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 by Nilius and Droogmans, 2003). Excluding the transmitter-gated GABA and glycine receptors (see separate tables), well-characterized 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 (Verkman and Galietta, 2009). No official recommendation exists regarding the classification of chloride channels. Functional chloride channels that have been cloned from, or characterized within, mammalian tissues are listed.

ClC-family: The mammalian ClC family (reviewed by Nilius and Droogmans, 2003; Chen, 2005; Dutzler, 2007; Jentsch, 2008) contains nine members that fall 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 as are ClC-Ka and ClC-Kb (largely expressed in the kidney) when associated with barttin (ENSG00000162399), a 320 amino acid 2TM protein (Estévez *et al.*, 2001). The localization of ClC-3, ClC-4 and ClC-5 is likely to be predominantly intracellular, and recent reports indicate that ClC-4, ClC-5 and ClC-7 (and by inference ClC-3 and ClC-6) function as Cl^-/H^+ antiporters, rather than classical Cl^- channels (Picollo and Pusch, 2005; Scheel *et al.*, 2005; Graves *et al.*, 2008; reviewed by Miller, 2006; Pusch *et al.*, 2006). An intracellular location has been demonstrated for ClC-6 and ClC-7 (reviewed by Jentsch, 2008). Alternative splicing increases the structural diversity within the ClC family. The crystal structure of two bacterial ClC channels has been described (Dutzler *et al.*, 2002). 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 by Chen, 2005; Pusch *et al.*, 2006; Dutzler, 2007; Jentsch, 2008). As found for ClC-4, ClC-5 and ClC-7, the prokaryotic ClC homologue (ClC-ec1) functions as an H^+/Cl^- antiporter, rather than as an ion channel (Accardi and Miller, 2004).

Nomenclature	ClC-1	ClC-2	ClC-Ka	ClC-Kb
Other names	skeletal muscle Cl^- channel	–	ClC-K1 (rodent)	ClC-K2 (rodent)
Ensembl ID	ENSG00000186544	ENSG00000114859	ENSG00000186510	ENSG00000184908
Activators	Constitutively active	Arachidonic acid, amidation, acid-activated omeprazole, lubiprostone (SPI-0211)	Constitutively active (when co-expressed with barttin)	Constitutively active (when co-expressed with barttin)
Blockers	*S*-(-)CPP, S-(-)CPB, 9-AC, Cd^{2+}, Zn^{2+}, niflumic acid	GaTx2 (apparent K_D = 15 pM at –100 mV), NPPB, DPC, Cd^{2+}, Zn^{2+}	Niflumic acid (10–1000 μM) 3-phenyl-CPP, DIDS, benzofuran derivatives	Niflumic acid (10–1000 μM) 3-phenyl-CPP, DIDS, benzofuran derivatives
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, 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; 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; no time dependence; inhibited by extracellular acidosis; potentiated by extracellular Ca^{2+}	Bidirectional rectification; no time dependence; inhibited by extracellular acidosis; potentiated by extracellular Ca^{2+}

Nomenclature	ClC-3	ClC-4	ClC-5
Ensembl ID	ENSG00000109572	ENSG00000073464	ENSG00000171365
Activators	–	–	–
Blockers	Insensitive to DIDS and NPPB	Zn^{2+}, Cd^{2+}	–
Functional characteristics	Possibly functions as a Cl^-/H^+ antiporter and ion channel; pronounced outward rectification; activity enhanced by CaM kinase II; inhibited by intracellular Ins(3,4,5,6)P4 and extracellular acidosis	Cl^-/H^+ antiporter (Picollo and Pusch, 2005; Scheel *et al.*, 2005); extreme outward rectification; voltage-dependent gating with midpoint of activation at positive voltages; inhibited by extracellular acidosis; ATP hydrolysis required for full activity	Cl^-/H^+ antiporter ($2Cl^-$: $1H^+$) (Picollo and Pusch, 2005; Scheel *et al.*, 2005; Zifarelli and Pusch, 2009); extreme outward rectification; voltage-dependent gating with midpoint of activation at positive voltages; potentiated and inhibited by intracellular and extracellular acidosis respectively

Nomenclature	ClC-6	ClC-7
Ensembl ID	ENSG00000011021	ENSG00000103249
Activators	–	–
Blockers	–	–
Functional characteristics	By homology with ClC-7, a Cl^-/H^+ antiporter	Cl^-/H^+ antiporter ($2Cl^-:1H^+$) (Graves *et al.* (2008)

