ION CHANNELS

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

Overview: Acid-sensing ion channels (ASICs, provisional nomenclature) are members of a Na^+ channel superfamily that includes the epithelial Na channel, ENaC, the FMRF-amide activated channel of *Helix aspersa*, the degenerins (DEG) of *Caenorhabitis elegans* (see Waldmann & Lazdunski, 1998; Mano & Discoll, 1999) and 'orphan' channels that include BLINaC (Sakai *et al*., 1999) and INaC (Schaefer *et al*., (2000)). ASIC subunits contain two putative TM domains and assemble as homo- or hetero-tetramers to form proton-gated, Na^+ permeable, channels. Splice variants of ASIC1 [provisionally termed ASIC1a (ASIC-α) (Waldmann *et al*., 1997a) and ASIC1b (ASIC-β) (Chen *et al*., 1998)] and ASIC2 [provisionally termed ASIC2a (MDEG1) and ASIC2b (MDEG2); Linguelia *et al*., 1997] have been cloned. Unlike ASIC2a (listed in table), heterologous expression of ASIC2b alone does not support H^+-gated currents. Transcripts encoding a fourth member of the acid-sensing ion channel family (ASIC4/SPASIC) do not produce a proton-gated channel in heterologous expression systems (Akopian *et al*., 2000; Grunder *et al*., 2000). ASIC channels are expressed in central and peripheral neurons and particularly in nociceptors where they participate in neuronal sensitivity to acidosis. The relationship of the cloned ASICs to endogenously expressed proton-gated ion channels is becoming established (Escoubas *et al*., 2000; Sutherland *et al*., 2001; Wemmie *et al*., 2002; 2003). Heterologously expressed heteromutimers of ASIC1/ASIC2a, ASIC2a/ASIC2b, ASIC2a/ASIC3 ASIC2b/ASIC3 and ASIC1a/ASIC3 form ion channels with altered kinetics, ion selectivity, pH- sensitivity and sensitivity to block by Gd^{3+} (Bassilana *et al*., 1997; Linguelia *et al*., 1997; Babinski *et al*., 2000, Escoubas *et al*., 2000). Channels assembled from ASIC2b/ASIC3 subunits support biphasic current responses, mediated by transient Na^+-selective and sustained non-selective cation conductances, that resemble a biphasic proton-activated current recorded from a subset of dorsal root ganglion neurones (Bevan & Yeats, 1991).

Nomenclature	**ASIC1**	**ASIC2**	**ASIC3**
Other names	ASIC; BNC2; BnaC2	BNC1; BnaC1; MDEG1	DRASIC
Ensembl ID	ENSG00000110881	ENSG00000108684	ENSG00000164881
Endogenous activators	Extracellular H^+ (ASIC1a, $pEC_{50} \approx 6.6$; ASIC1b, $pEC_{50} \approx 5.9$)	Extracellular H^+ ($pEC_{50} \approx 4.4$)	Extracellular H^+(transient component $pEC_{50} \approx 6.2$) (sustained component $pEC_{50} \approx 4.3$)
Blockers (IC_{50})	Psalmotoxin I (0.9 nM), amiloride (10 μM), EIPA, benzamil (10 μM), flurbiprofen (350 μM), ibuprofen	Amiloride (28 μM)	Amiloride (16–63 μM) (transient component only), diclofenac (92 μM), salicylic acid (260 μM), aspirin (sustained component only)
Functional characteristics	$\gamma \sim 14$pS; $P_{Na}/P_K = 13$, $P_{Na}/P_{Ca} = 2.5$; rapid activation and inactivation rates	$\gamma \sim 11$pS; $P_{Na}/P_K = 10$, $P_{Na}/P_{Ca} = 20$; rapid activation rate, moderate inactivation rate	$\gamma \sim 13$–15 pS; biphasic response; rapidly inactivating transient and sustained components

Psalmotoxin blocks ASIC1a, but has little effect upon ASIC1b, ASIC2a, ASIC3, or ASIC1a expressed as a heteromultimer with either ASIC2a, or ASIC3 (Escoubas *et al*., 2000). The pEC_{50} values for proton activation of ASIC1a, ASIC1b and ASIC3 are shifted to more acidic levels by increasing $[Ca^{2+}]_i$ (Babini *et al*., 2002; Immke & McCleskey, 2003). Rapid acidification is required for activation of ASIC1 and ASIC3 due to fast inactivation/desensitization. ASIC3 mediates a biphasic response to acidic pH consisting of rapidly inactivating transient and sustained currents; only the former is blocked by amiloride. The transient component appears partially inactivated at physiological pH (7.2). pEC_{50} values for H^+-activation of either component vary in the literature and may reflect species and/or methodological differences (Waldmann *et al*., 1997b; de Weille *et al*., 1998; Babinski *et al*., 1999). The transient and sustained current components mediated by rASIC3 are highly selective for Na^+ (Waldmann *et al*., 1997b); for hASIC3 the transient component is Na^+ selective, whereas the sustained current appears non-selective ($P_{Na}/P_K = 1.6$) (de Weille *et al*., 1998; Babinski *et al*., 1999). Non-steroidal anti-inflammatory drugs (NSAIDs) are direct blockers of ASIC currents within the therapeutic range of concentrations (Voilley *et al*., 2001). ASIC1a is blocked by flurbiprofen and ibuprofen and currents mediated by ASIC3 are inhibited by salicylic acid, aspirin and diclofenac. Extracellular Zn^{2+} potentiates proton activation of homomeric and heteromeric channels incorporating ASIC2a, but not homomeric ASIC1a or ASIC3 channels (Baron *et al*., 2001). The peptide FMRFamide acts upon ASIC1a, ASIC1b and ASIC3, but not ASIC2, to slow inactivation and induce/potentiate a sustained current during acidification (Askwith *et al*., 2000). In native receptors, the presence of ASIC3 within the receptor complex confers sensitivity to FMRF (Xie *et al*., 2003). Neuropeptides FF and SF slow the inactivation kinetics of ASIC3 (Askwith *et al*., 2000; Deval *et al*., 2003). Inflammatory conditions and particular pro-inflammatory mediators induce overexpression of ASIC-encoding genes and enhance ASIC currents (Mamet *et al*., 2002).

Abbreviations: **EIPA**, ethylisopropylamiloride; **FMRFamide**, Phe-Met-Arg-Phe-amide; **Neuropeptide FF**, Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-amide; **Neuropeptide SF**, Ser-Leu-Ala-Pro-Gln-Arg-Phe-amide

Further reading:

KRESS, M. & ZEILHOFER, H.U. (1999). Capsaicin, protons and heat: new excitement about nociceptors. *Trends Pharmacol. Sci*., **20,** 112–118.

