

THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Other ion channels

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Abstract

The Concise Guide to PHARMACOLOGY 2017/18 provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), 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. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at <http://onlinelibrary.wiley.com/doi/10.1111/bph.13881/full>. Other ion channels are one of the eight major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, ligand-gated ion channels, voltage-gated ion channels, nuclear hormone receptors, catalytic receptors, enzymes and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2017, and supersedes data presented in the 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature Committee of the Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

Conflict of interest

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

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Family structure

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Other ion channels S195

Aquaporins

Other ion channels → Aquaporins

Overview: Aquaporins and aquaglyceroporins are membrane channels that allow the permeation of water and certain other small solutes across the cell membrane. Since the isolation and cloning of the first aquaporin (AQP1) [77], 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](#) [41]. 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 [15]. Functional AQPs exist as tetramers but, unusually, each subunit contains a separate pore, so each channel has four pores.

Nomenclature	AQP0	AQP1	AQP2	AQP3	AQP4	AQP5
HGNC, UniProt	<i>MIP</i> , P30301	<i>AQP1</i> , P29972	<i>AQP2</i> , P41181	<i>AQP3</i> , Q92482	<i>AQP4</i> , P55087	<i>AQP5</i> , P55064
Permeability	water (low)	water (high)	water (high)	water (high), glycerol	water (high)	water (high)
Endogenous activators	–	cyclic GMP	–	–	–	–
Inhibitors	Hg ²⁺	Ag ⁺ , Hg ²⁺ , tetraethylammonium	Hg ²⁺	Hg ²⁺ (also inhibited by acid pH)	–	Hg ²⁺
Comments	–	–	–	AQP3 is also inhibited by acid pH	AQP4 is inhibited by PKC activation	–

Nomenclature	AQP6	AQP7	AQP8	AQP9	AQP10
HGNC, UniProt	<i>AQP6</i> , Q13520	<i>AQP7</i> , O14520	<i>AQP8</i> , O94778	<i>AQP9</i> , O43315	<i>AQP10</i> , Q96PS8
Permeability	water (low), anions	water (high), glycerol	water (high)	water (low), glycerol	water (low), glycerol
Inhibitors	Hg ²⁺	Hg ²⁺	Hg ²⁺	Hg ²⁺ , phloretin	Hg ²⁺
Comments	AQP6 is an intracellular channel permeable to anions as well as water [106]	–	–	–	–

Further reading on Aquaporins

Babey M *et al.* (2011) Familial forms of diabetes insipidus: clinical and molecular characteristics. *Nat Rev Endocrinol* **7**: 701-14 [PMID:21727914]
 Beitz E *et al.* (2015) Challenges and achievements in the therapeutic modulation of aquaporin functionality. *Pharmacol Ther* **155**: 22-35 [PMID:26277280]
 Bockenhauer D *et al.* (2015) Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. *Nat Rev Nephrol* **11**: 576-88 [PMID:26077742]

Papadopoulos MC *et al.* (2013) Aquaporin water channels in the nervous system. *Nat Rev Neurosci* **14**: 265-77 [PMID:23481483]
 Verkman AS *et al.* (2014) Aquaporins: important but elusive drug targets. *Nat Rev Drug Discov* **13**: 259-77 [PMID:24625825]

Chloride channels

Other ion channels → Chloride channels

Overview: Chloride channels are a functionally and structurally diverse group of anion selective channels involved in processes including the regulation of the excitability of neurones, skeletal, cardiac and smooth muscle, cell volume regulation, transepithelial salt transport, the acidification of internal and extracellular compartments, the cell cycle and apoptosis (reviewed in [22]).

Excluding the transmittergated GABA_A and glycine receptors (see separate tables), well characterised chloride channels can be classified as certain members of the voltage-sensitive ClC subfamily, calcium-activated channels, high (maxi) conductance channels, the cystic fibrosis transmembrane conductance regulator (CFTR) and volume regulated channels [101]. No official recommenda-

tion 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 [26].

ClC family

Other ion channels → Chloride channels → ClC family

Overview: The mammalian ClC family (reviewed in [2, 16, 22, 24, 40]) 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 [27]. 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 [34, 48, 62, 73, 87]; reviewed in [2, 79]). It has recently been reported that the activity of ClC-5 as a Cl⁻/H⁺ exchanger is important for renal endocytosis [64]. Alternative splicing increases the structural diversity within the ClC family. The crystal structure of two bacterial ClC proteins has been described [25] and a eukaryotic ClC transporter (CmClC) has recently been described at 3.5 Å resolution [30]. Each ClC subunit, with a complex topology of 18 intramembrane segments, contributes a single pore to a dimeric 'double-barrelled' ClC chan-

nel that contains two independently gated pores, confirming the predictions of previous functional and structural investigations (reviewed in [16, 24, 40, 79]). 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 [1, 30]. 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 [81].