ClC channels display the permeability sequence $Cl^- > Br^- > I^-$ (at physiological pH); for ClC-3 $I^- > Cl^-$ has also been claimed. 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, A-9-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 (Liantonio *et al*., 2007 and reviewed by Pusch *et al*., 2002). 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 (Thompson *et al*., 2009). Although ClC-2 can be activated by cell swelling, it does not correspond to the volume-regulated anion channel (VRAC) (see below). Alternative potential physiological functions for ClC-2 are reviewed by Planells-Cases and Jentsch (2009). Functional expression of human ClC-Ka and ClC-Kb requires the presence of barttin (Estévez *et al*., 2001; Scholl *et al*., 2006). The rodent homologue (ClC-K1) of ClC-Ka demonstrates limited expression as a homomer, but its function is enhanced by barttin that increases both channel opening probablility in the physiological range of potentials and single channel conductance (Estévez *et al*., 2001; Scholl *et al*., 2006). ClC-Ka is approximately fivefold to sixfold 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 (Liantonio *et al*., 2008). The biophysical and pharmacological properties of ClC-3 and the relationship of the protein to the endogenous VRAC (see Guan *et al*., 2006; Alekov and Fahlke, 2008) are controversial and further complicated by the possibility that ClC-3 may function as both a Cl^-/H^+ exchanger and an ion channel (Picollo and Pusch, 2005; Wang *et al*., 2006; Alekov and Fahlke, 2008). 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. CIC-4 can operate in two transport modes: a slippage mode in which behaves as an ion channel and an exchanger mode in which unitary transport rate is 10-fold lower (Alekov and Fahlke, 2009). ClC-7 associates with a β subunit, Ostm1, which increases the stability of the former (Lange *et al*., 2006).

CFTR: CFTR, a 12TM, ABC type protein, is a cAMP-regulated epithelial cell membrane Cl^- channel involved in normal fluid transport across various epithelia. The most common mutation in CFTR (i.e. the deletion mutant, ΔF508) results in impaired trafficking of CFTR and reduces its incorporation into the plasma membrane causing cystic fibrosis. Channels carrying the ΔF508 mutation that do traffic to the plasma membrane demonstrate gating defects. 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 VRAC, activation of the outwardly rectifying chloride channel (ORCC), and enhancement of the sulphonylurea sensitivity of the renal outer medullary potassium channel (ROMK2) (reviewed by Nilius and Droogmans, 2003). CFTR also regulates TRPV4, which provides the Ca^{2+} signal for regulatory volume decrease (RVD) in airway epithelia (Arniges *et al*., 2004). 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 (Ko *et al*., 2004).

Nomenclature	CFTR
Other names	ABCC7
Ensembl ID	ENSG00000001626
Potentiators	VX-770, VX-532, flavones (e.g. UCCF-339, UCCF-029, apigenin, genistein), benzimidazolones (e.g. UCCF-853, NS004), benzoquinolines (e.g. CBIQ), 1,4-dihydropyridines (e.g. felopidine, nimodipine), capsaicin, phenylglycines (e.g. 2-[(2-1*H*-indol-3-yl-acetyl)-methylamino]-*N*-(4-isopropylphenyl)-2-phenylacetamide), sulfonamides [e.g. 6-(ethylphenylsulfamoyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid cycloheptylamide]
Blockers	GaTx-1, GlyH-101 (extracellular application causes channel block), $CFTR_{inh}$-172 (intracellular application prolongs mean closed time), malonic acid hydrazide conjugates (see Verkman and Galietta, 2009), glibenclamide (non-selective)
Functional characteristics	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

Corrector compounds that aid the folding of ΔF508CFTR to increase the amount of protein expressed and potentially delivered to the cell surface include VX-532 (which is also a potentiator), Corr-3a and Corr-4a [see Verkman and Galietta (2009) for details and structures]. Inhibition of CFTR by intracellular application of the peptide GaTx1, from *Leiurus quinquestriatus herbareus venom*, occurs preferentially for the closed state of the channel (Fuller *et al*., 2007). CFTR contains two cytoplasmic nucleotide binding domains (NBDs) that bind ATP. A single open-closing cycle is hypothesized 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 (Aleksandrov *et al*., 2007; Muallem and Vergani, 2009). 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 guanylin-stimulated cGMP formation) positively regulate CFTR activity.