KRISHTAL, O. (2003). The ASICs: Signaling molecules? Modulators? *Trends Neurosci*., **26,** 477–483.

MANO, I. & DISCOLL. M. (1999). DEG/ENaC channels: a touchy superfamily that watches its salt. *Bioessays*, **21,** 568–578.

REEH, P.W. & KRESS, M. (2001). Molecular physiology of proton transduction in nociceptors. *Curr. Opin. Pharmacol*., **1,** 45–51.

SUTHERLAND, S.P., COOK, S.P. & MCCLESKEY, E.W. (2000). Chemical mediators of pain due to tissue damage and ischemia. *Prog. Brain Res*., **129,** 21–38.

VOILLEY, N. (2004). Acid-sensing ion channels (ASICs): new targets for the analgesic effects of non-steroid anti-inflammatory drugs (NSAIDs). *Curr. Drug Targets Inflamm. Allergy*, **3,** 71–79.

WALDMANN, R. & LAZDUNSKI, M. (1998). H^+-gated cation channels: neuronal acid sensors in the NaC/DEG family of ion channels *Curr. Opin. Neurobiol*., **8,** 418–424.

WALDMANN, R. (2001). Proton-gated cation channels-neuronal acid sensors in the central and peripheral nervous system. *Adv. Exp. Med. Biol*., **502,** 293–304.

References:

AKOPIAN, A.N. *et al*. (2000). *Neuroreport*, **11,** 2217–2222.

ASKWITH, C.C. *et al*. (2000). *Neuron*, **26,** 133–141.

BABINI, E. *et al*. (2002). *J. Biol. Chem*., **277,** 41597–41603.

BABINSKI, K. *et al*. (1999). *J. Neurochem*., **72,** 51–57.

BABINSKI, K. *et al*. (2000). *J. Biol. Chem*., **37,** 28519–28525.

BARON, A. *et al*. (2001). *J. Biol. Chem*., **276,** 35361–35367.

BASSILANA, F. *et al*. (1997). *J. Biol. Chem*., **272,** 28819–28822.

BEVAN, S. & YEATS, J. (1991). *J. Physiol. (Lond.)*, **433,** 145–161.

CHAMPIGNY, G. *et al*. (1998). *J. Biol. Chem*., **273,** 15418–15422.

CHEN, C.-C. *et al*. (1998). *Proc. Natl. Acad. Sci., U.S.A*., **95,** 10240–10245.

COSCOY, S. *et al*. (1999). *J. Biol. Chem*., **274,** 10129–10132.
DE WEILLE, J.R. *et al*. (1998). *FEBS Lett*., **433,** 257–260.
DEVAL, E. (2003). *Neuropharmacology*, **44,** 662–671.
ESCOUBAS, P. *et al*. (2000). *J. Biol. Chem*., **275,** 25116–25121.
GARCIA-ANOVEROS, J. *et al*. (1997). *Proc. Natl. Acad. Sci., U.S.A*., **94,** 1459–1464.
GRUNDER, S. *et al*. (2000). *Neuroreport*, **11,** 1607–1611.
IMMKE, D.C. & MCCLESKEY, E.W. (2003). *Neuron*, **37,** 75–84.
ISHIBASHI, K. & MARUMO, F. (1998). *Biochem. Biophys. Res. Commun*., **245,** 589–593.
LINGUEGLIA, E. *et al*. (1997). *J. Biol. Chem*., **272,** 29778–29783.
MAMET, J. *et al*. (2002). *J. Neurosci*., **22,** 10662–10670.
SAKAI, H. *et al*. (1999). *J. Physiol.(Lond.)*, **519,** 323–333.
SCHAEFER, L. *et al*. (2000). *FEBS Lett*., **471,** 205–210.
SUTHERLAND, S.P. *et al*. (2001). *Proc. Natl. Acad. Sci., U.S.A*., **98,** 711–716.
VOILLEY, N. *et al*. (2001). *J. Neurosci*., **21,** 8026–8033.
WALDMANN, R. *et al*. (1997a). *Nature*, **386,** 173–177.
WALDMANN. R. *et al*. (1997b). *J. Biol. Chem*., **272,** 20975–20978.
WEMMIE, J.A. *et al*. (2002). *Neuron*, **34,** 463–477.
WEMMIE, J.A. *et al*. (2003). *J. Neurosci*., **23,** 5496–5502.
XIE, J. *et al*. (2003). *J. Neurophysiol*., **89,** 2459–2465.

Calcium (voltage-gated)

Overview: Calcium (Ca^{2+}) channels are voltage-gated ion channels present in the membrane of most excitable cells. The nomenclature for Ca^{2+} channels was proposed by Ertel *et al*., (2000) and approved by the NC-IUPHAR subcommittee on Ca^{2+} channels (Catterall *et al*. 2002, 2003). Ca^{2+} channels form hetero-oligomeric complexes. The $\alpha 1$ subunit is pore-forming and provides the extracellular binding site(s) for practically all agonists and antagonists. The ten cloned α-subunits can be grouped into three families (1) the high voltage activated dihydropyridine-sensitive (L-type, $Ca_V1.x$) channels (2) the high-voltage activated dihydropyridine-insensitive ($Ca_V2.x$) channels and (3) the low-voltage-activated (T-type, $Ca_V3.x$) channels. Each $\alpha 1$ subunit has four homologous repeats (I–IV), each repeat having six transmembrane domains and a pore forming region between transmembrane domains S5 and S6. Gating is thought to be associated with the membrane spanning S4 segment which contains highly conserved positive charges. Many of the $\alpha 1$-subunit genes give rise to alternatively spliced products. At least for high-voltage activated channels, it is likely that native channels comprise co-assemblies of $\alpha 1$, β and $\alpha 2$-δ subunits. The γ subunits have not been proven to associate with channels other than $\alpha 1$s. The $\alpha 2$-$\delta 1$ and $\alpha 2$-$\delta 2$ subunits bind gabapentin and pregabalin.