Nomenclature	ClC-1	ClC-2
HGNC, UniProt	<i>CLCN1</i> , P35523	<i>CLCN2</i> , P51788
Endogenous activators	–	arachidonic acid
Activators	–	lubiprostone, omeprazole
Channel blockers	9-anthroic acid, S(-)CPB, S(-)CPP, Cd ²⁺ , Zn ²⁺ , fenofibric acid, niflumic acid	GaTx2 (pK _d 10.8) [voltage dependent -100mV], Cd ²⁺ , NPPB, Zn ²⁺ , diphenylamine-2-carboxylic acid
Functional Characteristics	γ = 1–1.5 pS; voltage-activated (depolarization) (by fast gating of single protopores and a slower common gate allowing both pores to open simultaneously); inwardly rectifying; incomplete deactivation upon repolarization, ATP binding to cytoplasmic cystathionine β-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

(continued)				
Nomenclature	CIC-1		CIC-2	
Comments	CIC-1 is constitutively active		CIC-2 is also activated by amidation	
Nomenclature	CIC-Ka	CIC-Kb	CIC-3	CIC-4
HGNC, UniProt	CLCNKA , P51800	CLCNKB , P51801	CLCN3 , P51790	CLCN4 , P51793
Activators	niflumic acid (pEC ₅₀ 3–5)	niflumic acid (pEC ₅₀ 3–5)	–	–
Channel blockers	3-phenyl-CPP, DIDS, niflumic acid	3-phenyl-CPP, DIDS	phloretin (pIC ₅₀ 4.5)	Zn ²⁺ (pIC ₅₀ 4.3) [68], Cd ²⁺ (pIC ₅₀ 4.2) [68]
Functional Characteristics	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⁺	Cl ⁻ /H ⁺ antiporter [58]; pronounced outward rectification; slow activation, fast deactivation; activity enhanced by CaM kinase II; inhibited by intracellular Ins(3,4,5,6)P ₄ and extracellular acidosis	Cl ⁻ /H ⁺ antiporter (2Cl ⁻ :1H ⁺) [3, 73, 87]; extreme outward rectification; voltage-dependent gating with midpoint of activation at +73 mV [67]; rapid activation and deactivation; inhibited by extracellular acidosis; non-hydrolytic nucleotide binding required for full activity
Comments	CIC-Ka is constitutively active (when co-expressed with barttin), and can be blocked by benzofuran derivatives	CIC-Kb is constitutively active (when co-expressed with barttin), and can be blocked by benzofuran derivatives	insensitive to the channel blockers DIDS, NPPB and tamoxifen (10 μM)	–
Nomenclature	CIC-5	CIC-6	CIC-7	
HGNC, UniProt	CLCN5 , P51795	CLCN6 , P51797	CLCN7 , P51798	
Channel blockers	–	DIDS (pIC ₅₀ 3)	DIDS (pIC ₅₀ 4.4) [90], NS5818 (pIC ₅₀ 4.3) [90], NPPB (pIC ₅₀ 3.8) [90]	
Functional Characteristics	Cl ⁻ /H ⁺ antiporter (2Cl ⁻ :1H ⁺) [73, 87, 94, 109]; 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 CIC-5	Cl ⁻ /H ⁺ antiporter (2Cl ⁻ :1H ⁺) [62]; outward rectification, rapid activation and deactivation	Cl ⁻ /H ⁺ antiporter (2Cl ⁻ :1H ⁺) [34, 48, 90]; strong outward rectification; voltage-dependent gating with a threshold more positive than $\bar{v} + 20$ mV; very slow activation and deactivation	

(continued)			
Nomenclature	CIC-5	CIC-6	CIC-7
Comments	insensitive to the channel blockers DIDS (1 mM), diphenylamine-2-carboxylic acid (1 mM), 9-anthroic acid (2 mM), NPPB (0.5 mM) and niflumic acid (1 mM)	–	active when co-expressed with Ostm1

