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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S199 & CIC family \\
S200 & Calcium activated chloride channel \\
S201 & Maxi chloride channel \\
S202 & Volume regulated chloride channels \\
S203 & Connexins and Pannexins \\
S205 & Sodium leak channel, non-selective
\end{tabular}

Searchable database: http://www.guidetopharmacology.org/index.jsp
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.

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

**Nomenclature**

AQP6, AQP7, AQP8, AQP9, AQP10

**Permeability**

water (low), glycerol, water (high)

**Inhibitors**

Hg$^{2+}$

**Comments**

AQP6 is an intracellular channel permeable to anions as well as water [106]

**Further reading on Aquaporins**


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, and glycine receptors (see separate tables), well characterised chloride channels can be classified as certain members of the voltage-sensitive CIC subfamily, calcium-activated channels, high (maxi) conductance channels, the cystic fibrosis transmembrane conductance regulator (CFTR) and volume regulated channels [101]. 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 [26].

CIC family
Other ion channels → Chloride channels → CIC family

Overview: The mammalian CIC family (reviewed in [2, 16, 22, 24, 40]) contains 9 members that fall, on the basis of sequence homology, into three groups: CIC-1, CIC-2, hCIC-Ka (rCIC-K1) and hCIC-Kb (rCIC-K2); CIC-3 to CIC-5, and CIC-6 and -7. CIC-1 and CIC-2 are plasma membrane chloride channels. CIC-Ka and CIC-Kb are also plasma membrane channels (largely expressed in the kidney and inner ear) when associated with barttin ([BSND, Q8W253), a 320 amino acid 2TM protein [27]. The localisation of the remaining members of the CIC 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 CIC-4, CIC-5, CIC-6 and CIC-7 (and by inference CIC-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 CIC-5 as a Cl-/H+ exchanger is important for renal endocytosis [64]. Alternative splicing increases the structural diversity within the CIC family. The crystal structure of two bacterial CIC proteins has been described [25] and a eukaryotic CIC transporter (CmCIC) has recently been described at 3.5 Å resolution [30]. Each CIC subunit, with a complex topology of 18 intramembrane segments, contributes a single pore to a dimeric ‘double-barrelled’ CIC channel that contains two independently gated pores, confirming the predictions of previous functional and structural investigations (reviewed in [16, 24, 40, 79]). As found for CIC-4, CIC-5, CIC-6 and CIC-7, the prokaryotic CIC homologue (CIC-ec1) and CmCIC function as H+/Cl antiporters, rather than ion channels [1, 30]. The generation of monomers from dimeric CIC-ec1 has firmly established that each CIC subunit is a functional unit for transport and that cross-subunit interaction is not required for Cl-/H+ exchange in CIC transporters [81].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>CIC-1</th>
<th>CIC-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>CLCNT, P35523</td>
<td>CLCN2, P51788</td>
</tr>
<tr>
<td>Endogenous activators</td>
<td>–</td>
<td>arachidonic acid</td>
</tr>
<tr>
<td>Activators</td>
<td>–</td>
<td>lubiprostone, omeprazole</td>
</tr>
<tr>
<td>Channel blockers</td>
<td>9-anthroic acid, S-(−)-CPB, S-(−)-CPP, Cd2+, Zn2+, fenofibric acid, niflumic acid</td>
<td>GaTx2 (pKd 10.8) [voltage dependent -100mV], Cd2+, NPPB, Zn2+, diphenylamine-2-carboxylic acid</td>
</tr>
<tr>
<td>Functional Characteristics</td>
<td>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 CIC-1 (by closure of the common gate), depending on its redox status</td>
<td>γ = 2–3 pS; voltage-activated by membrane hyperpolarization by fast protopore and slow cooperative gating; channels only open negative to EC0 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</td>
</tr>
<tr>
<td>Nomenclature</td>
<td>CIC-Ka</td>
<td>CIC-Kb</td>
</tr>
<tr>
<td>--------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>HGNC, UniProt</td>
<td>CLCNK4, PS1800</td>
<td>CLCNKB, PS1801</td>
</tr>
<tr>
<td>Activators</td>
<td>niflumic acid (pEC_{50} 3–5)</td>
<td>niflumic acid (pEC_{50} 3–5)</td>
</tr>
<tr>
<td>Channel blockers</td>
<td>3-phenyl-CPP, DIDS, niflumic acid</td>
<td>3-phenyl-CPP, DIDS</td>
</tr>
</tbody>
</table>

**Functional Characteristics**

- CIC-Ka: 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+}

- CIC-Kb: Bidirectional rectification; no time dependence; inhibited by extracellular protons; potentiated by extracellular Ca^{2+}