Nomenclature	**$Ca_V1.1$**	**$Ca_V1.2$**	**$Ca_V1.3$**	**$Ca_V1.4$**	**$Ca_V2.1$**
Alternative names	L-type, α_{1S}, skeletal muscle L	L-type, α_{1C}, cardiac or smooth muscle L	L-type, α_{1D}	L-type, α_{1F}	P-type, Q-type, α_{1a}
Ensembl ID	ENSG00000081248	ENSG00000151067	ENSG00000157388	ENSG00000102001	ENSG00000141837
Activators	(−)-(S)-BayK8644, SZ(+)-(S)-202–791, FPL64176	(−)-(S)-BayK8644 SZ(+)-(S)-202–791 FPL64176	(−)-(S)-BayK8644	(−)-(S)-BayK8644	—
Blockers	Dihydropyridine antagonists e.g. nifedipine, diltiazem, verapamil, calciseptine	Dihydropyridine antagonists, e.g. nifedipine, diltiazem, verapamil, calciseptine	Verapamil, less sensitive to dihydropyridine antagonists	Less sensitive to dihydropyridine antagonists	ω-Agatoxin IVA, (P: $IC_{50} \sim 1$ nM) (Q: $IC_{50} \sim 90$ nM) ω-agatoxin IVB, ω-conotoxin MVIIC
Functional characteristics	High voltage-activated, slow inactivation	High voltage-activated, slow inactivation (Ca^{2+} dependent)	Low-moderate voltage-activated, slow inactivation (Ca^{2+} dependent)	Moderate voltage-activated, slow inactivation (Ca^{2+} independent)	Moderate voltage-activated, moderate inactivation

Nomenclature	**$Ca_V2.2$**	**$Ca_V2.3$**	**$Ca_V3.1$**	**$Ca_V3.2$**	**$Ca_V3.3$**
Alternative names	N-type, α_{1B}	R-type, α_{1E}	T-type, α_{1G}	T-type, α_{1H}	T-type, α_{1I}
Ensembl ID	ENSG00000148408	ENSG00000198216	ENSG00000006283	ENSG00000196557	ENSG00000100346
Blockers	ω-conotoxin GVIA, ω-conotoxin MVIIC	SNX482 (may not be completely specific), high Ni^{2+}	Mibefradil, low sens. to Ni^{2+}, kurtoxin SB-209712	Mibefradil, high sens. to Ni^{2+}, kurtoxin SB-209712	Mibefradil, low sens. to Ni^{2+}, kurtoxin SB-209712
Functional characteristics	High voltage-activated, moderate inactivation	Moderate voltage-activated, fast inactivation	Low voltage-activated, fast inactivation	Low voltage-activated, fast inactivation	Low voltage-activated, moderate inactivation

In many cell types, P and Q current components cannot be adequately separated and many researchers in the field have adopted the terminology 'P/Q-type' current when referring to either component.

Abbreviations: **FPL64176,** 2,5-dimethyl-4-[2(phenylmethyl)benzoyl]-H-pyrrole-3-carboxylate; **SB-209712,** (1,6,bis{1-[4-(3-phenylpropyl)piperidinyl]}hexane); **(-)-(S)-BAYK8664,** (-)-(S)-methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluromethylphenyl)-pyridine-5-carboxylate; **SNX482,** 41 amino acid peptide - (GVDKAG-CRYMFGGCSVNDDCCPRLGCHSLFSYCAWDLTFSD); **SZ(+)-(S)-202-791,** isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridine-carboxylate

Further reading:

CATTERALL, W.A. (2000). Structure and regulation of voltage-gated Ca^{2+} channels. *Ann. Rev. Cell Dev. Biol.,* **16,** 521–555.

CATTERALL, W.A., STRIESSNIG, J., SNUTCH, T.P. & PEREZ-REYES, E. (2002). Voltage-gated calcium channels. In: *The IUPHAR compendium of voltage-gated ion channels* (Catterall, W.A., Chandy, K.G. & Gutman, G.A. Ed.) pp 31 –56.

CATTERALL, W.A., STRIESSNIG, J., SNUTCH, T.P. & PEREZ-REYES, E. (2003). International Union of Pharmacology. XL. Compendium of Voltage-Gated Ion Channels: Calcium Channels. *Pharmacol. Rev.*, **55,** 579–581.

DOLPHIN, A.C. (2003). G protein modulation of voltage-gated calcium channels. *Pharmacol. Rev.*, **55,** 607–627.

ELMSLIE, K.S. (2004). Calcium channel blockers in the treatment of disease. *J. Neurosci. Res.*, **75,** 733–741.

ERTEL, E.A., CAMPBELL, K.P., HARPOLD, M.M., HOFMANN, F., MORI, Y., PEREZ-REYES, E., SCHWARTZ, A., SNUTCH, T.P., TANABE, T., BIRNBAUMER, L., TSIEN, R.W. & CATTERALL, W.A. (2000). Nomenclature of voltage-gated calcium channels. *Neuron,* **25,** 533–535.

HOFMANN, F., LACINOVA, L. & KLUGBAUER, N. (1999). Voltage-dependent calcium channels; from structure to function. *Rev. Physiol. Biochem. Pharmacol.,* **139,** 35–87.

KOCHEGAROV, A. A. (2003). Pharmacological modulators of voltage-gated calcium channels and their therapeutic application. *Cell Calcium*, **33,** 145–162.

KOSTYUK, P.G. (1999). Low-voltage-activated calcium channels: achievements and problems. *Neurosci.,* **92,** 1157–1163.

LEWIS, R.J. & GARCIA, M.L. (2003). Therapeutic potential of venom peptides. *Nature Rev. Drug Discov.*, **2,** 790–802.

PEREZ-REYES, E. (2003). Molecular physiology of low-voltage-activated T-type calcium channels. *Physiol. Rev.*, **83,** 117–161.

TERLAU, H. & OLIVERA, B.M. (2004). Conus venoms: a rich source of novel ion channel-targeted peptides. *Physiol. Rev.*, **84,** 41–68.

TRIGGLE, D.J. (1999). The pharmacology of ion channels: with particular reference to voltage-gated Ca^{2+} channels. *Eur. J. Pharmacol.,* **375,** 311–325.

TRIMMER, J.S. & RHODES, K.J. (2004). Localisation of voltage-gated ion channels in mammalian brain. *Ann. Rev. Physiol.*, **66,** 477–519.

WALKER, D. & DEWAARD, M. (1998). Subunit interaction sites in voltage-dependent calcium channels. *Trends Neurosci.,* **21,** 148–154.

Chloride

Overview: Chloride channels are a functionally and structurally diverse group of anion selective channels involved in numerous 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 & Droogmans, 2003). Excluding the transmitter-gated GABA and glycine receptors (see separate tables), well characterised chloride channels can be classified as the voltage-sensitive ClC subfamily, calcium-activated channels, high (maxi) conductance channels, the cystic fibrosis transmembrane conductance regulator (CFTR) and volume regulated channels. 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.