Comments: CIC channels display the permeability sequence $\text{Cl}^- > \text{Br}^- > \text{I}^-$ (at physiological pH). CIC-1 has significant opening probability at resting membrane potential, accounting for 75% of the membrane conductance at rest in skeletal muscle, and is important for stabilization of the membrane potential. **S(-)CPP**, **9-anthroic acid** and **niflumic acid** act intracellularly and exhibit a strongly voltage-dependent block with strong inhibition at negative voltages and relief of block at depolarized potentials ([49] and reviewed in [78]). Inhibition of CIC-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 [98]. Although CIC-2 can be activated by cell swelling, it does not correspond to the VRAC channel (see below). Alternative potential physiological functions for CIC-2 are reviewed in

[76]. Functional expression of human CIC-Ka and CIC-Kb requires the presence of barttin [27, 88] reviewed in [29]. The properties of CIC-Ka/barttin and CIC-Kb/barttin tabulated are those observed in mammalian expression systems: in oocytes the channels display time- and voltage-dependent gating. The rodent homologue (CIC-K1) of CIC-Ka demonstrates limited expression as a homomer, but its function is enhanced by barttin which increases both channel opening probability in the physiological range of potentials [27, 32, 88] reviewed in [29]. CIC-Ka is approximately 5 to 6-fold more sensitive to block by **3-phenyl-CPP** and **DIDS** than CIC-Kb, while newly synthesized benzofuran derivatives showed the same blocking affinity ($<10 \mu\text{M}$) on both CLC-K isoforms [50]. The biophysical and pharmacological properties of CIC-3, and the relationship of the protein to the endogenous volume-regulated an-

ion channel(s) VRAC [4, 36] are controversial and further complicated by the possibility that CIC-3 may function as both a Cl^-/H^+ exchanger and an ion channel [4, 73, 104]. The functional properties tabulated are those most consistent with the close structural relationship between CIC-3, CIC-4 and CIC-5. Activation of heterologously expressed CIC-3 by cell swelling in response to hypotonic solutions is disputed, as are many other aspects of its regulation. Dependent upon the predominant extracellular anion (e.g. SCN^- versus Cl^-), CIC-4 can operate in two transport modes: a slip-page mode in which behaves as an ion channel and an exchanger mode in which unitary transport rate is 10-fold lower [3]. Similar findings have been made for CIC-5 [108]. CIC-7 associates with a β subunit, Ostm1, which increases the stability of the former [45] and is essential for its function [48].

CFTR

Other ion channels → Chloride channels → 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 [18]). Channels carrying the ΔF508 mutation that do traffic to the plasma membrane demonstrate gating defects. Thus, pharmacological restoration of 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 [18]. 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 sulpho-

nylurea sensitivity of the renal outer medullary potassium channel (ROMK2), (reviewed in [63]). CFTR also regulates TRPV4, which provides the Ca^{2+} signal for regulatory volume decrease in airway epithelia [6]. 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 [42].

Nomenclature	CFTR
HGNC, UniProt	CFTR, P13569
Activators	felodipine (Potentiation) (pK _i 8.4) [71], CBIQ (Potentiation), NS004 (Potentiation), UCCF-029 (Potentiation), UCCF-339 (Potentiation), UCCF-853 (Potentiation), apigenin (Potentiation), capsaicin (Potentiation), genistein (Potentiation), ivacaftor (Potentiation), nimodipine (Potentiation), phenylglycine-01 (Potentiation), sulfonamide-01 (Potentiation)
Selective inhibitors	crofelemer (pIC ₅₀ 5.2) [99]
Channel blockers	glibenclamide (pK _i 4.7) [91], intracellular CFTR _{inh} -172 (intracellular application prolongs mean closed time), GaTx1, extracellular GlyH-101
Functional Characteristics	$\gamma = 6\text{--}10$ pS; permeability sequence = Br ⁻ ≥ 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
Comments	UCCF-339, UCCF-029, apigenin and genistein are examples of flavones. UCCF-853 and NS004 are examples of benzimidazolones. CBIQ is an example of a benzoquinoline. felodipine and nimodipine are examples of 1,4-dihydropyridines. phenylglycine-01 is an example of a phenylglycine. sulfonamide-01 is an example of a sulfonamide. Malonic acid hydrazide conjugates are also CFTR channel blockers (see Verkman and Galiotta, 2009 [101])

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 [93]). 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 [101] for details and structures of Corr-3a and Corr-4a). Inhibition of CFTR by intracellular applica-

tion of the peptide GaTx1, from *Leiurus quinquestriatus herbareus* venom, occurs preferentially for the closed state of the channel [33]. 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 disso-

ciation of the dimer and channel closing, and the initiation of a new gating cycle [5, 59]. Phosphorylation by PKA at sites within a cytoplasmic regulatory (R) domain facilitates the interaction of the two NBD domains. PKC (and PKGII within intestinal epithelial cells via guanylinstimulated cyclic GMP formation) positively regulate CFTR activity.

