosine, nifedipine, sphingosine
Endogenous channel blockers (IC$_{50}$)	Zn^{2+} (1x10^{-6} M)	intracellular Mg^{2+}, extracellular Na$^+$ (TRPM3α2 only)
Channel Blockers (IC$_{50}$)	–	2-APB, Gd^{3+}, La^{3+}, mefenamic acid [281], pioglitazone (independent of PPAR-γ) [295], rosiglitazone, troglitazone
Functional characteristics	Conducts mono- and di-valent cations non-selectively, dual rectification (inward and outward)	TRPM3$_{1235}$: 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); Outwardly rectifying (magnitude varies between spice variants)

Nomenclature	HGNC, UniProt	Other chemical activators	Physical activators	Endogenous activators (EC$_{50}$)	Activators (EC$_{50}$)	Endogenous channel blockers (IC$_{50}$)	Channel Blockers (IC$_{50}$)	Functional characteristics
TRPM2	*TRPM2*, O94759	agents producing reactive oxygen (e.g. H_2O_2) and nitrogen (e.g. GEA 3162) species	heat ~ 35°C	intracellular ADP ribose, arachidonic acid (Potentiation), intracellular cADPR, intracellular Ca^{2+} (*via* calmodulin), H_2O_2	GEA 3162	extracellular H^+, Zn^{2+} (1×10^{-6} M)	2-APB, ACAA, clotrimazole, econazole, flufenamic acid, miconazole	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

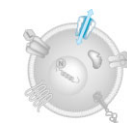| Nomenclature	TRPM4	TRPM5
HGNC, UniProt	*TRPM4*, Q8TD43	*TRPM5*, Q9NZQ8
Other channel blockers	intracellular nucleotides including ATP, ADP, AMP and AMP-PNP with an IC$_{50}$ range of 1.3–1.9 μM	–
Physical activators	membrane depolarization (V$_½$ = -20 mV to + 60 mV dependent upon conditions) in the presence of elevated [Ca^{2+}]$_i$, heat (Q$_{10}$ = 8.5 @ +25 mV between 15 and 25°C)	membrane depolarization (V$_½$ = 0 to + 120 mV dependent upon conditions), heat (Q$_{10}$ = 10.3 @ -75 mV between 15 and 25°C)
Endogenous activators (EC$_{50}$)	intracellular Ca^{2+} (transient activation of whole cell current) (3×10^{-7} – 2×10^{-5} M)	intracellular Ca^{2+} (transient activation) (6.35×10^{-7} – 8.4×10^{-7} M)
Activators (EC$_{50}$)	BTP2 (Potentiation), decavanadate	rosiglitazone [295]
Channel Blockers (IC$_{50}$)	9-phenanthrol, clotrimazole, flufenamic acid (2.8×10^{-6} M), intracellular spermine (3.5×10^{-5} – 6.1×10^{-5} M), adenosine (6.3×10^{-4} M)	flufenamic acid (2.4×10^{-5} M), intracellular spermine (3.7×10^{-5} M), Extracellular H^+ (6.3×10^{-4} M)
Functional characteristics	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	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+}]$_I$
Comment	–	TRPM5 is not blocked by ATP

Nomenclature	TRPM6	TRPM7
HGNC, UniProt	*TRPM6*, Q9BX84	*TRPM7*, Q96QT4
Other chemical activators	constitutively active, activated by reduction of intracellular Mg^{2+}	activation of PKA
Endogenous activators (EC_{50})	extracellular H^+ (Potentiation, µM range), intracellular Mg^{2+}	intracellular ATP (Potentiation), cAMP (elevated cAMP levels), Extracellular H^+ (Potentiation)
Activators (EC_{50})	2-APB (Potentiation)	2-APB (mM range)
Endogenous channel blockers (IC_{50})	Mg^{2+} (inward current mediated by monovalent cations is blocked) (1.1×10^{-6} – 3.4×10^{-6} M), Ca^{2+} (inward current mediated by monovalent cations is blocked) (4.8×10^{-6} – 5.4×10^{-6} M)	Mg^{2+}
Channel Blockers (IC_{50})	ruthenium red (1×10^{-7} M) [*voltage dependent* -120.0 mV]	2-APB (µM range), carvacrol, La^{3+}, spermine (permeant blocker)
Functional characteristics	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	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

Nomenclature	HGNC, UniProt	Other chemical activators	Physical activators	Activators (EC_{50})	Channel Blockers (IC_{50})	Functional characteristics	Comment
TRPM8	*TRPM8*, Q7Z2W7	agonist activities are temperature dependent and potentiated by cooling	depolarization ($V_{1/2}$ ~ +50 mV at 15°C), cooling (< 22–26°C)	icilin (requires intracellular Ca^{2+} as a co-factor for full agonist activity), (-)-menthol (inhibited by intracellular Ca^{2+}), WS-12	2-APB, 5-benzyloxytryptamine, ACAA, AMTB [286], anandamide, BCTC, cannabidiol, capsazepine, clotrimazole, Δ^9-tetrahydrocannabinol, La^{3+}, linoleic acid, NADA	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	cannabidiol and Δ^9-tetrahydrocannabinol are examples of cannabinoids. TRPM8 is insensitive to ruthenium red

Comments: Ca^{2+} activates all splice variants of TRPM2, but other activators listed are effective only at the full length isoform [254]. Inhibition of TRPM2 by clotrimazole, miconazole, econazole, flufenamic acid is largely irreversible. 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 [338]. The $V_{1/2}$ 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 $V_{1/2}$ is shifted in the hyperpolarizing direction both by decreasing temperature and by exogenous agonists, such as (-)-menthol [342] whereas antagonists produce depolarizing shifts in $V_{1/2}$ [301]. The $V_{1/2}$ for the native channel is far more positive than that of heterologously expressed TRPM8 [301]. 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 [293]. Intracellular pH modulates activation of TRPM8 by cold and icilin, but not (-)-menthol [231].

Nomenclature	HGNC, UniProt	Other chemical activators	Physical activators	Activators (EC$_{50}$)	Channel Blockers (IC$_{50}$)	Functional characteristics
TRPA1	*TRPA1*, O75762	isothiocyanates (covalent) and 1,4-dihydropyridines (non-covalent)	cooling (<17°C) (disputed)	chlorobenzylidene malononitrile (Activation, covalent), cinnamaldehyde (Activation, covalent), formalin (Activation, covalent), icilin (Activation, non-covalent), (-)-menthol (Activation, non-covalent) (Concentration range = 1×10^{-6} - 1×10^{-4} M), thymol (Activation, non-covalent) (Concentration range = 1×10^{-6} - 1×10^{-4} M), acrolein (Agonist, covalent) (5.011×10^{-6} M) [Physiological voltage] [238], allicin (Agonist, covalent) (7.943×10^{-6} M) [Physiological voltage] [239], Δ^9-tetrahydrocannabinol (Agonist, non-covalent) (1.259×10^{-5} M) [-60.0 mV] [272], nicotine (Activation, non-covalent) ($\sim2\times10^{-5}$ M), URB597 (Agonist, non-covalent) (2.4×10^{-5} M) [306]	ruthenium red (Inhibition) ($<1\times10^{-6}$ – 3×10^{-6} M), AP18 (Inhibition) (3.1×10^{-6} M) [319], HC030031 (Inhibition) (6.2×10^{-6} M) [296]	$\gamma = 87$–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: 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 [267,292]. 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 [235]. In addition, TRPA1 is potently activated by intracellular zinc (EC$_{50}$ = 8 nM) [232,269].

Nomenclature	TRPV1	TRPV2	TRPV3	TRPV4
HGNC, UniProt	*TRPV1*, Q8NER1	*TRPV2*, Q9Y5S1	*TRPV3*, Q8NET8	*TRPV4*, Q9HBA0
Other chemical activators	NO-mediated cysteine S-nitrosylation	–	NO-mediated cysteine S-nitrosylation	epoxyeicosatrieonic acids and NO-mediated cysteine S-nitrosylation
Physical activators	depolarization (V$_{\frac{1}{2}}$ ~ 0 mV at 35°C), noxious heat (> 43°C at pH 7.4)	noxious heat (> 35°C; rodent, not human) [305]	depolarization (V$_{\frac{1}{2}}$ ~ +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
Endogenous activators (EC$_{50}$)	12S-HPETE, 15S-HPETE, 5S-HETE, LTB$_4$, Extracellular H$^+$ (at 37°C) (3.98×10^{-6} M)	–	–	–
Activators (EC$_{50}$)	camphor, capsaicin, diphenylboronic anhydride, DkTx (Irreversible agonist), olvanil, phenylacetylrinvanil, resiniferatoxin	Δ^9-tetrahydrocannabinol, diphenylboronic anhydride, probenecid, 2-APB (1×10^{-5} M - Rat) [305,326], cannabidiol (Activation) (3.17×10^{-5} M) [326]	2-APB, 6-tert-butyl-*m*-cresol, camphor, carvacrol, diphenylboronic anhydride, eugenol, incensole acetate, (-)-menthol, thymol	4α-PDD, 4α-PDH, bisandrographolide, phorbol 12-myristate 13-acetate, GSK1016790A (2.1×10^{-9} M) [336], RN1747 (7.7×10^{-7} M) [341]
Selective activators (EC$_{50}$)	–	2-APB (Agonist) (Mouse) [Physiological voltage] [270,273,297-298]	–	–

Nomenclature	TRPV1	TRPV2	TRPV3	TRPV4
Channel Blockers (IC$_{50}$)	2-APB, allicin, anandamide, NADA, SB452533, AMG517 (9x10^{-10} M), 5′-iodoresiniferatoxin (3.9x10^{-9} M), AMG628 (3.7x10^{-9} M), SB705498 (3x10^{-9} – 6x10^{-9} M), A425619 (5x10^{-9} M), A778317 (5x10^{-9} M), 6-iodo-nordihydrocapsaicin (1x10^{-8} M), JYL1421 (9.2x10^{-9} M), BCTC (6x10^{-9} – 3.5x10^{-8} M), SB366791 (1.8x10^{-8} M), JNJ17203212 (6.5x10^{-8} M), capsazepine (4x10^{-8} – 2.8x10^{-7} M), ruthenium red (9x10^{-8} – 2.2x10^{-7} M)	amiloride, La^{3+}, SKF96365, TRIM, ruthenium red (6x10^{-7} M)	diphenyltetrahydrofuran (Concentration range = 6x10^{-6} - 1x10^{-5} M), ruthenium red (Concentration range = < 1x10^{-6} M)	Gd^{3+}, La^{3+}, ruthenium red [*voltage dependent*], HC067047 (1.7x10^{-8} M) [256], RN1734 (2.3x10^{-6} M) [341]
Radioligands (*K*$_d$)	[^{125}I]resiniferatoxin, [^{3}H]resiniferatoxin, [^{3}H]A778317 (3.4x10^{-9} M)	–	–	–
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	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)

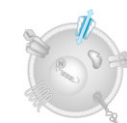| Nomenclature	TRPV5	TRPV6
HGNC, UniProt	*TRPV5*, Q9NQA5	*TRPV6*, Q9H1D0
Activators	constitutively active (with strong buffering of intracellular Ca^{2+})	constitutively active (with strong buffering of intracellular Ca^{2+})
Activators (EC$_{50}$)	–	2-APB (Potentiation)
Other channel blockers	Pb^{2+} = Cu^{2+} = Gd^{3+} > Cd^{2+} > Zn^{2+} > La^{3+} > Co^{2+} > Fe^{2+}	–
Channel Blockers (IC$_{50}$)	econazole, Mg^{2+}, miconazole, ruthenium red (1.21x10^{-7} M)	Cd^{2+}, La^{3+}, Mg^{2+}, ruthenium red (9x10^{-6} M)
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 downregulation; 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: Activation of TRPV1 by depolarisation is strongly temperature-dependent via a channel opening rate that increases with increasing temperature. The $V_{\frac{1}{2}}$ is shifted in the hyperpolarizing direction both by increasing temperature and by exogenous agonists [342]. 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 [311]). 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. 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.