ClC-family: The mammalian ClC family (reviewed by Jentsch *et al*., 2002; Nilius & Droogmans, 2003, Dutzler, 2004) contains 9 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 through to ClC-5 can be functionally expressed as plasma membrane chloride channels. Similarly, ClC-Ka and ClC-Kb (largely expressed in the kidney) form functional chloride channels in association with barttin (ENSG00000162399), a 320 amino acid 2TM protein (Estévez *et al*., 2001). However, the location of several of these channels *in vivo* (*i.e*. CIC-3, ClC-4 and ClC-5) is likely to be predominantly intracellular. An intracellular location has been demonstrated for ClC-6 (ENSG00000011021) and ClC-7 (ENSG00000103249) also (reviewed by Jentsch *et al*., 1999; Waldegger & Jentsch, 2000). Alternative splicing increases the structural diversity within the ClC family (*e.g*. for ClC-2, ClC-3, ClC-5 and ClC-6). The crystal structure of two bacterial ClC channels has recently been described (Dutzler *et al*., 2002). Each ClC subunit, with a complex topology of 18 membrane-associated α-helices, 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 Estévez & Jentsch, 2002; Babini & Pusch, 2004; Dutzler, 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	—	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+}	DPC, Cd^{2+}, Zn^{2+}	3-phenyl-CPP, DIDS	3-phenyl-CPP, DIDS
Functional characteristics	$\gamma = 1-2$ pS; voltage-activated (depolarization); inwardly rectifying; deactivation upon repolarization (by fast gating of single pores and a slower common gate)	$\gamma = \sim 3$ pS; voltage-activated (hyperpolarization); inward rectification (steady state currents); slow inactivation (seconds); activated by cell swelling, PKA and extracellular acidosis; inhibited by phosphorylation by p34(cdc2)/cyclin B	$\gamma = 1$ pS; slight outward rectification; largely time-independent currents; inhibited by extracellular acidosis; potentiated by extracellular Ca^{2+}	$\gamma = 1$ pS; slight outward rectification; largely time-independent currents; inhibited by extracellular acidosis; potentiated by extracellular Ca^{2+}

Nomenclature	**ClC-3**	**ClC-4**	**ClC-5**
Ensemble ID	ENSG00000109572	ENSG00000073464	ENSG00000171365
Activators	High constitutive activity (disputed)	—	—
Blockers	DIDS (disputed), tamoxifen, (not DPC or 9-AC)	—	—
Functional characteristics	$\gamma = 40$ pS (at depolarised potentials); outward rectification; activity enhanced by cell swelling (disputed) and by CaM kinase II; inhibited by PKC activation (disputed); inactivates at positive potentials	$\gamma = \sim 3$ pS (at depolarised potentials) (disputed); extreme outward rectification (due to voltage dependence of γ?); largely time-independent currents; inhibited by extracellular acidosis; ATP hydrolysis required for full activity	extreme outward rectification; largely time-independent currents; inhibited by extracellular acidosis

ClC channels other than ClC-3 display the permeability sequence $Cl^- > Br^- > I^-$ (at physiological pH); for ClC-3, $I^- > Cl^-$. 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 repolarization and for stabilization of the membrane potential. *S*-(−)CPP and 9-AC act intracellularly and exhibit a strongly voltage-dependent block with strong inhibition at negative voltages and relief of block at depolarized potentials (reviewed by Pusch *et al*., 2002). Mutations in the ClC-1 gene result in myotonia congenita that can be either autosomal dominant (Thomsen's disease), or recessive (Becker myotonia). The prokaryotic homologue of ClC functions as a H^+-Cl^- exchanger, rather than as an ion channel (Accardi & Miller, 2004). Although ClC-2 can be activated by cell swelling, it does not correspond to the VRAC channel (see below). Alternative potential physiological functions for ClC-2 are reviewed by Strange (2002). Disruption of the ClC-2 gene in mice is associated with the degeneration of male germ cells and photoreceptors (Bösl *et al*. (2001)). Functional expression of human ClC-Ka and ClC-Kb requires the presence of barttin (Estévez *et al*., 2001). The rodent homologue (ClC-K1) of ClC-Ka demonstrates limited expression as a homomer, but its function is enhanced by barttin (Estévez *et al*., 2001). Knock out of the ClC-K1 channel induces nephrogenic diabetes insipidus (Matsumura *et al*., 1999). Classic (type III) Bartter's syndrome and Gitelman's variant of Bartter's syndrome are associated with mutations of the ClC-Kb chloride channel (Simon *et al*., 1996, 1997). ClC-Ka is approximately 5 to 6-fold more sensitive to block by 3-phenyl-CPP and DIDS than ClC-Kb. The biophysical and pharmacological properties of ClC-3, and the relationship of the protein to the endogenous volume-regulated anion channel(s) VRAC (see below) are controversial. Activation of heterologously expressed ClC-3 by cell swelling in response to hypotonic solutions is disputed, as are other aspects of regulation, including inhibition by PKC. Lack of chloride ion channel function of ClC-3 heterologously expressed in HEK 293 cells, and inserted into the plasma membrane, has additionally been claimed. However, phosphorylation by exogenously introduced CaM kinase II may be required for high activity of ClC-3 in this paradigm. In ClC-3 knock-out mice ($Clcn3^{-/-}$), volume regulated anion currents ($I_{Cl,swell}$) persist (Srobrawa *et al*., 2001; Arreola *et al*., 2002), and demonstrate kinetic, ionic selectivity and pharmacological properties similar to $I_{Cl,swell}$ recorded from cells of wild-type ($Clcn3^{+/+}$) animals, indicating that ClC-3 is not indispensable for such regulation (Yamamoto-Mizuma *et al*., 2004). However, both ClC-3 antisense and novel anti-ClC-3 antibodies are reported to reduce VRAC function in several cell systems (*e.g*. Hermoso *et al*., 2002; Wang *et al*., 2003), and the sensitivity of $I_{Cl,swell}$ to regulators such as PKC, $[ATP]_i$ and $[Mg^{2+}]_i$ differs between cells of $Clcn3^{(+/+)}$ and $Clcn3^{(-/-)}$ mice (Yamamoto-Mizuma *et al*., 2004). A splice variant of ClC-3 (*i.e*. ClC-3B) upregulated by NHERF, is expressed in the plasma membrane of epithelial cells and mediates outwardly rectifying currents activated by depolarisation. In association with CFTR, ClC-3B is activated by PKA. ClC-3B is a candidate for the outwardly rectifying chloride channel ORCC (Ogura *et al*., 2002). Results obtained from ClC-3 knock-out mice suggest an endosomal/synaptic vesicle location for the channel and a role, *via* the dissipation of electrical potential, in the acidification of vesicles. Mice lacking ClC-3 display total degeneration of the hippocampus

and retinal degeneration (Srobrawa *et al*., 2001). Loss-of-function mutations of ClC-5 are associated with proteinuria, hypercalciuria and kidney stone formation (Dent's disease). A ClC 5 knock-out provides a mouse model of this disease (Günther *et al*., 2003). Disruption of the ClC-7 gene leads to osteopetrosis in mice due to the ablation of ClC-7 from endosomes that are important for the function of osteoclasts (Kornak *et al*., 2001).