Calcium-activated chloride channel: Chloride channels activated by intracellular calcium (CaCC) are widely expressed in excitable and non-excitable cells where they perform diverse functions (Hartzell *et al*., 2005). The molecular nature of CaCC is unclear with both CLCA genes and *BEST* genes having been considered as likely candidates (Loewen and Forsythe, 2005; Hartzell *et al*., 2008). 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 (Patel *et al*., 2009). The bestrophins encoded by genes *hbest*1-4 have a topology more consistent with ion channels (see Hartzell *et al*., 2008) and form chloride channels

that are activated by physiological concentrations of Ca^{2+}, but whether such activation is direct is not known (Hartzell *et al.*, 2008). However, currents generated by best overexpression do not resemble native CaCC currents. Recently, a new gene family, TMEM16 (anoctamin-1), has been identified that produces Ca^{2+}-activated Cl^- currents with kinetics similar to native CaCC currents recorded from different cell types (Caputo *et al.*, 2008; Schroeder *et al.*, 2008; Yang *et al.*, 2008; Pifferi *et al.*, 2009; Rock *et al.*, 2009). Knockout of TMEM16 abolishes CaCC in several epithelial tissues (Yang *et al.*, 2008)

Nomenclature	CaCC
Other names	Ca^{2+}-activated Cl^- channel
Activators	Intracellular Ca^{2+}
Blockers	Niflumic acid, flufenamic acid, DCDPC, DIDS, SITS, NPPB, A-9-C, Ins(3,4,5,6)P_4, mibefradil, fluoxetine
Functional characteristics	γ = 0.5–5 pS; permeability sequence, $SCN^- > NO_3^- > I^- > Br^- > Cl^- > F^-$; relative permeability of SCN^- : Cl^- ~8. I^- : Cl^- ~ 3, aspartate : Cl^- ~ 0.15, outward rectification (decreased by increasing $[Ca^{2+}]_i$); sensitivity to activation by $[Ca^{2+}]_i$ decreased at hyperpolarized potentials; slow activation at positive potentials (accelerated by increasing $[Ca^{2+}]_i$); rapid deactivation at negative potentials, deactivation kinetics modulated by anions binding to an external site; modulated by redox status

Blockade of $I_{Cl(Ca)}$ by niflumic acid, DIDS and 9-AC is voltage-dependent whereas block by NPPB is voltage-independent (Hartzell *et al.*, 2005). Extracellular niflumic acid, DCDPC and A-9-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 Leblanc *et al.*, 2005 for summary). Considerable crossover in pharmacology with large-conductance Ca^{2+}-activated K^+ channels also exists (see Greenwood and Leblanc, 2007 for overview). Two novel compounds, $CaCC_{inh}$-A01 and $CaCC_{inh}$-B01, have recently been identified as blockers of CaCC in T84 human intestinal epithelial cells (see De La Fuente *et al.*, 2008 for structures). CaMKII modulates CaCC in a tissue-dependent manner (reviewed by Hartzell *et al.*, 2005; Leblanc *et al.*, 2005). CaMKII inhibitors block activation of $I_{Cl(Ca)}$ in T_{84} 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 Leblanc *et al.*, 2005 for summary).

Maxi chloride channel: Maxi Cl^- channels are high-conductance, anion-selective, channels initially characterized 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 (Sabirov and Okada, 2009). 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 (Sabirov *et al.*, 2001; Dutta *et al.*, 2002). 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 (Bell *et al.*, 2003). A family of human high-conductance Cl^- channels (TTYH1-3) that resemble Maxi Cl^- channels has been cloned (Suzuki and Mizuno, 2004), but alternatively, Maxi Cl^- channels have also been suggested to correspond to the voltage-dependent anion channel, VDAC, expressed at the plasma membrane (Bahamonde *et al.*, 2003; Okada *et al.*, 2004).

Nomenclature	Maxi Cl^-
Other names	High-conductance anion channel, volume- and voltage-dependent ATP-conductive large-conductance (VDACL) anion channel
Activators	G protein-coupled receptors, cytosolic GTPγS, extracellular triphenylethylene anti-oestrogens (tamoxifen, toremifine), extracellular chlorpromazine and triflupromazine, cell swelling
Blockers	SITS, DIDS, NPPB, DPC, intracellular arachidonic acid, extracellular Zn^{2+} and Gd^{3+}
Functional characteristics	γ = 280–430 pS (main state); permeability sequence, I > Br > Cl > F > gluconate ($P_{Cl}P_{Cl}$ = ~1.5); ATP is a voltage-dependent permeant blocker of single channel activity (P_{ATP}/P_{Cl} = 0.08–0.1); channel activity increased by patch-excision; channel opening probability (at steady state) maximal within approximately ±20 mV of 0 mV, opening probability decreased at more negative and (commonly) positive potentials yielding a bell-shaped curve; channel conductance and opening probability regulated by annexin 6