- CIC-3: 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

- CIC-4: 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

- CIC-3 is also activated by amidation

- CIC-4 is insensitive to the channel blockers DIDS, NPPB and tamoxifen (10 µM)
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 sulphuric sensitivity of the renal outer medullary potassium channel (ROMK2), (reviewed in [63]). CFTR also regulates TRPV4, which provides the Ca²⁺ 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].
<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>CFTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGNC, UniProt</td>
<td>CFTR, P13569</td>
</tr>
<tr>
<td>Activators</td>
<td>felodipine (Potentiation) (pkCa 8.4) [71], CB1Q (Potentiation), NS004 (Potentiation), UCCF-029 (Potentiation), UCCF-339 (Potentiation), UCCF-853 (Potentiation), apigenin (Potentiation), capsaicin (Potentiation), genistein (Potentiation), ivacafactor (Potentiation), nimodipine (Potentiation), phenylglycine-01 (Potentiation), sulfonamide-01 (Potentiation)</td>
</tr>
<tr>
<td>Selective inhibitors</td>
<td>crofelemer (pIC50 5.2) [99]</td>
</tr>
<tr>
<td>Channel blockers</td>
<td>glibenclamide (pKa 4.7) [91], intracellular CFTRinh-172 (intracellular application prolongs mean closed time), GaTx1, extracellular GlyH-101</td>
</tr>
<tr>
<td>Functional Characteristics</td>
<td>γ = 6-10 pS; permeability sequence = Br &gt; Cl &gt; I &gt; F, (PBr/PCl = 0.1-0.85); slight outward rectification; phosphorylation necessary for activation by ATP binding at binding nucleotide binding domains (NBD1) 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</td>
</tr>
<tr>
<td>Comments</td>
<td>UCDF-339, UCCF-029, apigenin and genistein are examples of flavones. UCCF-853 and NS004 are examples of benzimidazolones. CB1Q is an example of a benzoquinoline. felodipine and nimodipine are examples of 1,4-dihydropyridines. phenylglycine-01 is an example of a phenylglycine. sulfonamide-01 is an example of a sulfonamide. Malonic acid hydrazide conjugates are also CFTR channel blockers (see Verkman and Galietta, 2009 [101])</td>
</tr>
</tbody>
</table>

**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 DFS08CFTR to increase the amount of protein expressed and potentially delivered to the cell surface include VX-809 (which is also a potentiatior), 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 application of the peptide GaTx1, from Leirias quinquestrilatus herbatus 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 disassociation 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, 44]. 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 [106] 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].
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].

Comments: Blockade of I_{Cl(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 I_{Cl(Ca)} in vascular smooth muscle, enhancing and inhibiting inwardly and outwardly directed currents in a manner dependent upon [Ca^{2+}]_i (see [46] for summary). Considerable crossover in pharmacology with large conductance Ca^{2+}-activated K⁺ channels also exists (see [35] for overview). Two novel compounds, CaCCinh-A01 and CaCCinh-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 TMEM16A 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 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 [46] for summary).
Nomenclature
Maxi Cl
Activators
cytosolic GTPγS, extracellular chlorpromazine, extracellular tamoxifen, extracellular toremifene, extracellular triflupromazine
Endogenous channel blockers
intracellular arachidonic acid
Channel blockers
DIDS (pIC₅₀ 4.4) [90], extracellular Zinc²⁺ (pIC₅₀ 4.3) [68], NPPB (pIC₅₀ 3.8) [90], extracellular Gad³⁺, SITS, diphenylamine-2-carboxylic acid

Functional Characteristics
γ = 280-430 pS (main state);
permeability sequence, I > Br > Cl > F > gluconate (PₐCl/PₐCl = ~1.5);
ATP is a voltage dependent permeant blocker of single channel activity (PₐATP/PₐCl = 0.08-0.1); channel activity increased by patch-excision; channel opening probability (at steady-state) maximal within approximately ± 20 mV of 0 mV, opening probability decreased at more negative and (commonly) positive potentials yielding a bell-shaped curve; channel conductance and opening probability regulated by annexin 6

Comments
Maxi Cl⁺ is also activated by G protein-coupled receptors and cell swelling. tamoxifen and toremifene are examples of triphenylethylene anti-oestrogens

Comments: Differing ionic conditions may contribute to variable estimates of γ reported in the literature. Inhibition by arachidonic acid (and cis-unsaturated fatty acids) is voltage-independent, occurs at an intracellular site, and involves both channel shut down (Kᵥ = 4-5 μM) and a reduction of γ (Kᵥ = 13-14 μM). 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 pretreatment with 17β-estradiol, bucladesine, or intracellular dialysis with GDPβS [20]. 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 [20]. 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 [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; VRAC, volume regulated channel and VSOAR, 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, transeellular 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 MDR1 (ABCB1 P-glycoprotein), Icln, Band 3 anion exchanger and phospholemman are also no longer considered likely to fulfil this function (see reviews [63, 86]).
### Volume regulated chloride channels