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, Δ508) results in impaired trafficking of CFTR and reduces its incorporation into the plasma membrane causing cystic fibrosis. In addition to acting as an anion channel *per se*, CFTR may act as a regulator of several other conductances including inhibition of the epithelial Na channel (ENaC), calcium activated chloride channels (CaCC) and volume regulated anion channel (VRAC), activation of the outwardly rectifying chloride channel (ORCC), and enhancement of the sulphonylurea sensitivity of the renal outer medullary potassium channel (ROMK2), (reviewed by Schwiebert *et al*., 1999; Nilius & Droogmans, 2003). CFTR also regulates TRPV4, which provides the Ca^{2+} signal for regulatory volume decrease 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 SLC26 transporters, an effect facilitated by PKA-mediated phosphorylation of the R domain of CFTR (Ko *et al*., 2004).

Nomenclature	**CFTR**
Ensemble ID	ENSG00000001626
Activators	Flavones (UCCF-339, UCCF-029, apigenin, genistein), benzimidazolones (UCCF-853, NS004), psoralens (8-methoxypsoralen), capsaicin
Blockers	$CFTR_{inh}$-172, glibenclamide
Functional characteristics	$\gamma = 6-10$ pS; permeability sequence $= Br \geqslant Cl > I > F$, ($P_{Na}/P_{Cl} = 0.1-0.03$); 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 like syntaxin 1A, Munc18 and PDZ domain proteins such as NHERF (EBP50) and CAP70

CFTR contains two cytoplasmic nucleotide binding domains (NBDs) that bind and hydrolyse ATP. A single open-closing cycle involves, in sequence: binding and hydrolysis of ATP at the N-terminal NBD1 (channel opening); ATP binding to the C-terminal NBD2 (stabilization of the open state) and subsequent ATP hydrolysis at NBD2 (channel closing). Phosphorylation, principally by PKA at sites that reside at least partially within a cytoplasmic regulatory (R) domain, regulates cycles of ATP hydrolysis and ADP/ATP exchange. PKC (and PKGII within intestinal epithelial cells *via* guanylin-stimulated cGMP formation) positively regulate CFTR activity (see Gadsby & Nairn, 1999). A recent model proposes that the regulation of channel activity by PKA is dependent upon interdomain interactions wherein acidic residues within the N-terminal cytoplasmic region associate with the R domain to stabilise channel activity.

Calcium activated chloride channel: Chloride channels activated by intracellular calcium (CaCC) are widely expressed in excitable and non-excitable cells. The molecular nature of CaCC is unclear. Numerous putative calcium-activated chloride channel proteins (the CLCA family) have been cloned from human and other species (reviewed by Frings *et al*., 2000; Fuller & Benos, 2000; Pauli *et al*., 2000), but their relationship to endogenous CaCC remains to be established (reviewed by Jentsch *et al*., 2002). Some CLCAs appear to function as cell adhesion proteins, or are secreted proteins. Calcium activated Cl^- currents ($I_{Cl(Ca)}$) can be recorded from Ehrlich ascites tumor cells in the absence of detectable expression of mCLCA1, 2 or 3 (Papassotiriou *et al*., 2001). In addition, the kinetics, pharmacological regulation, and the calcium sensitivity of CLCA family members and native CaCC differ significantly (*e.g*. Britton *et al*., 2002). However, a recent report raises the possibility that the properties of CLCA isoforms may modified by auxillary subunits (Greenwood *et al*., 2002). A member of a novel family of chloride channels (the bestrophins), with a phenotype distinct to that of CLCAs, has recently been shown to be an anion selective channel, activated by physiological concentrations of intracellular Ca^{2+}, in an heterologous expression system (Qu *et al*., 2003; 2004).

Nomenclature	**CaCC**
Other names	Ca^{2+}-activated Cl^- channel
Activators	Intracellular Ca^{2+}
Blockers	Niflumic acid, DPDPC, DIDS, SITS, NPPB, 9-AC, NPA, Ins(3,4,5,6)P_4, mibefradil, fluoxetine
Functional characteristics	$\gamma = 0.5-5$ pS; permeability sequence, $SCN > I > Br > Cl >$ gluconate; 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, 9-AC, NPA and Ins(3,4,5,6)P_4 is voltage-dependent whereas block by DIDS, mibefradil and NPPB is voltage-independent. Extracellular niflumic acid and DCDPC (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 $[Ca^{2+}]_i$ (Piper *et al*., 2002). CaMKII modulates CaCC in a tissue dependent manner. CaMKII inhibitors block activation of $I_{Cl(Ca)}$ in T_{84} cells but have no effect in parotid acinar cells (reviewed by Jentsch *et al*., 2002). 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.

Maxi chloride channel: 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 and human placenta syncytiotrophoblasts. The physiological significance of the maxi Cl^- channel is uncertain, but roles in cell volume regulation and apoptosis have been claimed. Recent 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 family of human high conductance Cl^- channels (TTYH1-3) that resemble Maxi Cl^- channels has recently been cloned (Suzuki & 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-estrogens (tamoxifen, toremifine), extracellular chlorpromazine and trifluprom azine, cell swelling
Blockers	SITS, DIDS, NPPB, DPC, intracellular arachidonic acid, extracellular Zn^{2+} and Gd^{3+}
Functional characteristics	$\gamma = 280-430$ pS (main state); permeability sequence, $I > Br > Cl > F >$ gluconate ($P_{Cl}/P_{Na} = 9-26$); 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 γ reported in the literature ($K_m = 120$ mM in symmetrical Cl^-). Inhibition by arachidonic acid (and *cis*-unsaturated fatty acids) is voltage-independent, occurs at an intracellular site, and involves both channel shut down ($K_d = 4-5\,\mu$M) and a reduction of γ ($K_d = 13-14\,\mu$M). 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 pre-treatment 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 (Henriquez and Riquelme, 2002).