Nomenclature	TRPML1	TRPML2	TRPML3
HGNC, UniProt	*MCOLN1*, Q9GZU1	*MCOLN2*, Q8IZK6	*MCOLN3*, Q8TDD5
Activators	TRPML1[Va]: Constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification)	TRPML2[Va]: Constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification)	TRPML3[Va]: Constitutively active, current inhibited by extracellular acidification (equivalent to intralysosomal acidicification), Wild type TRPML3: Activated by Na^+-free extracellular (extracytosolic) solution and membrane depolarization, current inhibited by extracellular acidification (equivalent to intralysosomal acidicification)
Channel Blockers (IC$_{50}$)	–	–	Gd^{3+}
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 ($Ba^{2+} > Mn2^+ > Fe^{2+} > Ca^{2+} > Mg^{2+} > Ni^{2+} > Co^{2+} > Cd^{2+} > Zn^{2+} >> Cu^{2+}$) protons; monovalent cation flux suppressed by divalent cations (*e.g.* Ca^{2+}, Fe^{2+}); inwardly rectifying	TRPML1[Va]: 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: 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 [253,261,275,304,352]. Data for wild type TRPML3 are also tabulated [275-276,304,352]. It should be noted that alternative methodologies, particularly in the case of TRPML1, have resulted in channels with differing biophysical characteristics (reviewed by [323]).

| Nomenclature	TRPP2	TRPP3
HGNC, UniProt	*PKD2L1*, Q9P0L9	*PKD2L2*, Q9NZM6
Activators	Low constitutive activity, enhanced by membrane depolarization; changes in cell volume affect voltage-dependent gating (increased channel opening probability with cell swelling)	–
Channel Blockers (IC_{50})	flufenamate, Gd^{3+}, La^{3+}, phenamil (1.4×10^{-7} M), benzamil (1.1×10^{-6} M), EIPA (1.05×10^{-5} M), amiloride (1.43×10^{-4} M)	–
Functional characteristics	γ = 105–137 pS (outward conductance) 184–399 pS (inward conductance), conducts mono- and di-valent cations with a preference for divalents (P_{Ca}/P_{Na} = 4.0–4.3); steady state currents rectify outwardly, whereas instantaneous currents show strong inward rectification; activated and subsequently inactivated by intracellular Ca^{2+} (human, but not mouse); inhibited by extracellular acidification and potentiated by extracellular alkalization	–

Comments: Data in the table are extracted from [247,251] and [332]. Broadly similar single channel conductance, mono- and di-valent cation selectivity and sensitivity to blockers are observed for TRPP2 co-expressed with TRPP1 [250]. 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.

Further reading

Abramowitz J, Birnbaumer L. (2009) Physiology and pathophysiology of canonical transient receptor potential channels. *FASEB J* 23: 297–328. [PMID:18940894]

Ambudkar IS, Ong HL. (2007) Organization and function of TRPC channelosomes. *Pflugers Arch* 455: 187–200. [PMID:17486362]

Baraldi PG, Preti D, Materazzi S, Geppetti P. (2010) Transient receptor potential ankyrin 1 (TRPA1) channel as emerging target for novel analgesics and anti-inflammatory agents. *J Med Chem* 53: 5085–5107. [PMID:20356305]

Bates-Withers C, Sah R, Clapham DE. (2011) TRPM7, the Mg(2+) inhibited channel and kinase. *Adv Exp Med Biol* 704: 173–183. [PMID:21290295]

Beech DJ. (2011) Integration of transient receptor potential canonical channels with lipids. *Acta Physiol (Oxf)* [Epub ahead of print]. [PMID:21624095]

Birnbaumer L. (2009) The TRPC class of ion channels: a critical review of their roles in slow, sustained increases in intracellular Ca(2+) concentrations. *Annu Rev Pharmacol Toxicol* 49: 395–426. [PMID:19281310]

Cheng KT, Ong HL, Liu X, Ambudkar IS. (2011) Contribution of TRPC1 and Orai1 to Ca(2+) entry activated by store depletion. *Adv Exp Med Biol* 704: 435–449. [PMID:21290310]

Clapham DE, Montell C, Schultz G, Julius D, International Union of Pharmacology. (2003) International Union of Pharmacology. XLIII. Compendium of voltage-gated ion channels: transient receptor potential channels. *Pharmacol Rev* 55: 591–596. [PMID:14657417]

de Groot T, Bindels RJ, Hoenderop JG. (2008) TRPV5: an ingeniously controlled calcium channel. *Kidney Int* 74: 1241–1246. [PMID:18596722]

Delmas P. (2005) Polycystins: polymodal receptor/ion-channel cellular sensors. *Pflugers Arch* 451: 264–276. [PMID:15889307]

Delmas P, Padilla F, Osorio N, Coste B, Raoux M, Crest M. (2004) Polycystins, calcium signaling, and human diseases. *Biochem Biophys Res Commun* 322: 1374–1383. [PMID:15336986]

Dhaka A, Viswanath V, Patapoutian A. (2006) Trp ion channels and temperature sensation. *Annu Rev Neurosci* 29: 135–161. [PMID:16776582]

Everaerts W, Nilius B, Owsianik G. (2010) The vanilloid transient receptor potential channel TRPV4: from structure to disease. *Prog Biophys Mol Biol* 103: 2–17. [PMID:19835908]

Fleig A, Penner R. (2004) The TRPM ion channel subfamily: molecular, biophysical and functional features. *Trends Pharmacol Sci* 25: 633–639. [PMID:15530641]

Freichel M, Vennekens R, Olausson J, Stolz S, Philipp SE, Weissgerber P, Flockerzi V. (2005) Functional role of TRPC proteins in native systems: implications from knockout and knock-down studies. *J Physiol (Lond)* 567 (Pt 1): 59–66. [PMID:15975974]

García-Añoveros J, Nagata K. (2007) TRPA1. *Handb Exp Pharmacol* 179: 347–362. [PMID:17217068]

Giamarchi A, Padilla F, Coste B, Raoux M, Crest M, Honoré E, Delmas P. (2006) The versatile nature of the calcium-permeable cation channel TRPP2. *EMBO Rep* 7: 787–793. [PMID:16880824]

Guinamard R, Sallé L, Simard C. (2011) The non-selective monovalent cationic channels TRPM4 and TRPM5. *Adv Exp Med Biol* 704: 147–171. [PMID:21290294]

Gunthorpe MJ, Chizh BA. (2009) Clinical development of TRPV1 antagonists: targeting a pivotal point in the pain pathway. *Drug Discov Today* 14: 56–67. [PMID:19063991]

Harteneck C. (2005) Function and pharmacology of TRPM cation channels. *Naunyn Schmiedebergs Arch Pharmacol* 371: 307–314. [PMID:15843919]

Harteneck C, Gollasch M. (2011) Pharmacological modulation of diacylglycerol-sensitive TRPC3/6/7 channels. *Curr Pharm Biotechnol* 12: 35–41. [PMID:20932261]

Harteneck C, Klose C, Krautwurst D. (2011) Synthetic modulators of TRP channel activity. *Adv Exp Med Biol* 704: 87–106. [PMID:21290290]

Hofherr A, Köttgen M. (2011) TRPP channels and polycystins. *Adv Exp Med Biol* 704: 287–313. [PMID:21290302]

Islam MS. (2011) TRP channels of islets. *Adv Exp Med Biol* 704: 811–830. [PMID:21290328]

Kiselyov K, Patterson RL. (2009) The integrative function of TRPC channels. *Front Biosci* 14: 45–58. [PMID:19273053]

Kiselyov K, Shin DM, Kim JY, Yuan JP, Muallem S. (2007) TRPC channels: interacting proteins. *Handb Exp Pharmacol* 179: 559–574. [PMID:17217079]

Kiselyov K, Soyombo A, Muallem S. (2007) TRPpathies. *J Physiol (Lond)* 578 (Pt 3): 641–653. [PMID:17138610]

Knowlton WM, McKemy DD. (2011) TRPM8: from cold to cancer, peppermint to pain. *Curr Pharm Biotechnol* 12: 68–77. [PMID:20932257]
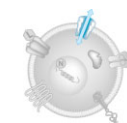
Koike C, Numata T, Ueda H, Mori Y, Furukawa T. (2010) TRPM1: a vertebrate TRP channel responsible for retinal ON bipolar function. *Cell Calcium* **48**: 95–101. [PMID:20846719]

Liman ER. (2007) TRPM5 and taste transduction. *Handb Exp Pharmacol* **179**: 287–298. [PMID:17217064]

Liu Y, Qin N. (2011) TRPM8 in health and disease: cold sensing and beyond. *Adv Exp Med Biol* **704**: 185–208. [PMID:21290296]

Moran MM, Xu H, Clapham DE. (2004) TRP ion channels in the nervous system. *Curr Opin Neurobiol* **14**: 362–369. [PMID:15194117]

Mälkiä A, Morenilla-Palao C, Viana F. (2011) The emerging pharmacology of TRPM8 channels: hidden therapeutic potential underneath a cold surface. *Curr Pharm Biotechnol* **12**: 54–67. [PMID:20932258]

Nilius B. (2007) TRP channels in disease. *Biochim Biophys Acta* **1772**: 805–812. [PMID:17368864]

Nilius B, Owsianik G. (2010) Transient receptor potential channelopathies. *Pflugers Arch* **460**: 437–450. [PMID:20127491]

Nilius B, Owsianik G, Voets T. (2008) Transient receptor potential channels meet phosphoinositides. *EMBO J* **27**: 2809–2816. [PMID:18923420]

Nilius B, Owsianik G, Voets T, Peters JA. (2007) Transient receptor potential cation channels in disease. *Physiol Rev* **87**: 165–217. [PMID:17237345]

Nilius B, Talavera K, Owsianik G, Prenen J, Droogmans G, Voets T. (2005) Gating of TRP channels: a voltage connection? *J Physiol (Lond)* **567** (Pt 1): 35–44. [PMID:15878939]

Nilius B, Voets T. (2005) TRP channels: a TR(I)P through a world of multifunctional cation channels. *Pflugers Arch* **451**: 1–10. [PMID:16012814]

Nilius B, Vriens J, Prenen J, Droogmans G, Voets T. (2004) TRPV4 calcium entry channel: a paradigm for gating diversity. *Am J Physiol, Cell Physiol* **286**: C195–205. [PMID:14707014]

Oberwinkler J, Phillipp SE. (2007) TRPM3. *Handb Exp Pharmacol* **179**: 253–67. [PMID:17217062]

Owsianik G, D'hoedt D, Voets T, Nilius B. (2006) Structure-function relationship of the TRP channel superfamily. *Rev Physiol Biochem Pharmacol* **156**: 61–90. [PMID:16634147]

Owsianik G, Talavera K, Voets T, Nilius B. (2006) Permeation and selectivity of TRP channels. *Annu Rev Physiol* **68**: 685–717. [PMID:16460288]

Patel A, Sharif-Naeini R, Folgering JR, Bichet D, Duprat F, Honoré E. (2010) Canonical TRP channels and mechanotransduction: from physiology to disease states. *Pflugers Arch* **460**: 571–581. [PMID:20490539]