Differing ionic conditions may contribute to variable estimates of γreported in the literature. Inhibition by arachinonic 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 (Sabirov *et al.*, 2001); (Dutta *et al.*, 2002). Channel activation by anti-oestrogens in whole cell recordings requires the presence of intracellular nucleotides and is prevented by pretreatment with 17β-oestradiol, dibutryl cAMP, or intracellular dialysis with GDPβS (Diaz *et al.*, 2001). 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 (Diaz *et al.*, 2001). 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 (Riquelme, 2009).

Volume-regulated chloride channels: 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 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 and glutamate release from astrocytes (reviewed by Nilius and Droogmans, 2003; Mulligan and MacVicar, 2006; Okada *et al.*, 2009). 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 phosphoholemman are also no longer considered likely to fulfil this function (see reviews by d'Anglemont de Tassigny *et al.*, 2003; Nilius and Droogmans, 2003; Sardini *et al.*, 2003).

Nomenclature	VRAC (volume-regulated anion channel), VSOAC (volume-sensitive organic osmolyte/anion channel), VRC (volume-regulated channel), VSOR (volume expansion-sensing outwardly rectifying anion channel)
Activators	cell swelling; low intracellular ionic strength; GTPγS
Blockers	NS3728, DCPIB, clomiphene, nafoxidine, mefloquine, tamoxifen, gossypol, arachidonic acid, mibefradil, NPPB, quinine, quinidine, chromones NDGA, A-9-C, DIDS, 1,9-dideoxyforskolin, oxalon dye (diBA-(5)-C4), extracellular nucleotides, nucleoside analogues, intracellular Mg^{2+}
Functional characteristics	γ = 10–20 pS (negative potentials), 50–90 pS (positive potentials); permeability sequence $SCN > I > NO^{3-} > Br^- > Cl^- > F^-$ > gluconate; outward rectification due to voltage dependence of γ; inactivates at positive potentials in many, but not all, cell types; time-dependent inactivation at positive potentials; intracellular ionic strength modulates sensitivity to cell swelling and rate of channel activation; rate of swelling-induced activation is modulated by intracellular ATP concentration; ATP dependence is independent of hydrolysis and modulated by rate of cell swelling; inhibited by increased intracellular free Mg^{2+} concentration; swelling-induced activation of several intracellular signalling cascades may be permissive of, but not essential to, the activation of VRAC including: the Rho-Rho kinase-MLCK; Ras-Raf-MEK-ERK; PIK3-NOX-H_2O_2 and Src-PLCγ-Ca^{2+} pathways; regulation by PKCα required for optimal activity; cholesterol depletion enhances activity; activated by direct stretch of β1-integrin

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 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 (Tsumura *et al*., 1998). 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 very different from the 'conventional' CaCC (see Matchkov *et al*., 2004; Piper and Large, 2004). A proton-activated, outwardly rectifying anion channel has also been described (Lambert and Oberwinkler, 2005).

Abbreviations: A-9-C, anthracene-9-carboxylic acid; **CBIQ**, 4-chlorobenzo[F]isoquinoline; **$CFTR_{inh}$-172**, 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; **DCPIB**, 4-(2-butyl-6,7-dichlor-2-cyclopentyl-indan-1-on-5-yl) oxybutyric acid; **diBA-(5)-C4**, bis-(1,3-dibutylbarbituric acid)pentamethine oxanol; **DIDS**, 4,4′-diisothiocyanostilbene-2,2′-disulphonic acid; **DNDS**, 4,4′-dinitrostilbene-2,2′-disulphonic acid; **GlyH-101**, *N*-(2-naphthalenyl)-[(3,5-dibromo-2,4-dihydroxyphenyl)methylene]glycine hydrazide; **NDGA**, nordihydroguiaretic acid; **NPA**, N-phenylanthracilic acid; **DPC**, diphenylamine carboxylic acid; **DPDPC**, dichloro-diphenylamine 2-carboxylic acid; **NPPB**, 5-nitro-2-(3-phenylpropylamino)benzoic acid; **NS004**, 5-trifluoromethyl-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2*H*-benzimidazole-2-one; **NS3728**, *N*-[3,5-bis(trifluromethyl)-phenyl]-*N′*[4-bromo-2-(1*H*-tetrazol-5yl)-phenyl]urea; ***S*-(-)CPP**, *S*-(-)2-(4-chlorophenoxy)propionic acid; ***S*-(-)CPB**, *S*-(-)2-(4-chlorophenoxy)butyric acid; **SITS**, 4′-isothiocyanostilbene-2,2′-disulphonic acid; **UCCF-029**, 2-(4-pyridinium)benzo[*h*]4H-chromen-4-one bisulfate; **UCCF-180**, 3-(3-butynyl)-5-methoxy-1-phenylpyrazole-4-carbaldehyde; **UCCF-853**, 1-(3-chlorophenyl)-5-trifluoromethyl-3-hydroxybenzimidazol-2-one, **VX-532**, 4-methyl-2-(5-phenyl-1*H*-pyrazol-3-yl)-phenol; **VX-770**, *N*-(2,4-Di-*tert*-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide