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 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 and apoptosis (reviewed by Nilius & Droogmans, 2003; Okada *et al*., 2004). 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. Although ClC-3, and most recently ClC-3B, has been suggested to form, or contribute to, VRAC in heart and smooth muscle the molecular identity of VRAC remains uncertain. Inconsistencies between studies that include lack of effect of hypotonic solutions upon currents attributed to heterologously expressed ClC-3 lack of expression, or function, of ClC-3 at the plasma membrane and the persistence of swelling-activated anion currents ($I_{Cl,swell}$) with the characteristics of VRAC in ClC-3, knock-out mice cast doubt upon the purported relationship between ClC-3 and VRAC. Evidence for a link between ClC-3 and VRAC is provided by the suppression, in native cells, of volume-activated Cl currents by anti-ClC-3 antibodies. However, the specificity one antibody employed (Alm C592-661) has been questioned. Several former VRAC candidates including *MDR1* P-glycoprotein, Icln, Band 3 anion exchanger and phospholemman are no longer considered likely to fulfil this function (see reviews by Nilius *et al*.,1999; Jentsch *et al*., 2002; d'Angelmont de Tassigny *et al*., 2003; Nilius & 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	DCPIB (most selective agent available), clomiphene, nafoxidine, mefloquine, tamoxifen, gossypol, arachidonic acid, mibefradil, NPPB, quinine, quinidine, chromones, NDGA, 9-AC, DIDS, 1,9-dideoxyforskolin, oxalon dye (diBA-(5)-C4), extracellular nucleotides, nucleoside analogues, intracellular Mg^{2+}
Functional characteristics	$\gamma = 10-20$ pS (negative potentials), 50–90 pS (positive potentials); permeability sequence $SCN > I > NO_3^- > Br^- > Cl^- > F^- >$ gluconate; outward rectifcation 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; tyrosine phosphorylation step(s) may modulate channel activation; swelling induced activation of VRAC requires a functional Rho-Rho kinase - MLCK phosphorylation pathway, but not activation of the pathway (*i.e*. a permissive effect); 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 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 and, as noted above, possibly ClC-3B (Ogura *et al*., 2002). A cAMP-activated Cl^- channel that does not correspond to CFTR has been described in intestinal Paneth cells (Tsumura *et al*., 1998). Bestrophins comprise a new group of molecularly identified Cl^- channels that, at least in one case, can be activated by intracellular calcium at physiological concentrations (Qu *et al*., 2003, 2004).

Abbreviations: **9-AC**, anthracene-9-carboxylic acid; **CFTR$_{inh}$-172**, 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; ***S*-(-) CPP**, *S*-(-)2-(4-chlorophenoxy)propionic acid; ***S*-(-)CPB**, *S*-(-)2-(4-chlorophenoxy)butyric acid; **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; **DPC**, diphenylamine carboxylic acid; **DPDPC**, dichloro-diphenylamine 2-carboxylic acid; **NDGA**, nordihydroguaiaretic acid; **NPA**, N-phenylanthracilic acid; **NPPB**, 5-nitro-2-(3-phenylpropylamino)benzoic acid; **NS004**, 5-trifluoromethyl-(5-chloro-2-hydroxyphenyl)-1,3-dihydro-2*H*-benzimidazole-2-one; **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

Further reading:

AKABAS, M.H. (2000). Cystic fibrosis transmembrane conductance regulator; structure and function of an epithelial chloride channel. *J. Biol. Chem*., **275,** 3729–3732.

BABINI, E. & PUSCH M.A. (2004). Two-holed story: Structural secrets about ClC proteins become unraveled? *Physiology (Bethesda)*, **19,** 293–299.

BEGENISICH, T. & MELVIN, J.T. (1998). Regulation of chloride channels in secretory epithelia. *J. Membr. Biol*., **163,** 77–85.

D'ANGLEMONT DE TASSINGNY, A., SOUKTANI, R., GHALEH, B., HENRY, P. & BERDEAUX, A. (2003). Structure and pharmacology of swelling-sensitive chloride channels, $I_{Cl,swell}$. *Fundam. Clin. Pharmacol*., **17,** 539–553.

DUTZLER, R. (2004). The structural basis of ClC chloride channel function. *Trends Neurosci*., **27,** 315–320.

EGGERMONT, J., TROUET, D., CARTON, I. & NILIUS, B. (2001). Cellular function and control of volume regulated anion channels. *Cell Biochem. Biophys*., **35,** 263–274.

ESTÉVEZ, R. & JENTSCH, T.J. (2002). CLC chloride channels: correlating structure with function. *Curr. Opin. Struct. Biol*., **12,** 531–539.

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

FRINGS, S., REUTER, D. & KLEENE, S.J. (2000). Neuronal Ca^{2+}-activated Cl^- channels – homing in on an elusive channel species. *Prog. Neurobiol*., **60,** 247–289.

FULLER, C.M. AND BENOS, D.J. (2000). Ca^{2+}-activated Cl^- channels: a newly emerging anion transport family. *News Physiol. Sci*., **15,** 165–171.

GADSBY, D. & NAIRN, A.C. (1999). Control of CFTR channel gating by phosphorylation and nucleotide hydrolysis. *Physiol. Rev*., **79** (Suppl 1), S77-S107.

GUNTHER, W., PIWON, N. & JENTSCH T.J. (2003). The ClC-5 chloride channel knock-out mouse–an animal model for Dent's disease. *Pflüger's Arch*., **445,** 456–462.

GREENWOOD, I.A. & LARGE, W.A. (1999). Properties and role of chloride channels in smooth muscle In: *Chloride Channels* (Kozlowski, R. Ed.) pp. 121–136, ISIS Medical Media, Oxford.

JENTSCH, T.J., STEIN, V., WEINREICH, F. & ZDEBIK, A.A. (2002). Molecular structure and physiological function of chloride channels. *Physiol. Rev*., **82,** 503–568.

KIDD, J.F. & THORN, P. (2000). Intracellular Ca^{2+} and Cl^- channel activation in secretory cells. *Annu. Rev. Physiol*., **62,** 493–513.

KIRK, K.L. (2000). New paradigms of CFTR chloride channel regulation *Cell Mol. Life Sci*., **57,** 623–634.

LARGE, W.A. & WANG, Q. (1996). Characteristics and physiological role of the Ca^{2+}-activated Cl^- conductance in smooth muscle. *Am. J. Physiol*., **271,** C435–C454.

NAREN, A.P. & KIRK, K.L. (2000). CFTR chloride channels: binding partners and regulatory networks. *News Physiol. Sci*., **15,** 57–61.

NILIUS, B. & DROOGMANS, G. (2003). Amazing chloride channels: an overview. *Acta. Physiol. Scand*., **177,** 119–147.

NILIUS, B., EGGERMONT, J. & DROOGMANS, G. (2000). The endothelial volume-regulated anion channel, VRAC. *Cell Physiol. Biochem*., **10,** 313–320.

NILIUS, B., VOETS, T., EGGERMONT, J. & DROOGMANS, G. (1999) VRAC: a multifunctional volume-regulated anion channel in vascular epithelium. In: *Chloride Channels* (Kozlowski, R. Ed.) pp. 47–63, ISIS Medical Media, Oxford.

OKADA, Y., MAENO, E., SHIMIZU, T., MANABE, K., MORI, S. & NABEKURA, T. (2004). Dual roles of plasmalemmal chloride channels in induction of cell death. *Pflügers Arch*., **448,** 287–295.