Pedersen SF, Owsianik G, Nilius B. (2005) TRP channels: an overview. *Cell Calcium* **38**: 233–252. [PMID:16098585]

Penner R, Fleig A. (2007) The Mg2+ and Mg(2+)-nucleotide-regulated channel-kinase TRPM7. *Handb Exp Pharmacol* **179**: 313–328. [PMID:17217066]

Pingle SC, Matta JA, Ahern GP. (2007) Capsaicin receptor: TRPV1 a promiscuous TRP channel. *Handb Exp Pharmacol* **179**: 155–171. [PMID:17217056]

Plant TD, Schaefer M. (2003) TRPC4 and TRPC5: receptor-operated Ca2+-permeable nonselective cation channels. *Cell Calcium* **33**: 441–450. [PMID:12765689]

Potier M, Trebak M. (2008) New developments in the signaling mechanisms of the store-operated calcium entry pathway. *Pflugers Arch* **457**: 405–415. [PMID:18536932]

Puertollano R, Kiselyov K. (2009) TRPMLs: in sickness and in health. *Am J Physiol Renal Physiol* **296**: F1245–F1254. [PMID:19158345]

Putney JW. (2005) Physiological mechanisms of TRPC activation. *Pflugers Arch* **451**: 29–34. [PMID:16133266]

Qian F, Noben-Trauth K. (2005) Cellular and molecular function of mucolipins (TRPML) and polycystin 2 (TRPP2). *Pflugers Arch* **451**: 277–285. [PMID:15971078]

Ramsey IS, Delling M, Clapham DE. (2006) An introduction to TRP channels. *Annu Rev Physiol* **68**: 619–647. [PMID:16460286]

Rohacs T. (2009) Phosphoinositide regulation of non-canonical transient receptor potential channels. *Cell Calcium* **45**: 554–565. [PMID:19376575]

Runnels LW. (2011) TRPM6 and TRPM7: A Mul-TRP-PLIK-cation of channel functions. *Curr Pharm Biotechnol* **12**: 42–53. [PMID:20932259]

Salido GM, Sage SO, Rosado JA. (2009) TRPC channels and store-operated Ca(2+) entry. *Biochim Biophys Acta* **1793**: 223–230. [PMID:19061922]

Schumacher MA, Eilers H. (2010) TRPV1 splice variants: structure and function. *Front Biosci* **15**: 872–882. [PMID:20515731]

Starowicz K, Nigam S, Di Marzo V. (2007) Biochemistry and pharmacology of endovanilloids. *Pharmacol Ther* **114**: 13–33. [PMID:17349697]

Szallasi A, Cortright DN, Blum CA, Eid SR. (2007) The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. *Nat Rev Drug Discov* **6**: 357–372. [PMID:17464295]

Trebak M, Lemonnier L, Smyth JT, Vazquez G, Putney JW. (2007) Phospholipase C-coupled receptors and activation of TRPC channels. *Handb Exp Pharmacol* **179**: 593–614. [PMID:17217081]

Vay L, Gu C, McNaughton PA. (2011) The thermo-TRP ion channel family: properties and therapeutic implications. *Br J Pharmacol* [Epub ahead of print]. [PMID:21797839]

Venkatachalam K, Montell C. (2007) TRP channels. *Annu Rev Biochem* **76**: 387–417. [PMID:17579562]

Vennekens R, Nilius B. (2007) Insights into TRPM4 function, regulation and physiological role. *Handb Exp Pharmacol* **179**: 269–285. [PMID:17217063]

Vennekens R, Owsianik G, Nilius B. (2008) Vanilloid transient receptor potential cation channels: an overview. *Curr Pharm Des* **14**: 18–31. [PMID:18220815]

Vincent F, Duncton MA. (2011) TRPV4 agonists and antagonists. *Curr Top Med Chem* **11**: 2216–2226. [PMID:21671873]

Voets T, Nilius B. (2007) Modulation of TRPs by PIPs. *J Physiol (Lond)* **582** (Pt 3): 939–944. [PMID:17395625]

Voets T, Owsianik G, Nilius B. (2007) TRPM8. *Handb Exp Pharmacol* **179**: 329–44. [PMID:17217067]

Voets T, Talavera K, Owsianik G, Nilius B. (2005) Sensing with TRP channels. *Nat Chem Biol* **1**: 85–92. [PMID:16408004]

Vriens J, Appendino G, Nilius B. (2009) Pharmacology of vanilloid transient receptor potential cation channels. *Mol Pharmacol* **75**: 1262–1279. [PMID:19297520]

Wissenbach U, Niemeyer BA. (2007) TRPV6. *Handb Exp Pharmacol* **179**: 221–234. [PMID:17217060]

Witzgall R. (2007) TRPP2 channel regulation. *Handb Exp Pharmacol* **179**: 363–375. [PMID:17217069]

Wu LJ, Sweet TB, Clapham DE. (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]

Yamamoto S, Takahashi N, Mori Y. (2010) Chemical physiology of oxidative stress-activated TRPM2 and TRPC5 channels. *Prog Biophys Mol Biol* **103**: 18–27. [PMID:20553742]

Yuan JP, Kim MS, Zeng W, Shin DM, Huang G, Worley PF, Muallem S. (2009) TRPC channels as STIM1-regulated SOCs. *Channels (Austin)* **3**: 221–225. [PMID:19574740]

Zeevi DA, Frumkin A, Bach G. (2007) TRPML and lysosomal function. *Biochim Biophys Acta* **1772**: 851–858. [PMID:17306511]

Zholos A. (2010) Pharmacology of transient receptor potential melastatin channels in the vasculature. *Br J Pharmacol* **159**: 1559–1571. [PMID:20233227]
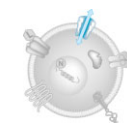
Voltage-gated calcium channels

Overview: Calcium (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 [359] and approved by the NC-IUPHAR subcommittee on Ca^{2+} channels [358]. Ca^{2+} channels form hetero-oligomeric complexes. The α1 subunit is pore-forming and provides the extracellular binding site(s) for practically all agonists and antagonists. The 10 cloned α-subunits can be grouped into three families: (1) the high-voltage activated dihydropyridine-sensitive (L-type, $Ca_v1.x$) channels; (2) the high-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 and a pore-forming region between transmembrane domains S5 and S6. Gating is thought to be associated with the membrane-spanning S4 segment, which contains highly conserved positive charges. Many 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. The γ subunits have not been proven to associate with channels other than α1s. The α2–δ1 and α2–δ2 subunits bind gabapentin and pregabalin.

Subunits

Nomenclature	$Ca_v1.1$	$Ca_v1.2$	$Ca_v1.3$	$Ca_v1.4$	$Ca_v2.1$
HGNC, UniProt	*CACNA1S*, Q13698	*CACNA1C*, Q13936	*CACNA1D*, Q01668	*CACNA1F*, O60840	*CACNA1A*, O00555
Activators (EC_{50})	FPL64176, (-)-(S)-BayK8644, SZ(+)-(*S*)-202-791	FPL64176, (-)-(S)-BayK8644, SZ(+)-(*S*)-202-791	(-)-(S)-BayK8644	(-)-(S)-BayK8644	–
Channel Blockers (IC_{50})	calciseptine, diltiazem, nifedipine, verapamil	calciseptine, diltiazem, nifedipine, verapamil	verapamil (less sensitive to dihydropyridine antagonists)	–	ω-agatoxin IVB, ω-conotoxin MVIIC, ω-agatoxin IVA (P current component) (~1×10^{-9} M), ω-agatoxin IVA (Q current component) (~9×10^{-8} M)
Functional characteristics	High voltage-activated, slow inactivation	High voltage-activated, slow inactivation (Ca^{2+} dependent)	Low-moderate voltage-activated, slow inactivation (Ca^{2+} dependent)	Moderate voltage-activated, slow inactivation (Ca^{2+} independent)	Moderate voltage-activated, moderate inactivation
Comment	nifedipine, diltiazem, verapamil and calciseptine are examples of dihydropyridine antagonists	nifedipine, diltiazem, verapamil and calciseptine are examples of dihydropyridine antagonists	verapamil is an example of a dihydropyridine antagonist	$Ca_v1.4$ is less sensitive to dihydropyridine antagonists	–

Nomenclature	$Ca_v2.2$	$Ca_v3.1$	$Ca_v3.2$	$Ca_v3.3$
HGNC, UniProt	*CACNA1B*, Q00975	*CACNA1G*, O43497	*CACNA1H*, O95180	*CACNA1I*, Q9P0X4
Channel Blockers (IC_{50})	ω-conotoxin GVIA, ω-conotoxin MVIIC	kurtoxin, mibefradil, Ni^{2+} (low sensitivity to Ni^{2+}), SB209712	kurtoxin, mibefradil, Ni^{2+} (high sensitivity to Ni^{2+}), SB209712	kurtoxin, mibefradil, Ni^{2+} (low sensitivity to Ni^{2+}), SB209712
Functional characteristics	High voltage-activated, moderate inactivation	Low voltage-activated, fast inactivation	Low voltage-activated, fast inactivation	Low voltage-activated, moderate inactivation

Comments: In many cell types, P and Q current components cannot be adequately separated and many researchers in the field have adopted the terminology 'P/Q-type' current when referring to either component. Ziconotide (a synthetic peptide equivalent to ω-conotoxin MVIIA) has been approved for the treatment of chronic pain [360].
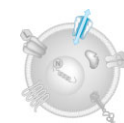
Further reading

Bauer CS, Tran-Van-Minh A, Kadurin I, Dolphin AC. (2010) A new look at calcium channel α2δ subunits. *Curr Opin Neurobiol* **20**: 563–571. [PMID:20579869]

Belardetti F, Zamponi GW. (2008) Linking calcium-channel isoforms to potential therapies. *Curr Opin Investig Drugs* **9**: 707–715. [PMID:18600576]

Buraei Z, Yang J. (2010) The ß subunit of voltage-gated Ca2+ channels. *Physiol Rev* **90**: 1461–1506. [PMID:20959621]

Catterall WA. (2000) Structure and regulation of voltage-gated Ca2+ channels. *Annu Rev Cell Dev Biol* **16**: 521–555. [PMID:11031246]

Catterall WA. (2011) Voltage-gated calcium channels. *Cold Spring Harb Perspect Biol* **3**: a003947. [PMID:21746798]

Catterall WA, Dib-Hajj S, Meisler MH, Pietrobon D. (2008) Inherited neuronal ion channelopathies: new windows on complex neurological diseases. *J Neurosci* **28**: 11768–11777. [PMID:19005038]

Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J. (2005) International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. *Pharmacol Rev* **57**: 411–425. [PMID:16382099]

Davies A, Hendrich J, Van Minh AT, Wratten J, Douglas L, Dolphin AC. (2007) Functional biology of the alpha(2)delta subunits of voltage-gated calcium channels. *Trends Pharmacol Sci* **28**: 220–228. [PMID:17403543]

Dolphin AC. (2003) G protein modulation of voltage-gated calcium channels. *Pharmacol Rev* **55**: 607–627. [PMID:14657419]

Dolphin AC. (2009) Calcium channel diversity: multiple roles of calcium channel subunits. *Curr Opin Neurobiol* **19**: 237–244. [PMID:19559597]

Elmslie KS. (2004) Calcium channel blockers in the treatment of disease. *J Neurosci Res* **75**: 733–741. [PMID:14994334]

Ertel EA, Campbell KP, Harpold MM, Hofmann F, Mori Y, Perez-Reyes E, Schwartz A, Snutch TP, Tanabe T, Birnbaumer L, Tsien RW, Catterall WA. (2000) Nomenclature of voltage-gated calcium channels. *Neuron* **25**: 533–535. [PMID:10774722]