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>VRAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activators</td>
<td>GTPγS</td>
</tr>
<tr>
<td>Endogenous channel blockers</td>
<td>intracellular Mg$^{2+}$, arachidonic acid</td>
</tr>
<tr>
<td>Channel blockers</td>
<td>1,9-dideoxyforskolin, 9-anthroic acid, DCPIB, DIDS, IAAs-94, NPPB, NS3728, carbeneoxolone, clomiphene, diBA-(5)-C4, gossypol, meploquine, mibebradil, nafoxidine, nordihydroguaretic acid, quinidine, quinine, tamoxifen</td>
</tr>
<tr>
<td>Functional Characteristics</td>
<td>$\gamma = 10\text{--}20$ pS (negative potentials), $50\text{--}90$ pS (positive potentials); permeability sequence SCN $&gt; I &gt; NO_3 &gt; Br^- &gt; Cl^- &gt; F^- &gt;$ gluconate; outward rectification due to voltage dependence of $\gamma$ 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-ERK; PIK3-NOX-H2 pathway; regulation by PKCα required for optimal activity; cholesterol depletion enhances activity; activated by direct stretch of β1-integrin</td>
</tr>
<tr>
<td>Comments</td>
<td>VRAC is also activated by cell swelling and low intracellular ionic strength. VRAC is also blocked by chromones, extracellular nucleotides and nucleoside analogues</td>
</tr>
</tbody>
</table>

**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 CI channel activated by cyclic GMP with a dependence on raised intracellular Ca$^{2+}$ has been recorded in various vascular smooth muscle cells types, which has a pharmacology and biophysical characteristics very different from the ‘conventional’ CaCC [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**


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 IP$_3$) as well as cations and anions. 21 connexin genes and 3 pannexin genes which are structurally related to the invertebrate innexin genes) code for gap junction proteins in humans. Each connexin gap junction comprises 2 hemichannels or ‘connexons’ which are themselves formed from 6 connexin molecules. The various connexins have been observed to combine into both homomeric and heteromeric combinations, each of which may exhibit different functional properties. It is also suggested that individual hemichannels formed by a number of different connexins might be functional in at least some cells [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].

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Cx23</th>
<th>Cx25</th>
<th>Cx26</th>
<th>Cx30</th>
<th>Cx30.2</th>
<th>Cx30.3</th>
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<td>extracellular Ca$^{2+}$ (blocked by raising external Ca$^{2+}$)</td>
<td>carbenoxolone, flufenamic acid, octanol</td>
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**Nomenclature**

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**Endogenous inhibitors**
- Extracellular Ca\(^{2+}\) (blocked by raising external Ca\(^{2+}\))

**Inhibitors**
- Carbenoxolone, flufenamic acid, octanol

**Nomenclature**

<table>
<thead>
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<th>Nomenclature</th>
<th>Px1</th>
<th>Px2</th>
<th>Px3</th>
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<td>PANX3, Q96Q90</td>
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**Inhibitors**
- Carbenoxolone, flufenamic acid (little block by flufenamic acid)
- 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**

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\textsubscript{Vi2.1}, W.A. Catterall, personal communication) is structurally a member of the family of voltage-gated sodium channel family (Na\textsubscript{v1.1} – Na\textsubscript{v1.9}) [47, 107]. In contrast to the latter, Na\textsubscript{Vi2.1}, is voltage-insensitive (denoted in the subscript ‘vi’ in the tentative nomenclature) and possesses distinctive ion selectivity and pharmacological properties. Na\textsubscript{Vi2.1}, which is insensitive to tetrodotoxin (10 \textmu M), has been proposed to mediate the tetrodotoxin-resistant and voltage-insensitive Na\textsuperscript{+} leak current (I\textsubscript{L}\textsubscript{-Na}) observed in many types of neurone [52]. However, whether Na\textsubscript{Vi2.1} is constitutively active has been challenged [96].

Na\textsubscript{Vi2.1} 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
- **HGNC, UniProt**
  - Na\textsubscript{vi2.1}
  - 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\textsuperscript{2+} concentration [54]

### Channel blockers
- Gd\textsuperscript{3+} (pIC\textsubscript{50} 5.6), Cd\textsuperscript{2+} (pIC\textsubscript{50} 3.8), Co\textsuperscript{2+} (pIC\textsubscript{50} 3.6), verapamil (pIC\textsubscript{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\textsubscript{Vi2.1} can be activated by stimulation of NK\textsubscript{1} (in hippocampal neurones), neurotensin (in ventral tegmental area neurones) and M3 muscarinic acetylcholine receptors (in MIN6 pancreatic \( \beta \)-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\textsubscript{Vi2.1} 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\textsubscript{Vi2.1} by decreased extracellular Ca\textsuperscript{2+} concentration is G-protein dependent and involves a Ca\textsuperscript{2+}-sensing G protein-coupled receptor and UNC80 which links Na\textsubscript{Vi2.1} to the protein UNC79 in the same complex [54]. Na\textsubscript{Vi2.1} null mutant mice have severe disturbances in respiratory rhythm and die within 24 hours of birth [52]. Na\textsubscript{Vi2.1} heterozygous knockout mice display increased serum sodium concentrations in comparison to wildtype littersmates and a role for the channel in osmoregulation has been postulated [92].

### Further reading on Sodium leak channel

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