Further Reading

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

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

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

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.

Babini E, Pusch MA (2004). Two-holed story: Structural secrets about ClC proteins become unraveled? *Physiology (Bethesda)* **19**: 293–299

Chen T-Y (2005). Structure and function of CLC channels. *Annu Rev Physiol* **67**: 809–839.

Chen T-Y, Hwang TC (2008). CLC-0 and CFTR: chloride channels evolved from transporters. *Physiol Rev* **88**: 351–387.

d'Anglemont de Tassigny A, Souktane R, Ghaleb B, Henry P, Berdeaux A (2003). Structure and pharmacology of swelling-sensitive chloride channels, $I_{Cl,\ swell}$. *Fundam Clin Pharmacol* **17**: 539–553.

Duan D (2009). Phenomics of cardiac chloride channels: the systematic study of chloride channel function in the heart. *J Physiol* **587**: 2163–2177.

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

Eggermont J, Trouet D, Carton I, Nilius B (2001). Cellular function and control of volume regulated anion channels. *Cell Biochem Biophys* **35**: 263–274.

Fahlke C (2001). Ion permeation and selectivity in ClC-type chloride channels. *Am J Physiol* **280**: F748–F757.

Gadsby DC, Vergani P, Csanady l (2006). The ABC protein turned chloride channel whose failure causes cystic fibrosis. *Nature* **440**: 477–483.

Greenwood IA, Leblanc N (2007). Overlapping pharmacology of Ca^{2+}-activated Cl^- and K^+ channels. *Trends Pharmacol Sci* **28**: 1–5.

Guan Y-Y, Wang G-L, Zhou J-G (2006). The ClC-3 Cl- channel in cell volume regulation, proliferation and apoptosis in vascular smooth muscle cells. *Trends Pharmacol Sci* **27**: 290–296.

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

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

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

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.

Leblanc N, Ledoux J, Saleh S, Sanguinetti A, Angermann J, O'Driscoll K *et al*. (2005). Regulation of calcium-activated chloride channels in smooth muscle cells: a complex picture is emerging. *Can J Physiol Pharmacol* **83**: 541–556.