Gao L. (2010) An update on peptide drugs for voltage-gated calcium channels. *Recent Pat CNS Drug Discov* **5**: 14–22. [PMID:19751208]

Han TS, Teichert RW, Olivera BM, Bulaj G. (2008) Conus venoms - a rich source of peptide-based therapeutics. *Curr Pharm Des* **14**: 2462–2479. [PMID:18781995]

Hofmann F, Lacinová L, Klugbauer N. (1999) Voltage-dependent calcium channels: from structure to function. *Rev Physiol Biochem Pharmacol* **139**: 33–87. [PMID:10453692]

Kochegarov AA. (2003) Pharmacological modulators of voltage-gated calcium channels and their therapeutical application. *Cell Calcium* **33**: 145–162. [PMID:12600802]

Lewis RJ, Garcia ML. (2003) Therapeutic potential of venom peptides. *Nat Rev Drug Discov* **2**: 790–802. [PMID:14526382]

Lory P, Chemin J. (2007) Towards the discovery of novel T-type calcium channel blockers. *Expert Opin Ther Targets* **11**: 717–722. [PMID:17465728]

Nelson MT, Todorovic SM, Perez-Reyes E. (2006) The role of T-type calcium channels in epilepsy and pain. *Curr Pharm Des* **12**: 2189–2197. [PMID:16787249]

Perez-Reyes E. (2003) Molecular physiology of low-voltage-activated t-type calcium channels. *Physiol Rev* **83**: 117–161. [PMID:12506128]

Pexton T, Moeller-Bertram T, Schilling JM, Wallace MS. (2011) Targeting voltage-gated calcium channels for the treatment of neuropathic pain: a review of drug development. *Expert Opin Investig Drugs* **20**: 1277–1284. [PMID:21740292]

Taylor CP, Angelotti T, Fauman E. (2007) Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. *Epilepsy Res* **73**: 137–150. [PMID:17126531]

Terlau H, Olivera BM. (2004) Conus venoms: a rich source of novel ion channel-targeted peptides. *Physiol Rev* **84**: 41–68. [PMID:14715910]

Triggle DJ. (2006) L-type calcium channels. *Curr Pharm Des* **12**: 443–457. [PMID:16472138]

Triggle DJ. (2007) Calcium channel antagonists: clinical uses–past, present and future. *Biochem Pharmacol* **74**: 1–9. [PMID:17276408]

Trimmer JS, Rhodes KJ. (2004) Localization of voltage-gated ion channels in mammalian brain. *Annu Rev Physiol* **66**: 477–519. [PMID:14977411]

Williams JA, Day M, Heavner JE. (2008) Ziconotide: an update and review. *Expert Opin Pharmacother* **9**: 1575–1583. [PMID:18518786]

Yamamoto T, Takahara A. (2009) Recent updates of N-type calcium channel blockers with therapeutic potential for neuropathic pain and stroke. *Curr Top Med Chem* **9**: 377–395. [PMID:19442208]

Yu FH, Catterall WA. (2004) The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* **2004**: re15. [PMID:15467096]

Zamponi GW, Lewis RJ, Todorovic SM, Arneric SP, Snutch TP. (2009) Role of voltage-gated calcium channels in ascending pain pathways. *Brain Res Rev* **60**: 84–89. [PMID:19162069]
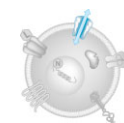
Voltage-gated proton channel

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 [361–363,372,374]. 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 [372,374]. Proton flux through H_v1 is instead most likely mediated by a water wire completed in a crevice of the protein when the voltage-sensing S4 helix moves in response to a change in transmembrane potential [371,377]. H_v1 expresses largely as a dimer mediated by intracellular C-terminal coiled-coil interactions [367] but individual promoters nonetheless support gated H^+ flux via separate conduction pathways [365–366,370,375]. Within dimeric structures, the two protomers do not function independently, but display co-operative interactions during gating resulting in increased voltage sensitivity, but slower activation, of the dimeric, *versus* monomeric, complexes [364,376].

Subunits

Nomenclature	HGNC, UniProt	Channel Blockers (IC$_{50}$)	Functional characteristics
H_v1	*HVCN1*, Q96D96	Zn^{2+} ($\sim5 \times 10^{-7} - 2 \times 10^{-6}$ M), Cd^{2+} ($\sim1 \times 10^{-5}$ M)	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 [361–363]. Phosphorylation of H_v1 within the N-terminal domain by PKC enhances the gating of the channel [368]. Tabulated IC$_{50}$ values for Zn^{2+} and Cd^{2+} are for heterologously expressed human and mouse H_v1 [372,374]. Zn^{2+} is not a conventional pore blocker, but is coordinated by two, or more, external protonation sites involving histamine residues [372]. Zn^{2+} binding may occur at the dimer interface between pairs of histamine residues from both monomers where it may interfere with channel opening [369]. Mouse knockout studies demonstrate that H_v1 participates in charge compensation in granulocytes during the respiratory burst of NADPH oxidase-dependent reactive oxygen species production that assists in the clearance of bacterial pathogens [373]. Additional physiological functions of H_v1 are reviewed by [361].

Further reading

Capasso M, DeCoursey TE, Dyer MJ. (2011) pH regulation and beyond: unanticipated functions for the voltage-gated proton channel, HVCN1. *Trends Cell Biol* **21**: 20–8. [PMID:20961760]

DeCoursey TE. (2008) Voltage-gated proton channels. *Cell Mol Life Sci* **65**: 2554–73. [PMID:18463791]

DeCoursey TE. (2008) Voltage-gated proton channels: what's next?. *J Physiol (Lond)* **586** (Pt 22): 5305–24. [PMID:18801839]

DeCoursey TE, Cherny VV. (2007) Pharmacology of voltage-gated proton channels. *Curr Pharm Des* **13**: 2400–20. [PMID:17692009]

Tombola F, Ulbrich MH, Isacoff EY. (2009) Architecture and gating of Hv1 proton channels. *J Physiol (Lond)* **587** (Pt 22): 5325–9. [PMID:19915215]
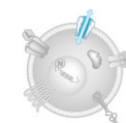
Voltage-gated sodium channels

Overview: Sodium channels are voltage-gated sodium-selective ion channels present in the membrane of most excitable cells. Sodium channels comprise of one pore-forming α subunit, which may be associated with either one or two β subunits [380]. 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 [381]. 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 [381]. Auxiliary β1, β2, β3 and β4 subunits consist of a large extracellular N-terminal domain, a single transmembrane segment and a shorter cytoplasmic domain.

The nomenclature for sodium channels was proposed by Goldin *et al.*, (2000) [379] and approved by the NC-IUPHAR subcommittee on sodium channels (Catterall *et al.*, 2005, [378]).

Subunits

| Nomenclature	$Na_v1.1$	$Na_v1.2$	$Na_v1.3$	$Na_v1.4$	$Na_v1.5$	$Na_v1.6$	$Na_v1.7$	$Na_v1.8$	$Na_v1.9$
HGNC, UniProt	*SCN1A*, P35498	*SCN2A*, Q99250	*SCN3A*, Q9NY46	*SCN4A*, P35499	*SCN5A*, Q14524	*SCN8A*, Q9UQD0	*SCN9A*, Q15858	*SCN10A*, Q9Y5Y9	*SCN11A*, Q9UI33
Activators (EC_{50})	batrachotoxin, veratridine	batrachotoxin, veratridine	batrachotoxin, veratridine	batrachotoxin, veratridine	batrachotoxin, veratridine	batrachotoxin, veratridine	batrachotoxin, veratridine	–	–
Channel Blockers (IC_{50})	saxitoxin, tetrodotoxin (Concentration range = 1×10^{-8} M)	saxitoxin, tetrodotoxin (Concentration range = 1×10^{-8} M)	saxitoxin, tetrodotoxin (Concentration range = 2×10^{-9} - 1.5×10^{-8} M)	μ-conotoxin GIIIA, saxitoxin, tetrodotoxin (Concentration range = 5×10^{-9} M)	tetrodotoxin (Concentration range = 2×10^{-6} M)	saxitoxin, tetrodotoxin (Concentration range = 6×10^{-9} M)	saxitoxin, tetrodotoxin (Concentration range = 4×10^{-9} M)	tetrodotoxin (Concentration range = 6×10^{-5} M)	tetrodotoxin (Concentration range = 4×10^{-5} M)
Functional characteristics	Fast inactivation (0.7 ms)	Fast inactivation (0.8 ms)	Fast inactivation (0.8 ms)	Fast inactivation (0.6 ms)	Fast inactivation (1 ms)	Fast inactivation (1 ms)	Fast inactivation (0.5 ms)	Slow inactivation (6 ms)	Slow inactivation (16 ms)

Comments: Sodium channels are also blocked by local anaesthetic agents, antiarrythmic drugs and antiepileptic drugs. 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 inactivation ($Na_V1.8$ and particularly $Na_V1.9$ inactivate more slowly).

Further reading

Andavan GS, Lemmens-Gruber R. (2011) Voltage-gated sodium channels: mutations, channelopathies and targets. *Curr Med Chem* **18**: 377–397. [PMID:21143119]

Baker MD, Wood JN. (2001) Involvement of Na+ channels in pain pathways. *Trends Pharmacol Sci* **22**: 27–31. [PMID:11165669]

Bean BP. (2007) The action potential in mammalian central neurons. *Nat Rev Neurosci* **8**: 451–465. [PMID:17514198]

Cantrell AR, Catterall WA. (2001) Neuromodulation of Na+ channels: an unexpected form of cellular plasticity. *Nat Rev Neurosci* **2**: 397–407. [PMID:11389473]

Catterall WA. (1995) Structure and function of voltage-gated ion channels. *Annu Rev Biochem* **64**: 493–531. [PMID:7574491]

Catterall WA. (2000) From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron* **26**: 13–25. [PMID:10798388]

Catterall WA, Dib-Hajj S, Meisler MH, Pietrobon D. (2008) Inherited neuronal ion channelopathies: new windows on complex neurological diseases. *J Neurosci* **28**: 11768–11777. [PMID:19005038]

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

Dib-Hajj SD, Cummins TR, Black JA, Waxman SG. (2010) Sodium channels in normal and pathological pain. *Annu Rev Neurosci* **33**: 325–347. [PMID:20367448]

England S, de Groot MJ. (2009) Subtype-selective targeting of voltage-gated sodium channels. *Br J Pharmacol* **158**: 1413–1425. [PMID:19845672]

Fozzard HA, Hanck DA. (1996) Structure and function of voltage-dependent sodium channels: comparison of brain II and cardiac isoforms. *Physiol Rev* **76**: 887–926. [PMID:8757791]
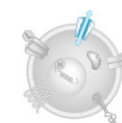
Fozzard HA, Lee PJ, Lipkind GM. (2005) Mechanism of local anesthetic drug action on voltage-gated sodium channels. *Curr Pharm Des* **11**: 2671–2686. [PMID:16101448]

George AL. (2005) Inherited disorders of voltage-gated sodium channels. *J Clin Invest* **115**: 1990–1999. [PMID:16075039]

Goldin AL. (2001) Resurgence of sodium channel research. *Annu Rev Physiol* **63**: 871–894. [PMID:11181979]

Han TS, Teichert RW, Olivera BM, Bulaj G. (2008) Conus venoms - a rich source of peptide-based therapeutics. *Curr Pharm Des* **14**: 2462–2479. [PMID:18781995]