PAULI, B.U., ABDEL-GHANY, M., CHENG, H.C., GRUBER, A.D., ARCHIBALD, H.A. & ELBLE, R.C. (2000). Molecular characteristics and functional diversity of Clca family members. *Clin. Exp. Pharmacol. Physiol*., **27,** 901–905.

PUSCH, M., ACCARDI, A., LIANTONIO, A., GUIDA, P., TRAVERSO, S., CAMERINO, D.C. & CONTI, F. (2002). Mechanisms of block of muscle type CLC chloride channels. *Mol. Membr. Biol*. **19,** 285–292.

PUSCH, M. (2004). Structural insights into chloride and proton-mediated gating of CLC chloride channels. *Biochemistry*, **43,** 1135–1144.

SARDINI, A., AMEY, J.S., WEYLANDT, K.H., NOBLES, M., VALVERDE, M.A. & HIGGINS, C.F. Cell volume regulation and swelling-activated chloride channels. *Biochim. Biophys. Acta*., **1618,** 153–162.

SCHULTZ, R.D., SINGH, A.K., DEVOR, D.C. & BRIDGES, R.J. (1999). Pharmacology of CFTR chloride channel activity. *Physiol. Rev*., **79** (Suppl 1), S109–S144.

SCHWIEBERT, E.M., BENOS, D.J., EGAN, M.E., STUTTS, M.J. & GUGGINO, W.B. (1999). CFTR is a conductance regulator as well as a chloride channel. *Physiol. Rev*., **79** (Suppl 1), S145-S166.

STRANGE, K. (2002). Of mice and worms: Novel insights into ClC-2 anion channel physiology. *News Physiol. Sci*., **17,** 11–16.

THIAGARAJAH, J.R. & VERKMAN, A.S. (2003). cftr pharmacology and its role in intestinal fluid secretion. *Curr. Opin. Pharmacol*., **3,** 594–599.

WALDEGGER, S. & JENTSCH, T.J. (2000). From tonus to tonicity: physiology of ClC chloride channels. *J. Am. Soc. Nephrol*., **11,** 1331–1339.

References:

ACCARDI, A. & MILLER, C. (2004). *Nature*, **427,** 803–807.

ARNIGES, M. *et al*. (2004). *J. Biol. Chem*., Oct 15 **297**, 54062–54068.

ARREOLA, J. *et al*. (2002). *J. Physiol*., **545.1,** 207–216.

BAHAMONDE, M.I. *et al*., *J. Biol. Chem*. **278,** 33284–33289.

BRITTON, F.C. *et al*. (2002). *J. Physiol*., **539.1,** 107–117.

BÖSL, M.R. *et al*. (2001). *EMBO J*., **20,** 1289–1299.

DIAZ, M. *et al*. (2001). *J. Physiol*., **536.1,** 79–88.

DUTTA, A.K. *et al*. (2002). *J. Physiol*., **542.3,** 803–816.

DUTZLER, R. *et al*. (2002). *Nature*, **415,** 287–294.

ESTÉVEZ, R. *et al*. (2001). *Nature*, **414,** 558–561.

GREENWOOD, I.A. *et al*. (2002). *J. Biol. Chem*., **277,** 22119–22122.

HENRIQUEZ, M. & RIQUELME, G. (2002). *J. Membrane Biol*., **191,** 59–68.

HERMOSO, M. *et al*. (2002). *J. Biol. Chem*., **277,** 40066–40074.

KO, S.B.H. *et al*. (2004). *Nat. Cell. Biol*., **6,** 343–350.

KORNAC, U. *et al*. (2001). *Cell*, **104,** 205–215.

LIANTONIO, A. *et al*. (2002). *Mol. Pharmacol*., **62,** 265–271.

MATSUMURA, Y. *et al*. (1999). *Nat. Genet*., **21,** 95–98.

OGURA, T. *et al*. (2002). FASEB J. **16,** 863–865.

OKADA, S.F. *et al*. (2004). *J. Gen. Physiol*. **124,** 513–526.

PAPASSOTIRIOU, J. *et al*. (2001). *Pflügers Arch*., **442,** 273–279.

PIPER, A.S. *et al*. (2002). *J. Physiol*., **539.1,** 119–131.

QU, Z *et al*. (2003). *J. Biol. Chem*., **278,** 49563–49572.

QU, Z *et al*. (2004). *J. Gen. Physiol*. **123,** 327–340.

SABIROV, R.Z. *et al*. (2001). *J. Gen. Physiol*., **118,** 251–266.

SIMON, D.B. *et al*. (1996). *Nature Genet*., **12,** 24–30.

SIMON, D.B. *et al*. (1997). *Nature Genet*., **17,** 171–178.

STALEY, K. *et al*. (1996). *Neuron*, **17,** 543–551.

STOBRAWA, S.M. *et al*. (2001). *Neuron*, **29,** 185–196.

SUZUKI, M. & MIZUNO, A. (2004). *J. Biol. Chem*., **279,** 22461–22468.

TSUMURA, T. *et al*. (1998). *J. Physiol*., **512,** 765–777.

WANG, G.X. *et al*. (2003). *Am. J. Physiol. Heart Circ. Physiol*., **285,** H1453–463.

YAMAMOTO-MIZUMA, S. *et al*. (2004). *J. Physiol*., **557,** 439–356.

Cyclic nucleotide-gated (CNG)

Overview: Cyclic nucleotide-gated (CNG) channels are responsible for signalling in the primary sensory cells of the vertebrate visual and olfactory systems. A standardised nomenclature for CNG channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels (see Hofmann *et al*., 2002, 2003).

CNG channels are voltage-independent cation channels formed as tetramers. Each subunit has 6TM with the pore-forming domain between TM5 and TM6. CNG channels were first found in rod photoreceptors (Fesenko *et al*., 1985; Kaupp *et al*., 1989), where light signals through rhodopsin and transducin to stimulate phosphodiesterase and reduce intracellular cGMP level. This results in a closure of CNG channels and a reduced 'dark current'. Similar channels were found in the cilia of olfactory neurons (Nakamura & Gold, 1987) and the pineal gland (Dryer & Henderson, 1991). The cyclic nucleotides bind to a domain in the C terminus of the subunit protein: other channels directly binding cyclic nucleotides include HCN, eag and certain plant potassium channels.