Calcium activated chloride channel

Other ion channels → Chloride channels → 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 [37]. The molecular nature of CaCC has been uncertain with both *CLCA*, *TWEETY* and *BEST* genes having been considered as likely candidates [22, 38, 51]. 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 [70]. 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 [38] and form chloride channels that are activated by

physiological concentrations of Ca²⁺, but whether such activation is direct is not known [38]. 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.* [22]. 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 [21, 43]. TMEM16A (anoctamin 1; Ano 1) produces Ca²⁺-activated Cl⁻ currents with kinetics similar to native CaCC currents recorded from different cell types [14, 82, 89, 105]. Knockdown of TMEM16A

greatly reduces currents mediated by calcium-activated chloride channels in submandibular gland cells [105] and smooth muscle cells from pulmonary artery [55]. In TMEM16A^(-/-) mice secretion of Ca²⁺-dependent Cl⁻ secretion by several epithelia is reduced [69, 82]. Alternative splicing regulates the voltage- and Ca²⁺-dependence of TMEM16A and such processing may be tissue-specific manner and thus contribute to functional diversity [31]. There are also reports that TMEM16B (anoctamin 2; Ano 2) supports CaCC activity (*e.g.*[74]) and in TMEM16B^(-/-) mice Ca-activated Cl⁻ currents in the main olfactory epithelium (MOE) and in the vomeronasal organ are virtually absent [11].

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Calcium activated chloride channel S200

Nomenclature	CaCC
HGNC, UniProt	ANO1 , Q5XXA6
Endogenous activators	intracellular Ca^{2+}
Selective inhibitors	crofelemer (pIC_{50} 5.2) [99]
Endogenous channel blockers	Ins(3,4,5,6)P_4
Channel blockers	9-anthroic acid , DCDPC , DIDS , NPPB , SITS , flufenamic acid , fluoxetine , mibefradil , niflumic acid , tannic acid
Functional Characteristics	$\gamma = 0.5\text{--}5$ pS; permeability sequence, $\text{SCN}^- > \text{NO}_3^- > \text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$; relative permeability of $\text{SCN}^-:\text{Cl}^- \sim 8$, $\text{I}^-:\text{Cl}^- \sim 3$, aspartate: $\text{Cl}^- \sim 0.15$, outward rectification (decreased by increasing $[\text{Ca}^{2+}]_i$); sensitivity to activation by $[\text{Ca}^{2+}]_i$; decreased at hyperpolarized potentials; slow activation at positive potentials (accelerated by increasing $[\text{Ca}^{2+}]_i$); rapid deactivation at negative potentials, deactivation kinetics modulated by anions binding to an external site; modulated by redox status

Comments: Blockade of $\text{I}_{\text{Cl}(\text{Ca})}$ by [niflumic acid](#), [DIDS](#) and [9-anthroic acid](#) is voltage-dependent whereas block by [NPPB](#) is voltage-independent [37]. Extracellular [niflumic acid](#); [DCDPC](#) and [9-anthroic acid](#) (but not [DIDS](#)) exert a complex effect upon $\text{I}_{\text{Cl}(\text{Ca})}$ in vascular smooth muscle, enhancing and inhibiting inwardly and outwardly directed currents in a manner dependent upon $[\text{Ca}^{2+}]_i$ (see [46] for summary). Considerable crossover in pharmacology with large conductance Ca^{2+} -activated K^+ chan-

nels also exists (see [35] for overview). Two novel compounds, $\text{CaCC}_{\text{inh-A01}}$ and $\text{CaCC}_{\text{inh-B01}}$ have recently been identified as blockers of calcium-activated chloride channels in T84 human intestinal epithelial cells [19] 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 [TMEM116A](#) is not the predominant CaCC in such cells [61]. CaMKII modulates CaCC in a tissue

dependent manner (reviewed by [37, 46]). CaMKII inhibitors block activation of $\text{I}_{\text{Cl}(\text{Ca})}$ 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 $\text{I}_{\text{Cl}(\text{Ca})}$. Intracellular [Ins\(3,4,5,6\) \$\text{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 [46] for summary).

Maxi chloride channel

Other ion channels → [Chloride channels](#) → [Maxi chloride channel](#)

Overview: Maxi Cl^- channels are high conductance, anion selective, channels initially characterised in skeletal muscle and subsequently found in many cell types including neurones, glia, cardiac muscle, lymphocytes, secreting and absorbing epithelia, macula densa cells of the kidney and human placenta syncytiotrophoblasts [84]. 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 [23, 83]. 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 [9]. A family of human high conductance Cl^- channels (TTYH1-3) that resemble Maxi Cl^- channels has been cloned [95], but alternatively, Maxi Cl^- channels have also been suggested to correspond to the voltage-dependent anion channel, VDAC, expressed at the plasma membrane [7, 65].