Isom LL. (2001) Sodium channel beta subunits: anything but auxiliary. *Neuroscientist* **7**: 42–54. [PMID:11486343]

Kyle DJ, Ilyin VI. (2007) Sodium channel blockers. *J Med Chem* **50**: 2583–2588. [PMID:17489575]

Lai J, Porreca F, Hunter JC, Gold MS. (2004) Voltage-gated sodium channels and hyperalgesia. *Annu Rev Pharmacol Toxicol* **44**: 371–397. [PMID:14744251]

Lewis RJ, Garcia ML. (2003) Therapeutic potential of venom peptides. *Nat Rev Drug Discov* **2**: 790–802. [PMID:14526382]

Mantegazza M, Curia G, Biagini G, Ragsdale DS, Avoli M. (2010) Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders. *Lancet Neurol* **9**: 413–424. [PMID:20298965]

Matulenko MA, Scanio MJ, Kort ME. (2009) Voltage-gated sodium channel blockers for the treatment of chronic pain. *Curr Top Med Chem* **9**: 362–376. [PMID:19442207]

Priest BT, Kaczorowski GJ. (2007) Blocking sodium channels to treat neuropathic pain. *Expert Opin Ther Targets* **11**: 291–306. [PMID:17298289]

Priestley T. (2004) Voltage-gated sodium channels and pain. *Curr Drug Targets CNS Neurol Disord* **3**: 441–456. [PMID:15578963]

Terlau H, Olivera BM. (2004) Conus venoms: a rich source of novel ion channel-targeted peptides. *Physiol Rev* **84**: 41–68. [PMID:14715910]

Trimmer JS, Rhodes KJ. (2004) Localization of voltage-gated ion channels in mammalian brain. *Annu Rev Physiol* **66**: 477–519. [PMID:14977411]

Wood JN, Boorman J. (2005) Voltage-gated sodium channel blockers; target validation and therapeutic potential. *Curr Top Med Chem* **5**: 529–537. [PMID:16022675]

Yu FH, Catterall WA. (2004) The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* **2004**: re15. [PMID:15467096]

References

1. Akopian AN *et al*. (2000) *Neuroreport* **11**: 2217–2222. [PMID:10923674]
2. Andrey F *et al*. (2005) *Biochim Biophys Acta* **1745**: 1–6. [PMID:16085050]
3. Babinski K *et al*. (2000) *J Biol Chem* **275**: 28519–28525. [PMID:10842183]
4. Babinski K *et al*. (1999) *J Neurochem* **72**: 51–57. [PMID:9886053]
5. Baron A *et al*. (2001) *J Biol Chem* **276**: 35361–35367. [PMID:11457851]
6. Baron A *et al*. (2008) *J Neurosci* **28**: 1498–1508. [PMID:18256271]
7. Cadiou H *et al*. (2007) *J Neurosci* **27**: 13251–13260. [PMID:18045919]
8. Chen CC *et al*. (1998) *Proc Natl Acad Sci USA* **95**: 10240–10245. [PMID:9707631]
9. Chu XP *et al*. (2006) *J Neurosci* **26**: 5329–5339. [PMID:16707785]
10. Chu XP *et al*. (2004) *J Neurosci* **24**: 8678–8689. [PMID:15470133]
11. de Weille JR *et al*. (1998) *FEBS Lett* **433**: 257–260. [PMID:9744806]
12. Deval E *et al*. (2011) *J Neurosci* **31**: 6059–6066. [PMID:21508231]
13. Deval E *et al*. (2008) *EMBO J* **27**: 3047–3055. [PMID:18923424]
14. Diochot S *et al*. (2004) *EMBO J* **23**: 1516–1525. [PMID:15044953]
15. Diochot S *et al*. (2007) *Toxicon* **49**: 271–284. [PMID:17113616]
16. Donier E *et al*. (2008) *Eur J Neurosci* **28**: 74–86. [PMID:18662336]
17. Duan B *et al*. (2011) *J Neurosci* **31**: 2101–2112. [PMID:21307247]
18. Dubé GR *et al*. (2005) *Pain* **117**: 88–96. [PMID:16061325]
19. Escoubas P *et al*. (2000) *J Biol Chem* **275**: 25116–25121. [PMID:10829030]
20. Friese MA *et al*. (2007) *Nat Med* **13**: 1483–1489. [PMID:17994101]
21. García-Añoveros J *et al*. (1997) *Proc Natl Acad Sci USA* **94**: 1459–1464. [PMID:9037075]
22. Gonzales EB *et al*. (2009) *Nature* **460**: 599–604. [PMID:19641589]
23. Gründer S, Chen X. (2010) *Int J Physiol Pathophysiol Pharmacol* **2**: 73–94. [PMID:21383888]
24. Gründer S *et al*. (2000) *Neuroreport* **11**: 1607–1611. [PMID:10852210]
25. Hattori T *et al*. (2009) *Circ Res* **105**: 279–286. [PMID:19590043]
26. Jasti J *et al*. (2007) *Nature* **449**: 316–323. [PMID:17882215]
27. Lingueglia E. (2007) *J Biol Chem* **282**: 17325–17329. [PMID:17430882]
28. Lingueglia E *et al*. (1997) *J Biol Chem* **272**: 29778–29783. [PMID:9368048]
29. Lingueglia E *et al*. (2006) *Peptides* **27**: 1138–1152. [PMID:16516345]
30. Mamet J *et al*. (2002) *J Neurosci* **22**: 10662–10670. [PMID:12486159]
31. Mazzuca M *et al*. (2007) *Nat Neurosci* **10**: 943–945. [PMID:17632507]
32. Pidoplichko VI, Dani JA. (2006) *Proc Natl Acad Sci USA* **103**: 11376–11380. [PMID:16847263]
33. Price MP *et al*. (1996) *J Biol Chem* **271**: 7879–7882. [PMID:8626462]
34. Sakai H *et al*. (1999) *J Physiol* **2**: 323–333.
35. Schaefer L *et al*. (2000) *FEBS Lett* **471**: 205–210. [PMID:10767424]
36. Sherwood TW *et al*. (2011) *J Neurosci* **31**: 9723–9734. [PMID:21715637]
37. Smith ES *et al*. (2007) *Neuroscience* **145**: 686–698. [PMID:17258862]
38. Sutherland SP *et al*. (2001) *Proc Natl Acad Sci USA* **98**: 711–716. [PMID:11120882]
39. Ugawa S *et al*. (2001) *Neuroreport* **12**: 2865–2869. [PMID:11588592]
40. Voilley N. (2004) *Curr Drug Targets Inflamm Allergy* **3**: 71–79. [PMID:15032643]
41. Vukicevic M *et al*. (2006) *J Biol Chem* **281**: 714–722. [PMID:16282326]
42. Waldmann R *et al*. (1997) *J Biol Chem* **272**: 20975–20978. [PMID:9261094]
43. Waldmann R *et al*. (1997) *Nature* **386**: 173–177. [PMID:9062189]
44. Waldmann R *et al*. (1996) *J Biol Chem* **271**: 10433–10436. [PMID:8631835]
45. Wemmie JA *et al*. (2003) *J Neurosci* **23**: 5496–5502. [PMID:12843249]
46. Wemmie JA *et al*. (2002) *Neuron* **34**: 463–477. [PMID:11988176]
47. Wemmie JA *et al*. (2006) *Trends Neurosci* **29**: 578–586. [PMID:16891000]
48. Xiong ZG *et al*. (2007) *Front Biosci* **12**: 1376–1386. [PMID:17127388]
49. Yu Y *et al*. (2010) *Neuron* **68**: 61–72. [PMID:20920791]
50. Zha XM *et al*. (2009) *Proc Natl Acad Sci USA* **106**: 3573–3578. [PMID:19218436]
51. Ziemann AE *et al*. (2008) *Nat Neurosci* **11**: 816–822. [PMID:18536711]
52. Castle NA. (2005) *Drug Discov Today* **10**: 485–493. [PMID:15809194]
53. King LS *et al*. (2004) *Nat Rev Mol Cell Biol* **5**: 687–698. [PMID:15340377]
54. Preston GM *et al*. (1992) *Science* **256**: 385–387. [PMID:1373524]
55. Yasui M *et al*. (1999) *Nature* **402**: 184–187. [PMID:10647010]
56. Carlson AE *et al*. (2005) *J Biol Chem* **280**: 32238–32244. [PMID:16036917]
57. Carlson AE *et al*. (2003) *Proc Natl Acad Sci USA* **100**: 14864–14868. [PMID:14657352]
58. Chung JJ *et al*. (2011) *Nat Commun* **2**: 153. [PMID:21224844]
59. Clapham DE, Garbers DL. (2005) *Pharmacol Rev* **57**: 451–454. [PMID:16382101]
60. Hildebrand MS *et al*. (2010) *Eur J Hum Genet* **18**: 1178–1184. [PMID:20648059]
61. Jin JL *et al*. (2005) *Biol Reprod* **73**: 1235–1242. [PMID:16107607]
62. Kirichok Y *et al*. (2006) *Nature* **439**: 737–740. [PMID:16467839]
63. Lishko PV *et al*. (2011) *Nature* **471**: 387–391. [PMID:21412339]
64. Lishko PV, Kirichok Y. (2010) *J Physiol (Lond)* **588** (Pt 23): 4667–4672. [PMID:20679352]
65. Liu J *et al*. (2007) *J Biol Chem* **282**: 18945–18952. [PMID:17478420]
66. Lobley A *et al*. (2003) *Reprod Biol Endocrinol* **1**: 53. [PMID:12932298]
67. Martínez-López P *et al*. (2009) *Biochem Biophys Res Commun* **381**: 204–209. [PMID:19338774]
68. Navarro B *et al*. (2007) *Proc Natl Acad Sci USA* **104**: 7688–7692. [PMID:17460039]
69. Qi H *et al*. (2007) *Proc Natl Acad Sci USA* **104**: 1219–1223. [PMID:17227845]
70. Quill TA *et al*. (2001) *Proc Natl Acad Sci USA* **98**: 12527–12531. [PMID:11675491]
71. Ren D *et al*. (2001) *Nature* **413**: 603–609. [PMID:11595941]
72. Strünker T *et al*. (2011) *Nature* **471**: 382–386. [PMID:21412338]
73. Wang H *et al*. (2009) *Biol Reprod* **81**: 539–544. [PMID:19516020]
74. Xia J, Ren D. (2009) *Biol Reprod* **80**: 1092–1098. [PMID:19211808]
75. Zeng XH *et al*. (2011) *Proc Natl Acad Sci USA* **108**: 5879–5884. [PMID:21427226]
76. Accardi A, Miller C. (2004) *Nature* **427**: 803–807. [PMID:14985752]
77. Accardi A, Picollo A. (2010) *Biochim Biophys Acta* **1798**: 1457–1464. [PMID:20188062]
78. Alekov AK, Fahlke C. (2008) *Curr Biol* **18**: R1061–R1064. [PMID:19036336]
79. Alekov AK, Fahlke C. (2009) *J Gen Physiol* **133**: 485–496. [PMID:19364886]
80. Aleksandrov AA *et al*. (2007) *Pflugers Arch* **453**: 693–702. [PMID:17021796]
81. Arniges M *et al*. (2004) *J Biol Chem* **279**: 54062–54068. [PMID:15489228]
82. Bahamonde MI *et al*. (2003) *J Biol Chem* **278**: 33284–33289. [PMID:12794078]
83. Bell PD *et al*. (2003) *Proc Natl Acad Sci USA* **100**: 4322–4327. [PMID:12655045]
84. Best L *et al*. (2010) *Islets* **2**: 59–64. [PMID:21099297]
85. Billig GM *et al*. (2011) *Nat Neurosci* **14**: 763–769. [PMID:21516098]
86. Caputo A *et al*. (2008) *Science* **322**: 590–594. [PMID:18772398]
87. Chen TY. (2005) *Annu Rev Physiol* **67**: 809–839. [PMID:15709979]
88. Cuthbert AW. (2011) *Br J Pharmacol* **163**: 173–183. [PMID:21108631]
89. De La Fuente R *et al*. (2008) *Mol Pharmacol* **73**: 758–768. [PMID:18083779]
90. Diaz M *et al*. (2001) *J Physiol (Lond)* **536** (Pt 1): 79–88. [PMID:11579158]
91. Duran C, Hartzell HC. (2011) *Acta Pharmacol Sin* **32**: 685–692. [PMID:21642943]
92. Duran C *et al*. (2010) *Annu Rev Physiol* **72**: 95–121. [PMID:19827947]
93. Dutta AK *et al*. (2002) *J Physiol (Lond)* **542** (Pt 3): 803–816. [PMID:12154180]
94. Dutzler R. (2007) *FEBS Lett* **581**: 2839–2844. [PMID:17452037]