Loewen ME, Forsyth GW (2005). Structure and function of CLCA proteins. *Physiol Rev* **85**: 1061–1092.
Miller C (2006). ClC chloride channels viewed through a transporter lens. *Nature* **440**: 484–489.
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.
Mulligan SJ, MacVicar BA (2006). VRACs CARVe a path for novel mechanisms of communication in the CNS. *Sci STKE* **357**: pe42.
Nilius B, Droogmans G (2003). Amazing chloride channels: an overview. *Acta Physiol Scand* **177**: 119–147.
Okada Y (2006). Cell-volume sensitive chloride channels: phenotypic properties and molecular identity. *Contrib Nephrol* **152**: 9–24.
Okada Y, Sato K, Numata T (2009). Pathophysiology and puzzles of the volume-sensitive outwardly rectifying anion channel. *J Physiol* **587**: 2141–1459.
Patel AC, Brett TJ, Holtzman MJ (2009). The role of CLCA proteins in inflammatory airway disease. *Annu Rev Physiol* **71**: 425–449.
Planells-Cases R, Jentsch TJ (2009). Chloride channelopathies. *Biochim Biophys Acta* **1792**: 173–189.
Plans V, Rickheit G, Jentsch TJ (2009). Physiological roles of CLC Cl^-/H^+ exchangers in renal proximal tubules. *Pflügers Arch* **458**: 23–37.
Puljak L, Kilic G (2006). Emerging roles of chloride channels in human diseases. *Biochim Biopsy Acta* **1762**: 404–413.
Pusch M, Accardi A, Liantonio A, Guida P, Traverso S, Camerino DC *et al.* (2002). Mechanisms of block of muscle type CLC chloride channels. *Mol Membr Biol* **19**: 285–292.
Pusch M, Zifarelli G, Murgia AR, Picollo A, Babini E (2006). Channel or transporter? The CLC saga continues. *Exp Physiol* **91**: 149–152.
Riordan JR (2005). Assembly of functional CFTR chloride channels. *Annu Rev Physiol* **67**: 701–718.
Riquelme G (2009). Placental chloride channels: a review. *Placenta* **30**: 659–669.
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.
Sardini A, Amey JS, Weylandt KH, Nobles M, Valverde MA, Higgins CF (2003). Cell volume regulation and swelling-activated chloride channels. *Biochim Biophys Acta* **1618**: 153–162.
Suzuki M, Mizuno A (2004). A novel human Cl^- channel family related to *Drosophila* flightless locus. *J Biol Chem* **279**: 22461–22468.
Uchida S, Sasaki S (2005). Function of chloride channels in the kidney. *Annu Rev Physiol* **67**: 759–778.
Verkman AS, Galietta LJ (2009). Chloride channels as drug targets. *Nat Rev Drug Discov* **8**: 153–171.

References

Accardi A, Miller C (2004). *Nature* **427**: 803–807.
Alekov AK, Fahlke C (2009). *J Gen Physiol* **133**: 485–496.
Arniges M *et al.* (2004). *J Biol Chem* **279**: 54062–54068.
Bahamonde MI *et al.* (2003). *J Biol Chem* **278**: 33284–33289.
Bell PD *et al.* (2003). *Proc Natl Acad Sci USA* **100**: 4322–4327.
Caputo A *et al.* (2008). *Science* **322**: 590–594.
De La Fuente R *et al.* (2008). *Mol Pharmacol* **73**: 758–568.
Diaz M *et al.* (2001). *J Physiol* **536**: 79–88.
Dutta AK *et al.* (2002). *J Physiol* **542**: 803–816.
Dutzler R *et al.* (2002). *Nature* **415**: 287–294.
Estévez R *et al.* (2001). *Nature* **414**: 558–561.
Fuller MD *et al.* (2007). *J Biol Chem* **282**: 37545–37355.
Graves AR *et al.* (2008). *Nature* **453**: 788–792.
Ko SBH *et al.* (2004). *Nat Cell Biol* **6**: 343–350.
Lambert S, Oberwinkler J (2005). *J Physiol* **576**: 191–213.
Lange PF *et al.* (2006). *Nature* **440**: 220–223.
Liantonio A *et al.* (2007). *Br J Pharmacol* **150**: 235–247.
Liantonio A *et al.* (2008). *Proc Natl Acad Sci USA* **105**: 1369–1373.
Matchkov VV *et al.* (2004). *J Gen Physiol* **123**: 121–134.
Okada SF *et al.* (2004). *J Gen Physiol* **124**: 513–526.
Picollo A, Pusch M (2005). *Nature* **436**: 420–423.
Pifferi S *et al.* (2009). *Pflugers Arch* **458**: 1023–1038.
Piper AS, Large WA (2004). *J Physiol* **555**: 397–408.
Rock JR *et al.* (2009). *J Biol Chem* **284**: 14875–14880.
Sabirov RZ *et al.* (2001). *J Gen Physiol* **118**: 251–266.
Scheel O *et al.* (2005). *Nature* **436**: 424–427.
Scholl U *et al.* (2006). *Proc Natl Acad Sci USA* **103**: 11411–11416.
Schroeder BC *et al.* (2008). *Cell* **134**: 1019–1029.
Suzuki M, Mizuno A (2004). *J Biol Chem* **279**: 22461–22468.
Thompson CH *et al.* (2009). *J Biol Chem* **284**: 26051–26062.
Tsumura T *et al.* (1998). *J Physiol* **512**: 765–777.
Wang XQ *et al.* (2006). *Neuron* **52**: 321–333.
Yang YD *et al.* (2008). *Nature* **455**: 1210–1215.
Zifarelli G, Pusch M (2009). *EMBO J* **28**: 175–182.