Nomenclature	Maxi Cl ⁻
Activators	cytosolic GTP γ S, extracellular chlorpromazine, extracellular tamoxifen, extracellular toremifene, extracellular triflupromazine
Endogenous channel blockers	intracellular arachidonic acid
Channel blockers	DIDS (pIC ₅₀ 4.4) [90], extracellular Zn ²⁺ (pIC ₅₀ 4.3) [68], NPPB (pIC ₅₀ 3.8) [90], extracellular Gd ³⁺ , SITS, diphenylamine-2-carboxylic acid
Functional Characteristics	γ = 280–430 pS (main state); permeability sequence, I > Br > Cl > F > gluconate (P _{Cl} /P _{Cl} = ~1.5); ATP is a voltage dependent permeant blocker of single channel activity (P _{ATP} /P _{Cl} = 0.08–0.1); channel activity increased by patch-excision; channel opening probability (at steady-state) maximal within approximately \pm 20 mV of 0 mV, opening probability decreased at more negative and (commonly) positive potentials yielding a bell-shaped curve; channel conductance and opening probability regulated by annexin 6
Comments	Maxi Cl ⁻ is also activated by G protein-coupled receptors and cell swelling. tamoxifen and toremifene are examples of triphenylethylene anti-oestrogens

Comments: Differing ionic conditions may contribute to variable estimates of γ reported in the literature. Inhibition by arachidonic acid (and cis-unsaturated fatty acids) is voltage-independent, occurs at an intracellular site, and involves both channel shut down (K_d = 4–5 μ M) and a reduction of γ (K_d = 13–14 μ M). Blockade of channel activity by SITS, DIDS,

Gd³⁺ and arachidonic acid is paralleled by decreased swelling-induced release of ATP [23, 83]. Channel activation by anti-oestrogens in whole cell recordings requires the presence of intracellular nucleotides and is prevented by pre-treatment with 17 β -estradiol, bucladesine, or intracellular dialysis with GDP β S [20]. Activation by tamoxifen is suppressed by low concentra-

tions of okadaic acid, suggesting that a dephosphorylation event by protein phosphatase PP2A occurs in the activation pathway [20]. In contrast, 17 β -estradiol and tamoxifen appear to directly inhibit the maxi Cl⁻ channel of human placenta reconstituted into giant liposomes and recorded in excised patches [80].

Volume regulated chloride channels

Other ion channels → Chloride channels → 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 [10, 60, 63, 66]). 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 CIC-3 expression products (see above) several former VRAC candidates including MDRI (ABCB1 P-glycoprotein), Icln, Band 3 anion exchanger and phospholemman are also no longer considered likely to fulfil this function (see reviews [63, 86]).

Nomenclature	VRAC
Activators	GTP γ S
Endogenous channel blockers	intracellular Mg ²⁺ , arachidonic acid
Channel blockers	1,9-dideoxyforskolin, 9-anthroic acid, DCPIB, DIDS, IAA-94, NPPB, NS3728, carbenoxolone, clomiphene, diBA-(5)-C4, gossypol, mefloquine, mibefradil, nafoxidine, nordihydroguaiaretic acid, quinidine, quinine, tamoxifen
Functional Characteristics	γ = 10–20 pS (negative potentials), 50–90 pS (positive potentials); permeability sequence SCN > I > NO ₃ > Br ⁻ > Cl ⁻ > F ⁻ > gluconate; outward rectification due to voltage dependence of γ ; inactivates at positive potentials in many, but not all, cell types; time dependent inactivation at positive potentials; intracellular ionic strength modulates sensitivity to cell swelling and rate of channel activation; rate of swelling-induced activation is modulated by intracellular ATP concentration; ATP dependence is independent of hydrolysis and modulated by rate of cell swelling; inhibited by increased intracellular free Mg ²⁺ concentration; swelling induced activation of several intracellular signalling cascades may be permissive of, but not essential to, the activation of VRAC including: the Rho-Rho kinase-MLCK; Ras-Raf-MEK-ERK; PIK3-NOX-H ₂ O ₂ and Src-PLC γ -Ca ²⁺ pathways; regulation by PKC α required for optimal activity; cholesterol depletion enhances activity; activated by direct stretch of β 1-integrin
Comments	VRAC is also activated by cell swelling and low intracellular ionic strength. VRAC is also blocked by chromones, extracellular nucleotides and nucleoside analogues