95. Dutzler R *et al*. (2002) *Nature* **415**: 287–294. [PMID:11796999]
96. Edwards JC, Kahl CR. (2010) *FEBS Lett* **584**: 2102–2111. [PMID:20100480]
97. Estévez R *et al*. (2001) *Nature* **414**: 558–561. [PMID:11734858]
98. Fahlke C, Fischer M. (2010) *Front Physiol* **1**: 155. [PMID:21423394]
99. Feng L *et al*. (2010) *Science* **330**: 635–641. [PMID:20929736]
100. Ferrera L *et al*. (2009) *J Biol Chem* **284**: 33360–33368. [PMID:19819874]
101. Fischer M *et al*. (2010) *J Am Soc Nephrol* **21**: 1281–1289. [PMID:20538786]
102. Fuller MD *et al*. (2007) *J Biol Chem* **282**: 37545–37555. [PMID:17951250]
103. Graves AR *et al*. (2008) *Nature* **453**: 788–792. [PMID:18449189]
104. Greenwood IA, Leblanc N. (2007) *Trends Pharmacol Sci* **28**: 1–5. [PMID:17150263]
105. Guan YY *et al*. (2006) *Trends Pharmacol Sci* **27**: 290–296. [PMID:16697056]
106. Hartzell C *et al*. (2005) *Annu Rev Physiol* **67**: 719–758. [PMID:15709976]
107. Hartzell HC *et al*. (2008) *Physiol Rev* **88**: 639–672. [PMID:18391176]
108. Jentsch TJ. (2008) *Crit Rev Biochem Mol Biol* **43**: 3–36. [PMID:18307107]
109. Ko SB *et al*. (2004) *Nat Cell Biol* **6**: 343–350. [PMID:15048129]
110. Kunzelmann K *et al*. (2011) *Pflugers Arch* **462**: 195–208. [PMID:21607626]
111. Lambert S, Oberwinkler J. (2005) *J Physiol (Lond)* **567** (Pt 1): 191–213. [PMID:15961423]
112. Lange PF *et al*. (2006) *Nature* **440**: 220–223. [PMID:16525474]
113. Leblanc N *et al*. (2005) *Can J Physiol Pharmacol* **83**: 541–556. [PMID:16091780]
114. Leisle L *et al*. (2011) *EMBO J* **30**: 2140–2152. [PMID:21527911]
115. Liantonio A *et al*. (2007) *Br J Pharmacol* **150**: 235–247. [PMID:17128287]
116. Liantonio A *et al*. (2008) *Proc Natl Acad Sci USA* **105**: 1369–1373. [PMID:18216243]
117. Loewen ME, Forsyth GW. (2005) *Physiol Rev* **85**: 1061–1092. [PMID:15987802]
118. Manoury B *et al*. (2010) *J Physiol (Lond)* **588** (Pt 13): 2305–2314. [PMID:20421283]
119. Matchkov VV *et al*.(2004) *J Gen Physiol* **123**: 121–134. [PMID:14718479]
120. Matchkov VV *et al*. (2008) *Circ Res* **103**: 864–872. [PMID:18776041]
121. Matsuda JJ *et al*. (2008) *Am J Physiol, Cell Physiol* **294**: C251–C262. [PMID:17977943]
122. Muallem D, Vergani P. (2009) *Philos Trans R Soc Lond, B, Biol Sci* **364**: 247–255. [PMID:18957373]
123. Mulligan SJ, MacVicar BA. (2006) *Sci STKE* **2006**: pe42. [PMID:17047222]
124. Namkung W *et al*. (2011) *J Biol Chem* **286**: 2365–2374. [PMID:21084298]
125. Neagoe I *et al*. (2010) *J Biol Chem* **285**: 21689–21697. [PMID:20466723]
126. Nilius B, Droogmans G. (2003) *Acta Physiol Scand* **177**: 119–147. [PMID:12558550]
127. Novarino G *et al*. (2010) *Science* **328**: 1398–1401. [PMID:20430979]
128. Okada SF *et al*. (2004) *J Gen Physiol* **124**: 513–526. [PMID:15477379]
129. Okada Y *et al*. (2009) *J Physiol (Lond)* **587** (Pt 10): 2141–2149. [PMID:19171657]
130. Orhan G *et al*. (2011) *Biophys J* **100**: 1233–1241. [PMID:21354396]
131. Osteen JD, Mindell JA. (2008) *Biophys J* **95**: 4668–4675. [PMID:18658230]
132. Ousingsawat J *et al*. (2009) *J Biol Chem* **284**: 28698–28703. [PMID:19679661]
133. Patel AC *et al*. (2009) *Annu Rev Physiol* **71**: 425–449. [PMID:18954282]
134. Picollo A, Pusch M. (2005) *Nature* **436**: 420–423. [PMID:16034421]
135. Pifferi S *et al*. (2009) *Pflugers Arch* **458**: 1023–1038. [PMID:19475416]
136. Piper AS, Large WA. (2004) *J Physiol (Lond)* **555** (Pt 2): 397–408. [PMID:14724180]
137. Planells-Cases R, Jentsch TJ. (2009) *Biochim Biophys Acta* **1792**: 173–189. [PMID:19708126]
138. Pusch M *et al*. (2002) *Mol Membr Biol* **19**: 285–292. [PMID:12512775]
139. Pusch M *et al*. (2006) *Exp Physiol* **91**: 149–152. [PMID:16179405]
140. Riquelme G. (2009) *Placenta* **30**: 659–669. [PMID:19604577]
141. Robertson JL *et al*. (2010) *Nature* **468**: 844–847. [PMID:21048711]
142. Rock JR *et al*. (2009) *J Biol Chem* **284**: 14875–14880. [PMID:19363029]
143. Sabirov RZ *et al*. (2001) *J Gen Physiol* **118**: 251–266. [PMID:11524456]
144. Sabirov RZ, Okada Y. (2009) *J Physiol Sci* **59**: 3–21. [PMID:19340557]
145. Sardini A *et al*. (2003) *Biochim Biophys Acta* **1618**: 153–162. [PMID:14729152]
146. Scheel O *et al*. (2005) *Nature* **436**: 424–427. [PMID:16034422]
147. Scholl U *et al*. (2006) *Proc Natl Acad Sci USA* **103**: 11411–11416. [PMID:16849430]
148. Schroeder BC *et al*. (2008) *Cell* **134**: 1019–1029. [PMID:18805094]
149. Schulz P *et al*. (2010) *PLoS ONE* **5**: e12585. [PMID:20830208]
150. Sloane PA, Rowe SM. (2010) *Curr Opin Pulm Med* **16**: 591–597. [PMID:20829696]
151. Smith AJ, Lippiat JD. (2010) *FASEB J* **24**: 3696–3705. [PMID:20501796]
152. Suzuki M, Mizuno A. (2004) *J Biol Chem* **279**: 22461–22468. [PMID:15010458]
153. Thompson CH *et al*. (2009) *J Biol Chem* **284**: 26051–26062. [PMID:19574231]
154. Tsumura T *et al*. (1998) *J Physiol (Lond)* **512** (Pt 3): 765–777. [PMID:9769420]
155. Verkman AS, Galietta LJ. (2009) *Nat Rev Drug Discov* **8**: 153–171. [PMID:19153558]
156. Wang XQ *et al*. (2006) *Neuron* **52**: 321–333. [PMID:17046694]
157. Yang YD *et al*. (2008) *Nature* **455**: 1210–1215. [PMID:18724360]
158. Zdebik AA *et al*. (2008) *J Biol Chem* **283**: 4219–4227. [PMID:18063579]
159. Zifarelli G, Pusch M. (2009) *EMBO J* **28**: 175–182. [PMID:19131966]
160. Bai D *et al*. (2006) *J Pharmacol Exp Ther* **319**: 1452–1458. [PMID:16985167]
161. Bruzzone R *et al*. (2005) *J Neurochem* **92**: 1033–1043. [PMID:15715654]
162. Bruzzone R *et al*. (2003) *Proc Natl Acad Sci USA* **100**: 13644–13649. [PMID:14597722]
163. Connors BW, Long MA. (2004) *Annu Rev Neurosci* **27**: 393–418. [PMID:15217338]
164. Evans WH, Martin PE. (2002) *Mol Membr Biol* **19**: 121–136. [PMID:12126230]
165. Hervé JC *et al*. (2007) *Prog Biophys Mol Biol* **94**: 29–65. [PMID:17507078]
166. Pelegrin P, Surprenant A. (2007) *J Biol Chem* **282**: 2386–2394. [PMID:17121814]
167. Salameh A, Dhein S. (2005) *Biochim Biophys Acta* **1719**: 36–58. [PMID:16216217]
168. Söhl G *et al*. (2005) *Nat Rev Neurosci* **6**: 191–200. [PMID:15738956]
169. Vogt A *et al*. (2005) *Brain Res Mol Brain Res* **141**: 113–120. [PMID:16143426]
170. Altomare C, *et al*. (2003) *J Physiol (Lond)* **549** (Pt 2): 347–359. [PMID:12702747]
171. BoSmith RE, *et al*. (1993) *Br J Pharmacol* **110**: 343–349. [PMID:7693281]
172. Bucchi A, *et al*. (2002) *J Gen Physiol* **120**: 1–13. [PMID:12084770]
173. DiFrancesco D. (1993) *Annu Rev Physiol* **55**: 455–472. [PMID:7682045]
174. Dryer SE, Henderson D. (1991) *Nature* **353**: 756–758. [PMID:1719422]
175. Fesenko EE, *et al*. (1985) *Nature* **313**: 310–313. [PMID:2578616]
176. Hofmann F, *et al*. (2005) *Pharmacol Rev* **57**: 455–462. [PMID:16382102]
177. Kaupp UB, *et al*. (1989) *Nature* **342**: 762–766. [PMID:2481236]
178. Nakamura T, Gold GH. (1987) *Nature* **325**: 442–444. [PMID:3027574]
179. Pape HC. (1996) *Annu Rev Physiol* **58**: 299–327. [PMID:8815797]
180. Peng C, *et al*. (2004) *Neuron* **42**: 401–410. [PMID:15134637]
181. Weitz D, *et al*. (2002) *Neuron* **36**: 881–889. [PMID:12467591]
182. Zheng J, *et al*. (2002) *Neuron* **36**: 891–896. [PMID:12467592]
183. Zheng J, Zagotta WN. (2004) *Neuron* **42**: 411–421. [PMID:15134638]
184. Zhong H, *et al*. (2002) *Nature* **420**: 193–198. [PMID:12432397]
185. Barker PM *et al*. (1990) *J Physiol (Lond)* **424**: 473–485. [PMID:2391659]
186. Boase NA *et al*. (2011) *Nat Commun* **2**: 287. [PMID:21505443]
187. Bonny O, Hummler E. (2000) *Kidney Int* **57**: 1313–1318. [PMID:10760060]
188. Canessa CM *et al*. (1993) *Nature* **361**: 467–470. [PMID:8381523]
189. Canessa CM *et al*. (1994) *Nature* **367**: 463–467. [PMID:8107805]
190. Debonneville C *et al*. (2001) *EMBO J* **20**: 7052–7059. [PMID:11742982]
191. Friedrich B *et al*. (2003) *Pflugers Arch* **445**: 693–696. [PMID:12632189]
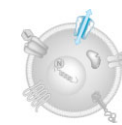