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

Comments on Chloride channels: Other chloride channels

In addition to some intracellular chloride channels that are not considered here, plasma membrane channels other than those listed have been functionally described. Many cells and tissues contain outwardly rectifying chloride channels (ORCC) that

may correspond to VRAC active under isotonic conditions. A cyclic AMP-activated Cl⁻ channel that does not correspond to CFTR has been described in intestinal Paneth cells [100]. A Cl channel activated by cyclic GMP with a dependence on raised intracellular Ca²⁺ has been recorded in various vascular smooth

muscle cells types, which has a pharmacology and biophysical characteristics very different from the 'conventional' CaCC [56, 75]. It has been proposed that bestrophin-3 (BEST3, Q8N1M1) is an essential component of the cyclic GMP-activated channel [57]. A proton-activated, outwardly rectifying anion channel has also been described [44].

Further reading on Chloride channels

Adkins GB *et al.* (2015) Potential role of cardiac chloride channels and transporters as novel therapeutic targets. *Pharmacol Ther* **145**: 67-75 [PMID:25160469]
Huang F *et al.* (2012) International Union of Basic and Clinical Pharmacology. LXXXV: calcium-activated chloride channels. *Pharmacol Rev* **64**: 1-15 [PMID:22090471]
Kamaleddin MA. (2017) Molecular, biophysical, and pharmacological properties of calcium-activated chloride channels. *J Cell Physiol* [PMID:28121009]
Kunzelmann K. (2015) TMEM16, LRRC8A, bestrophin: chloride channels controlled by Ca(2+) and cell volume. *Trends Biochem Sci* **40**: 535-43 [PMID:26254230]
Pedersen SF *et al.* (2016) Biophysics and Physiology of the Volume-Regulated Anion Channel (VRAC)/Volume-Sensitive Outwardly Rectifying Anion Channel (VSOR). *Pflügers Arch* **468**: 371-83 [PMID:26739710]

Peretti M *et al.* (2015) Chloride channels in cancer: Focus on chloride intracellular channel 1 and 4 (CLIC1 AND CLIC4) proteins in tumor development and as novel therapeutic targets. *Biochim Biophys Acta* **1848**: 2523-31 [PMID:25546839]
Poroca DR *et al.* (2017) ClC Channels and Transporters: Structure, Physiological Functions, and Implications in Human Chloride Channelopathies. *Front Pharmacol* **8**: 151 [PMID:28386229]
Sabirov RZ *et al.* (2016) The properties, functions, and pathophysiology of maxi-anion channels. *Pflügers Arch* **468**: 405-20 [PMID:26733413]
Zegarra-Moran O *et al.* (2017) CFTR pharmacology. *Cell Mol Life Sci* **74**: 117-128 [PMID:27704174]

Connexins and Pannexins

Other ion channels → [Connexins and Pannexins](#)

Overview: Gap junctions are essential for many physiological processes including cardiac and smooth muscle contraction, regulation of neuronal excitability and epithelial electrolyte transport [13, 17, 28]. 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 IP₃) as well as cations and anions. 21 connexin genes and 3 pannexin genes which are structurally related to the invertebrate innexin genes) code for gap junction proteins in humans. Each connexin gap junction

comprises 2 hemichannels or 'connexons' which are themselves formed from 6 connexin molecules. The various connexins have been observed to combine into both homomeric and heteromeric combinations, each of which may exhibit different functional properties. It is also suggested that individual hemichannels formed by a number of different connexins might be functional in at least some cells [39]. 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 [97]. 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 [102]. Like the connexins, at least some of the pannexins can form hemichannels [13, 72].

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

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

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

Nomenclature	Px1	Px2	Px3
HGNC, UniProt	PANX1, Q96RD7	PANX2, Q96RD6	PANX3, Q96QZ0
Inhibitors	carbenoxolone, flufenamic acid (little block by flufenamic acid)		
Comments	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](#) [85]. At least some pannexin hemichannels are more sensitive to [carbenoxolone](#) than connexins but much less sensitive to [flufenamic acid](#) [12]. 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, [8]).

Further reading on Connexins and Pannexins

- Decrock E *et al.* (2015) Connexin and pannexin signaling pathways, an architectural blueprint for CNS physiology and pathology? *Cell Mol Life Sci* **72**: 2823-51 [PMID:26118660]
- Esseltine JL *et al.* (2016) Next-Generation Connexin and Pannexin Cell Biology. *Trends Cell Biol* **26**: 944-955 [PMID:27339936]
- Freund-Michel V *et al.* (2016) Expression and role of connexin-based gap junctions in pulmonary inflammatory diseases. *Pharmacol Ther* **164**: 105-19 [PMID:27126473]
- Saez JC *et al.* (2015) Regulation of pannexin and connexin channels and their functional role in skeletal muscles. *Cell Mol Life Sci* **72**: 2929-35 [PMID:26084874]
- Thompson RJ (2015) Pannexin channels and ischaemia. *J Physiol* **593**: 3463-70 [PMID:25384783]

Sodium leak channel, non-selective

Other ion channels → [Sodium leak channel, non-selective](#)

Overview: The sodium leak channel, non selective (**NC-IUPHAR tentatively recommends the nomenclature $Na_{vi}2.1$, W.A. Catterall, personal communication**) is structurally a member of the family of voltage-gated sodium channel family ($Na_v1.1$ – $Na_v1.9$) [47, 107]. 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 μ M), has been proposed to mediate the tetrodotoxin-resistant and voltage-insensitive Na^+ leak

current (I_L -Na) observed in many types of neurone [52]. However, whether $Na_{vi}2.1$ is constitutively active has been challenged [96]. $Na_{vi}2.1$ 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 [47, 52].

Nomenclature	$Na_{vi}2.1$
HGNC, UniProt	NALCN , Q8IZF0
Activators	Constitutively active [52], or activated downstream of Src family tyrosine kinases (SFKs) [53, 96]; positively modulated by decreased extracellular Ca^{2+} concentration [54]
Channel blockers	Gd^{3+} (pIC ₅₀ 5.6), Cd^{2+} (pIC ₅₀ 3.8), Co^{2+} (pIC ₅₀ 3.6), verapamil (pIC ₅₀ 3.4)
Functional Characteristics	$\gamma = 27$ 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 [53, 96]. Pharmacological and molecular biological evidence indicates such modulation to occur through 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 [96] and peptide receptors [53], in the latter instance in association with the protein UNC-80, which recruits Src to the channel complex [53, 103]. 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 recep-

tor and UNC80 which links $Na_{vi}2.1$ to the protein UNC79 in the same complex [54]. $Na_{vi}2.1$ null mutant mice have severe disturbances in respiratory rhythm and die within 24 hours of birth [52]. $Na_{vi}2.1$ heterozygous knockout mice display increased serum sodium concentrations in comparison to wildtype littermates and a role for the channel in osmoregulation has been postulated [92].

Further reading on Sodium leak channel

Cochet-Bissuel M *et al.* (2014) The sodium leak channel, NALCN, in health and disease. *Front Cell Neurosci* **8**: 132 [PMID:24904279]
 Lu TZ *et al.* (2012) NALCN: a regulator of pacemaker activity. *Mol Neurobiol* **45**: 415-23 [PMID:22476981]

Waxman SG *et al.* (2014) Regulating excitability of peripheral afferents: emerging ion channel targets. *Nat Neurosci* **17**: 153-63 [PMID:24473263]