192. Garcia-Caballero A *et al*. (2009) *Proc Natl Acad Sci USA* **106**: 11412–11417. [PMID:19541605]
193. Gonzales EB *et al*. (2009) *Nature* **460**: 599–604. [PMID:19641589]
194. Guan Y *et al*. (2005) *Nat Med* **11**: 861–866. [PMID:16007095]
195. Hummler E *et al*. (1996) *Nat Genet* **12**: 325–328. [PMID:8589728]
196. Kellenberger S *et al*. (2003) *Mol Pharmacol* **64**: 848–856. [PMID:14500741]
197. Kitamura K, Tomita K. (2010) *Clin Exp Nephrol* **14**: 405–410. [PMID:20535627]
198. Kleyman TR *et al*. (2009) *J Biol Chem* **284**: 20447–20451. [PMID:19401469]
199. Loffing J, Korbmacher C. (2009) *Pflugers Arch* **458**: 111–135. [PMID:19277701]
200. Lu M *et al*. (2008) *J Biol Chem* **283**: 11981–11994. [PMID:18326490]
201. Ma HP *et al*. (2007) *Pflugers Arch* **455**: 169–180. [PMID:17605040]
202. Maekawa A *et al*. (2009) *J Hypertens* **27**: 181–189. [PMID:19145783]
203. Morris RG, Schafer JA. (2002) *J Gen Physiol* **120**: 71–85. [PMID:12084777]
204. Planès C, Caughey GH. (2007) *Curr Top Dev Biol* **78**: 23–46. [PMID:17338914]
205. Pochynyuk O *et al*. (2008) *J Biol Chem* **283**: 36599–36607. [PMID:18981175]
206. Richard K *et al*. (2004) *FEBS Lett* **576**: 339–342. [PMID:15498559]
207. Rossier BC, Stutts MJ. (2009) *Annu Rev Physiol* **71**: 361–379. [PMID:18928407]
208. Rotin D, Schild L. (2008) *Curr Drug Targets* **9**: 709–716. [PMID:18691017]
209. Sayegh R *et al*. (1999) *J Biol Chem* **274**: 12431–12437. [PMID:10212217]
210. Schild L. (2010) *Biochim Biophys Acta* **1802**: 1159–1165. [PMID:20600867]
211. Staub O *et al*. (1996) *EMBO J* **15**: 2371–2380. [PMID:8665844]
212. Yang LM *et al*. (2006) *J Biol Chem* **281**: 9859–9868. [PMID:16476738]
213. Goldstein SA *et al*. (2005) *Pharmacol Rev* **57**: 527–540. [PMID:16382106]
214. Gutman GA *et al*. (2005) *Pharmacol Rev* **57**: 473–508. [PMID:16382104]
215. Kubo Y *et al*. (2005) *Pharmacol Rev* **57**: 509–526. [PMID:16382105]
216. Wei AD *et al*. (2005) *Pharmacol Rev* **57**: 463–472. [PMID:16382103]
217. Gao L *et al*. (2000) *Biophys J* **79**: 828–840. [PMID:10920015]
218. Sutko JL, Airey JA. (1996) *Physiol Rev* **76**: 1027–1071. [PMID:8874493]
219. Yamaguchi N *et al*. (2003) *J Biol Chem* **278**: 23480–23486. [PMID:12707260]
220. Zhao M *et al*. (1999) *J Biol Chem* **274**: 25971–25974. [PMID:10473538]
221. Lee JH *et al*. (1999) *FEBS Lett* **445**: 231–236. [PMID:10094463]
222. Lu B *et al*. (2007) *Cell* **129**: 371–383. [PMID:17448995]
223. Lu B *et al*. (2009) *Nature* **457**: 741–744. [PMID:19092807]
224. Lu B *et al*. (2010) *Neuron* **68**: 488–499. [PMID:21040849]
225. Sinke AP *et al*. (2011) *Physiol Genomics* **43**: 265–270. [PMID:21177381]
226. Swayne LA *et al*. (2009) *EMBO Rep* **10**: 873–880. [PMID:19575010]
227. Wang H, Ren D. (2009) *Channels (Austin)* **3**: 161–163. [PMID:19535918]
228. Yu FH, Catterall WA. (2004) *Sci STKE* **2004**: re15. [PMID:15467096]
229. Abramowitz J, Birnbaumer L. (2009) *FASEB J* **23**: 297–328. [PMID:18940894]
230. Ambudkar IS, Ong HL. (2007) *Pflugers Arch* **455**: 187–200. [PMID:17486362]
231. Andersson DA *et al*. (2004) *J Neurosci* **24**: 5364–5369. [PMID:15190109]
232. Andersson DA *et al*. (2009) *Proc Natl Acad Sci USA* **106**: 8374–8379. [PMID:19416844]
233. Babich V *et al*. (2004) *J Biol Chem* **279**: 25582–25589. [PMID:15060061]
234. Bandell M *et al*. (2004) *Neuron* **41**: 849–857. [PMID:15046718]
235. Baraldi PG *et al*. (2010) *J Med Chem* **53**: 5085–5107. [PMID:20356305]
236. Barbet G *et al*. (2008) *Nat Immunol* **9**: 1148–56. [PMID:18758465]
237. Bates-Withers C *et al*. (2011) *Adv Exp Med Biol* **704**: 173–183. [PMID:21290295]
238. Bautista DM *et al*. (2006) *Cell* **124**: 1269–1282. [PMID:16564016]
239. Bautista DM *et al*. (2005) *Proc Natl Acad Sci USA* **102**: 12248–12252. [PMID:16103371]
240. Bautista DM *et al*. (2007) *Nature* **448**: 204–208. [PMID:17538622]
241. Beech DJ. (2011) *Acta Physiol (Oxf)* [Epub ahead of print]. [PMID:21624095]
242. Birnbaumer L. (2009) *Annu Rev Pharmacol Toxicol* **49**: 395–426. [PMID:19281310]
243. Cheng KT *et al*. (2011) *Adv Exp Med Biol* **704**: 435–449. [PMID:21290310]
244. Clapham DE *et al*. International Union of Pharmacology. (2003) *Pharmacol Rev* **55**: 591–596. [PMID:14657417]
245. Colburn RW *et al*. (2007) *Neuron* **54**: 379–386. [PMID:17481392]
246. Corey DP *et al*. (2004) *Nature* **432**: 723–730. [PMID:15483558]
247. Dai XQ *et al*. (2007) *Mol Pharmacol* **72**: 1576–1585. [PMID:17804601]
248. de Groot T *et al*. (2008) *Kidney Int* **74**: 1241–1246. [PMID:18596722]
249. Delmas P. (2005) *Pflugers Arch* **451**: 264–276. [PMID:15889307]
250. Delmas P *et al*. (2004) *FASEB J* **18**: 740–742. [PMID:14766803]
251. Delmas P *et al*. (2004) *Biochem Biophys Res Commun* **322**: 1374–1383. [PMID:15336986]
252. Dhaka A *et al*. (2007) *Neuron* **54**: 371–378. [PMID:17481391]
253. Dong XP *et al*. (2008) *Nature* **455**: 992–996. [PMID:18794901]
254. Du J *et al*. (2009) *Proc Natl Acad Sci USA* **106**: 7239–7244. [PMID:19372375]
255. Everaerts W *et al*. (2010) *Prog Biophys Mol Biol* **103**: 2–17. [PMID:19835908]
256. Everaerts W *et al*. (2010) *Proc Natl Acad Sci USA* **107**: 19084–19089. [PMID:20956320]
257. Fleig A, Penner R. (2004) *Trends Pharmacol Sci* **25**: 633–639. [PMID:15530641]
258. Freichel M *et al*. (2005) *J Physiol (Lond)* **567** (Pt 1): 59–66. [PMID:15975974]
259. García-Añoveros J, Nagata K. (2007) *Handb Exp Pharmacol* **179**: 347–362. [PMID:17217068]
260. Giamarchi A *et al*. (2006) *EMBO Rep* **7**: 787–793. [PMID:16880824]
261. Grimm C *et al*. (2007) *Proc Natl Acad Sci USA* **104**: 19583–19588. [PMID:18048323]
262. Guinamard R *et al*. (2011) *Adv Exp Med Biol* **704**: 147–171. [PMID:21290294]
263. Gunthorpe MJ, Chizh BA. (2009) *Drug Discov Today* **14**: 56–67. [PMID:19063991]
264. Hanaoka K *et al*. (2000) *Nature* **408**: 990–994. [PMID:11140688]
265. Harteneck C. (2005) *Naunyn Schmiedebergs Arch Pharmacol* **371**: 307–314. [PMID:15843919]
266. Harteneck C, Gollasch M. (2011) *Curr Pharm Biotechnol* **12**: 35–41. [PMID:20932261]
267. Hinman A *et al*. (2006) *Proc Natl Acad Sci USA* **103**: 19564–19568. [PMID:17164327]
268. Hofherr A, Köttgen M. (2011) *Adv Exp Med Biol* **704**: 287–313. [PMID:21290302]
269. Hu H *et al*. (2009) *Nat Chem Biol* **5**: 183–190. [PMID:19202543]
270. Hu HZ *et al*. (2004) *J Biol Chem* **279**: 35741–35748. [PMID:15194687]
271. Islam MS. (2011) *Adv Exp Med Biol* **704**: 811–830. [PMID:21290328]
272. Jordt SE *et al*. (2004) *Nature* **427**: 260–265. [PMID:14712238]
273. Juvin V *et al*. (2007) *Mol Pharmacol* **72**: 1258–1268. [PMID:17673572]
274. Karashima Y *et al*. (2009) *Proc Natl Acad Sci USA* **106**: 1273–1278. [PMID:19144922]
275. Kim HJ, Li Q *et al*. (2007) *J Biol Chem* **282**: 36138–36142. [PMID:17962195]
276. Kim HJ, Li Q *et al*. (2008) *EMBO J* **27**: 1197–1205. [PMID:18369318]
277. Kiselyov K, Patterson RL. (2009) *Front Biosci* **14**: 45–58. [PMID:19273053]
278. Kiselyov K *et al*. (2007) *Handb Exp Pharmacol* **179**: 559–574. [PMID:17217079]
279. Kiselyov K *et al*. (2007) *J Physiol (Lond)* **578** (Pt 3): 641–653. [PMID:17138610]
280. Kiyonaka S *et al*. (2009) *Proc Natl Acad Sci USA* **106**: 5400–5405. [PMID:19289841]
281. Klose C *et al*. (2011) *Br J Pharmacol* **162**: 1757–1769. [PMID:21198543]
282. Knowlton WM, McKemy DD. (2011) *Curr Pharm Biotechnol* **12**: 68–77. [PMID:20932257]
283. Koike C *et al*. (2010) *Cell Calcium* **48**: 95–101. [PMID:20846719]
284. Kwan KY *et al*. (2006) *Neuron* **50**: 277–289. [PMID:16630838]
285. Lambert S *et al*. (2011) *J Biol Chem* **286**: 12221–12233. [PMID:21278253]
286. Lashinger ES *et al*. (2008) *Am J Physiol Renal Physiol* **295**: F803–F810. [PMID:18562636]
287. Leuner K *et al*. (2010) *Mol Pharmacol* **77**: 368–377. [PMID:20008516]
288. Leuner K *et al*. (2007) *FASEB J* **21**: 4101–4111. [PMID:17666455]