References

1. Accardi A *et al.* (2004) [14985752]
2. Accardi A *et al.* (2010) [20188062]
3. Alekov AK *et al.* (2009) [19364886]
4. Alekov AK *et al.* (2008) [19036336]
5. Aleksandrov AA *et al.* (2007) [17021796]
6. Arniges M *et al.* (2004) [15489228]
7. Bahamonde MI *et al.* (2003) [12794078]
8. Bai D *et al.* (2006) [16985167]
9. Bell PD *et al.* (2003) [12655045]
10. Best L *et al.* (2010) [21099297]
11. Billig GM *et al.* (2011) [21516098]
12. Bruzzone R *et al.* (2005) [15715654]
13. Bruzzone R *et al.* (2003) [14597722]
14. Caputo A *et al.* (2008) [18772398]
15. Castle NA. (2005) [15809194]
16. Chen TY. (2005) [15709979]
17. Connors BW *et al.* (2004) [15217338]
18. Cuthbert AW. (2011) [21108631]
19. De La Fuente R *et al.* (2008) [18083779]
20. Diaz M *et al.* (2001) [11579158]
21. Duran C *et al.* (2011) [21642943]
22. Duran C *et al.* (2010) [19827947]
23. Dutta AK *et al.* (2002) [12154180]
24. Dutzler R. (2007) [17452037]
25. Dutzler R *et al.* (2002) [11796999]
26. Edwards JC *et al.* (2010) [20100480]
27. Estévez R *et al.* (2001) [11734858]
28. Evans WH *et al.* (2002) [12126230]
29. Fahlke C *et al.* (2010) [21423394]
30. Feng L *et al.* (2010) [20929736]
31. Ferrera L *et al.* (2009) [19819874]
32. Fischer M *et al.* (2010) [20538786]
33. Fuller MD *et al.* (2007) [17951250]
34. Graves AR *et al.* (2008) [18449189]
35. Greenwood IA *et al.* (2007) [17150263]
36. Guan YY *et al.* (2006) [16697056]
37. Hartzell C *et al.* (2005) [15709976]
38. Hartzell HC *et al.* (2008) [18391176]
39. Hervé JC *et al.* (2007) [17507078]
40. Jentsch TJ. (2008) [18307107]
41. King LS *et al.* (2004) [15340377]
42. Ko SB *et al.* (2004) [15048129]
43. Kunzelmann K *et al.* (2011) [21607626]
44. Lambert S *et al.* (2005) [15961423]
45. Lange PF *et al.* (2006) [16525474]
46. Leblanc N *et al.* (2005) [16091780]
47. Lee JH *et al.* (1999) [10094463]
48. Leisle L *et al.* (2011) [21527911]
49. Liantonio A *et al.* (2007) [17128287]
50. Liantonio A *et al.* (2008) [18216243]
51. Loewen ME *et al.* (2005) [15987802]
52. Lu B *et al.* (2007) [17448995]
53. Lu B *et al.* (2009) [19092807]
54. Lu B *et al.* (2010) [21040849]
55. Manoury B *et al.* (2010) [20421283]
56. Matchkov VV *et al.* (2004) [14718479]
57. Matchkov VV *et al.* (2008) [18776041]
58. Matsuda JJ *et al.* (2008) [17977943]
59. Muallem D *et al.* (2009) [18957373]
60. Mulligan SJ *et al.* (2006) [17047222]
61. Namkung W *et al.* (2011) [21084298]
62. Neagoe I *et al.* (2010) [20466723]
63. Nilius B *et al.* (2003) [12558550]
64. Novarino G *et al.* (2010) [20430975]
65. Okada SF *et al.* (2004) [15477379]
66. Okada Y *et al.* (2009) [19171657]
67. Orhan G *et al.* (2011) [21354396]
68. Osteen JD *et al.* (2008) [18658230]
69. Ousingsawat J *et al.* (2009) [19679661]
70. Patel AC *et al.* (2009) [18954282]
71. Pedemonte N *et al.* (2007) [17452495]
72. Pelegrin P *et al.* (2007) [17121814]
73. Picollo A *et al.* (2005) [16034421]
74. Pifferi S *et al.* (2009) [19475416]
75. Piper AS *et al.* (2004) [14724180]
76. Planells-Cases R *et al.* (2009) [19708126]
77. Preston GM *et al.* (1992) [1373524]
78. Pusch M *et al.* (2002) [12512775]
79. Pusch M *et al.* (2006) [16179405]
80. Riquelme G. (2009) [19604577]
81. Robertson JL *et al.* (2010) [21048711]
82. Rock JR *et al.* (2009) [19363029]
83. Sabirov RZ *et al.* (2001) [11524456]
84. Sabirov RZ *et al.* (2009) [19340557]
85. Salameh A *et al.* (2005) [16216217]
86. Sardini A *et al.* (2003) [14729152]
87. Scheel O *et al.* (2005) [16034422]
88. Scholl U *et al.* (2006) [16849430]
89. Schroeder BC *et al.* (2008) [18805094]
90. Schulz P *et al.* (2010) [20830208]
91. Sheppard DN *et al.* (1992) [1281220]
92. Sinke AP *et al.* (2011) [21177381]
93. Sloane PA *et al.* (2010) [20829696]
94. Smith AJ *et al.* (2010) [20501796]
95. Suzuki M *et al.* (2004) [15010458]
96. Swayne LA *et al.* (2009) [19575010]
97. Söhl G *et al.* (2005) [15738956]
98. Thompson CH *et al.* (2009) [19574231]
99. Tradtrantip L *et al.* (2010) [19808995]
100. Tsumura T *et al.* (1998) [9769420]
101. Verkman AS *et al.* (2009) [19153558]
102. Vogt A *et al.* (2005) [16143426]
103. Wang H *et al.* (2009) [19535918]
104. Wang XQ *et al.* (2006) [17046694]
105. Yang YD *et al.* (2008) [18724360]
106. Yasui M *et al.* (1999) [10647010]
107. Yu FH *et al.* (2004) [15467096]
108. Zdebek AA *et al.* (2008) [18063579]