289. Liman ER. (2007) *Handb Exp Pharmacol* **179**: 287–298. [PMID:17217064]
290. Link TM *et al.* (2010) *Nat Immunol* **11**: 232–239. [PMID:20118928]
291. Liu Y, Qin N. (2011) *Adv Exp Med Biol* **704**: 185–208. [PMID:21290296]
292. Macpherson LJ *et al.* (2007) *Nature* **445**: 541–545. [PMID:17237762]
293. Mahieu F *et al.* (2007) *J Biol Chem* **282**: 3325–3336. [PMID:17142461]
294. Majeed Y *et al.* (2010) *Br J Pharmacol* **161**: 430–441. [PMID:20735426]
295. Majeed Y *et al.* (2011) *Mol Pharmacol* **79**: 1023–1030. [PMID:21406603]
296. McNamara CR *et al.* (2007) *Proc Natl Acad Sci USA* **104**: 13525–13530. [PMID:17686976]
297. Mercado J *et al.* (2010) *J Neurosci* **30**: 13338–13347. [PMID:20926660]
298. Mihara H *et al.* (2010) *J Neurosci* **30**: 16536–16544. [PMID:21147993]
299. Miller M *et al.* (2011) *J Biol Chem* **286**: 33436–33446. [PMID:21795696]
300. Moran MM *et al.* (2004) *Curr Opin Neurobiol* **14**: 362–369. [PMID:15194117]
301. Mälkiä A *et al.* (2007) *J Physiol (Lond)* **581** (Pt 1): 155–174. [PMID:17317754]
302. Mälkiä A *et al.* (2011) *Curr Pharm Biotechnol* **12**: 54–67. [PMID:20932258]
303. Nagata K *et al.* (2005) *J Neurosci* **25**: 4052–4061. [PMID:15843607]
304. Nagata K *et al.* (2008) *Proc Natl Acad Sci USA* **105**: 353–358. [PMID:18162548]
305. Neeper MP *et al.* (2007) *J Biol Chem* **282**: 15894–15902. [PMID:17395593]
306. Niforatos W *et al.* (2007) *Mol Pharmacol* **71**: 1209–1216. [PMID:17314320]
307. Nilius B. (2007) *Biochim Biophys Acta* **1772**: 805–812. [PMID:17368864]
308. Nilius B, Owsianik G. (2010) *Pflugers Arch* **460**: 437–450. [PMID:20127491]
309. Nilius B *et al.* (2008) *EMBO J* **27**: 2809–2816. [PMID:18923420]
310. Nilius B *et al.* (2007) *Physiol Rev* **87**: 165–217. [PMID:17237345]
311. Nilius B *et al.* (2004) *Am J Physiol, Cell Physiol* **286**: C195–C205. [PMID:14707014]
312. Oancea E *et al.* (2009) *Sci Signal* **2**: ra21. [PMID:19436059]
313. Oberwinkler J, Phillipp SE. (2007) *Handb Exp Pharmacol* **179**: 253–267. [PMID:17217062]
314. Owsianik G *et al.* (2006) *Annu Rev Physiol* **68**: 685–717. [PMID:16460288]
315. Park U *et al.* (2011) *J Neurosci* **31**: 11425–11436. [PMID:21832173]
316. Patel A *et al.* (2010) *Pflugers Arch* **460**: 571–581. [PMID:20490539]
317. Pedersen SF *et al.* (2005) *Cell Calcium* **38**: 233–252. [PMID:16098585]
318. Penner R, Fleig A. (2007) *Handb Exp Pharmacol* **179**: 313–328. [PMID:17217066]
319. Petrus M *et al.* (2007) *Mol Pain* **3**: 40. [PMID:18086313]
320. Pingle SC *et al.* (2007) *Handb Exp Pharmacol* **179**: 155–171. [PMID:17217056]
321. Plant TD, Schaefer M. (2003) *Cell Calcium* **33**: 441–450. [PMID:12765689]
322. Potier M, Trebak M. (2008) *Pflugers Arch* **457**: 405–415. [PMID:18536932]
323. Puertollano R, Kiselyov K. (2009) *Am J Physiol Renal Physiol* **296**: F1245–F1254. [PMID:19158345]
324. Putney JW. (2005) *Pflugers Arch* **451**: 29–34. [PMID:16133266]
325. Qian F, Noben-Trauth K. (2005) *Pflugers Arch* **451**: 277–285. [PMID:15971078]
326. Qin N *et al.* (2008) *J Neurosci* **28**: 6231–6238. [PMID:18550765]
327. Rohacs T. (2009) *Cell Calcium* **45**: 554–565. [PMID:19376575]
328. Runnels LW. (2011) *Curr Pharm Biotechnol* **12**: 42–53. [PMID:20932259]
329. Salido GM *et al.* (2009) *Biochim Biophys Acta* **1793**: 223–230. [PMID:19061922]
330. Sawada Y *et al.* (2007) *Brain Res* **1160**: 39–46. [PMID:17588549]
331. Schumacher MA, Eilers H. (2010) *Front Biosci* **15**: 872–882. [PMID:20515731]
332. Shimizu T *et al.* (2009) *Pflugers Arch* **457**: 795–807. [PMID:18663466]
333. Starowicz K *et al.* (2007) *Pharmacol Ther* **114**: 13–33. [PMID:17349697]
334. Story GM *et al.* (2003) *Cell* **112**: 819–829. [PMID:12654248]
335. Szallasi A *et al.* (2007) *Nat Rev Drug Discov* **6**: 357–372. [PMID:17464295]
336. Thorneloe KS *et al.* (2008) *J Pharmacol Exp Ther* **326**: 432–442. [PMID:18499743]
337. Trebak M *et al.* (2007) *Handb Exp Pharmacol* **179**: 593–614. [PMID:17217081]
338. Ullrich ND *et al.* (2005) *Cell Calcium* **37**: 267–278. [PMID:15670874]
339. Vennekens R, Nilius B. (2007) *Handb Exp Pharmacol* **179**: 269–285. [PMID:17217063]
340. Vennekens R *et al.* (2008) *Curr Pharm Des* **14**: 18–31. [PMID:18220815]
341. Vincent F *et al.* (2009) *Biochem Biophys Res Commun* **389**: 490–494. [PMID:19737537]
342. Voets T *et al.* (2004) *Nature* **430**: 748–754. [PMID:15306801]
343. Voets T, Nilius B. (2007) *J Physiol (Lond)* **582** (Pt 3): 939–944. [PMID:17395625]
344. Voets T *et al.* (2007) *Handb Exp Pharmacol* **179**: 329–344. [PMID:17217067]
345. Vriens J *et al.* (2009) *Mol Pharmacol* **75**: 1262–1279. [PMID:19297520]
346. Vriens J *et al.* (2011) *Neuron* **70**: 482–494. [PMID:21555074]
347. Wagner TF *et al.* (2008) *Nat Cell Biol* **10**: 1421–1430. [PMID:18978782]
348. Wissenbach U, Niemeyer BA. (2007) *Handb Exp Pharmacol* **179**: 221–334. [PMID:17217060]
349. Witzgall R. (2007) *Handb Exp Pharmacol* **179**: 363–375. [PMID:17217069]
350. Wong CO *et al.* (2010) *Br J Pharmacol* **159**: 1486–1496. [PMID:20233211]
351. Wu LJ *et al.* (2010) *Pharmacol Rev* **62**: 381–404. [PMID:20716668]
352. Xu H *et al.* (2007) *Proc Natl Acad Sci USA* **104**: 18321–18326. [PMID:17989217]
353. Yamamoto S *et al.* (2010) *Prog Biophys Mol Biol* **103**: 18–27. [PMID:20553742]
354. Yuan JP *et al.* (2009) *Channels (Austin)* **3**: 221–225. [PMID:19574740]
355. Zeevi DA *et al.* (2007) *Biochim Biophys Acta* **1772**: 851–858. [PMID:17306511]
356. Zholos A. (2010) *Br J Pharmacol* **159**: 1559–1571. [PMID:20233227]
357. Zurborg S *et al.* (2007) *Nat Neurosci* **10**: 277–279. [PMID:17259981]
358. Catterall WA *et al.* (2005) *Pharmacol Rev* **57**: 411–425. [PMID:16382099]
359. Ertel EA *et al.* (2000) *Neuron* **25**: 533–535. [PMID:10774722]
360. Williams JA *et al.* (2008) *Expert Opin Pharmacother* **9**: 1575–1583. [PMID:18518786]
361. Capasso M *et al.* (2011) *Trends Cell Biol* **21**: 20–28. [PMID:20961760]
362. DeCoursey TE. (2008) *Cell Mol Life Sci* **65**: 2554–2573. [PMID:18463791]
363. DeCoursey TE. (2008) *J Physiol (Lond)* **586** (Pt 22): 5305–5324. [PMID:18801839]
364. Gonzalez C *et al.* (2010) *Nat Struct Mol Biol* **17**: 51–56. [PMID:20023639]
365. Koch HP *et al.* (2008) *Proc Natl Acad Sci USA* **105**: 9111–9116. [PMID:18583477]
366. Lee SY *et al.* (2008) *Proc Natl Acad Sci USA* **105**: 7692–7695. [PMID:18509058]
367. Li SJ *et al.* (2010) *J Biol Chem* **285**: 12047–12054. [PMID:20147290]
368. Musset B *et al.* (2010) *J Biol Chem* **285**: 5117–5121. [PMID:20037153]
369. Musset B *et al.* (2010) *J Physiol (Lond)* **588** (Pt 9): 1435–1449. [PMID:20231140]
370. Petheo GL *et al.* (2010) *PLoS ONE* **5**: e14081. [PMID:21124855]
371. Ramsey IS *et al.* (2010) *Nat Struct Mol Biol* **17**: 869–875. [PMID:20543828]
372. Ramsey IS *et al.* (2006) *Nature* **440**: 1213–1216. [PMID:16554753]
373. Ramsey IS *et al.* (2009) *Proc Natl Acad Sci USA* **106**: 7642–7647. [PMID:19372380]
374. Sasaki M *et al.* (2006) *Science* **312**: 589–592. [PMID:16556803]
375. Tombola F *et al.* (2008) *Neuron* **58**: 546–556. [PMID:18498736]
376. Tombola F *et al.* (2010) *Nat Struct Mol Biol* **17**: 44–50. [PMID:20023640]
377. Wood ML *et al.* (2011) *Biochim Biophys Acta* [Epub ahead of print]. [PMID:21843503]
378. Catterall WA *et al.* (2005) *Pharmacol Rev* **57**: 397–409. [PMID:16382098]
379. Goldin AL *et al.* (2000) *Neuron* **28**: 365–368. [PMID:11144347]
380. Isom LL. (2001) *Neuroscientist* **7**: 42–54. [PMID:11486343]
381. Payandeh J *et al.* (2011) *Nature* **475**: 353–358. [PMID:21743477]