Nomenclature	**CNGA1**	**CNGA2**	**CNGA3**
Other Names	CNG1, CNGα1, RCNC1	CNG2, CNGα3, OCNC1	CNG3, CNGα2, CCNC1
Ensembl ID	ENSG00000198515	ENSG00000183862	ENSG00000144191
Activators	Intracellular cyclic nucleotides: cGMP ($EC_{50} \approx 30\ \mu M$) $\gg$ cAMP	Intracellular cyclic nucleotides: cGMP $\approx$ cAMP ($EC_{50} \approx 1\ \mu M$)	Intracellular cyclic nucleotides: cGMP ($EC_{50} \approx 30\ \mu M$) $\gg$ cAMP
Inhibitors	L-*cis* diltiazem	—	L-*cis* diltiazem
Functional characteristics	$\gamma = 25-30$ pS P_{Ca}/P_{Na} 3.1	$\gamma = 35$ pS P_{Ca}/P_{Na} 6.8	$\gamma = 40$ pS P_{Ca}/P_{Na} 10.9

CNGA1, CNGA2 and CNGA3 express functional channels as homomers. Three additional subunits CNGA4 (Genbank protein AAH40277), CNGB1 (Q14028) and CNGB3 (NP_061971) do not, and are referred to as auxiliary subunits. The subunit composition of the native channels is believed to be as follows. Rod: $CNGA1_3$/CNGB1a; Cone: $CNGA3_2$/$CNGB3_2$; Olfactory neurons: $CNGA2_2$/CNGA4/CNGB1b (Weitz *et al*., 2002; Zheng *et al*., 2002; Zhong *et al*., 2002; Peng *et al*., 2004; Zheng & Zagotta, 2004).

Further reading:

HOFMANN, F., BIEL, M. & KAUPP, U.B. (2002). Cyclic nucleotide-modulated channels. In: *The IUPHAR compendium of voltage-gated ion channels* (Catterall, W.A., Chandy, K.G. & Gutman, G.A. Ed.) pp 191–206.

HOFMANN, F., BIEL, M. & KAUPP, U.B. (2003) International Union of Pharmacology. XLII. Compendium of Voltage-Gated Ion Channels: Cyclic Nucleotide-Modulated Channels. *Pharmacol. Rev*., **55,** 587–589.

KAUPP, U.B. &, SEIFERT, R. (2002). Cyclic nucleotide-gated ion channels. *Physiol. Rev.,* **82**, 769–824.

References:

DRYER, S.E. & HENDERSON, D. (1991). *Nature*, **353,** 756–758.

FESENKO, E.E. *et al*. (1985). *Nature*, **313,** 310–313.

KAUPP, U.B., *et al*. (1989). *Nature*, **342,** 762–766.

NAKAMURA, T. & GOLD, G.H. (1987). *Nature,* **325**, 442–444.

PENG, C.H. *et al*. (2004) *Neuron*, **42,** 401–410.

WEITZ, D. *et al*. (2002). *Neuron*, **36**, 881–889.

ZHENG, J. *et al*. (2002). *Neuron,* **36**, 891–896.

ZHENG, J. & ZAGOTTA, W.N. (2004). *Neuron*, **42,** 411–421.

ZHONG, H. *et al*. (2002). *Nature*, **420,** 193–198.

Epithelial sodium channels (ENaC)

Overview: Epithelial sodium channels are responsible for sodium reabsorption by the epithelia lining the distal part of the kidney tubule, and fulfil similar functional roles in some other tissues such as the alveolar epithelium and the distal colon. This reabsorption of sodium is regulated by aldosterone, vasopressin and glucocorticoids, and is one of the essential mechanisms in the regulation of sodium balance, blood volume and blood pressure. ENaC expression is also vital for lung fluid balance (Hummler *et al*., 1996). Sodium reabsorption is suppressed by the 'potassium-sparing' diuretics amiloride and triamterene. The first ENaC subunit (α) was isolated by expression cloning, using a cDNA library derived from the colon of salt-deprived rats, as a current sensitive to inhibition by amiloride (Canessa *et al*., 1993). Two further subunits (β and γ) were identified by functional complementation of the α subunit (Canessa *et al*., 1994). A related δ subunit was later identified (Waldmann *et al*., 1995) that has a wider tissue distribution. ENaC subunits contain 2 putative TM domains connected by a large extracellular loop and short cytoplasmic amino- and carboxy-termini. The stoichiometry of the epithelial sodium channel in the kidney and related epithelia is thought to be predominantly a heterotetramer of 2α:1β:1γ subunits (Firsov *et al*., 1998).

Nomenclature	**Epithelial sodium channel (ENaC)**
Ensembl ID	α subunit, ENSG00000111319; β subunit, ENSG00000168447; γ subunit, ENSG00000166828; δ subunit, ENSG00000162572
Blockers (IC_{50})	Amiloride (100–200 nM), benzamil ($\sim$10 nM), triamterene ($\sim 5\,\mu$M) (Canessa *et al*., 1994; Kellenberger *et al*., 2003)
Functional characteristics	$\gamma \approx 4$–5 pS, $P_{Na}/P_K > 20$; tonically open at rest; expression and ion flux regulated by circulating aldosterone-mediated changes in gene transcription, action of aldosterone competitively antagonised by spironolactone and its more active metabolite, canrenone. Glucocorticoids are important functional regulators in lung/airways and this control is potentiated by thyroid hormone, but the mechanism underlying such potentiation is unclear (Barker *et al*., 1990; Sayegh *et al*., 1999; Richard *et al*., 2004). The density of channels in the apical membrane, and hence G_{Na}, can be controlled *via* cAMP/PKA (Morris and Schafer, 2002).

Data in the table refer to the $2\alpha\beta\gamma$ heteromer. There are several human diseases resulting from mutations in ENaC subunits, or their regulation, most of which lead to over-expression or under-expression of the channel in epithelia. The best known of these is Liddle's syndrome, usually associated with gain-of-function mutations in the β and γ subunits that result in decreased downregulation of ENaC (Rotin *et al*., 1994; Staub *et al*., 1996). Pseudohypoaldosteronism type 1 (PHA-1) can occur through either mutations in the gene encoding the mineralocorticoid receptor, or mutations in genes encoding ENaC subunits (see Bonny & Hummler, 2000).

Further reading:

ALVAREZ DE LA ROSA, D., CANESSA, C.M., FYFE, G.K. & ZHANG, P. (2000). Structure and regulation of amiloride-sensitive sodium channels. *Annu. Rev. Physiol*., **62,** 573–594.

BONNY, O. & HUMMLER, E. (2000). Dysfunction of epithelial sodium transport: from human to mouse. *Kidney Int*., **57,** 1313–1318.

GORMLEY, K., DONG, Y. & SAGNELLA, G.A. (2003). Regulation of the epithelial sodium channel by accessory proteins. *Biochem. J*., **371,** 1–14.

KELLENBERGER, S. & SCHILD, L. (2002). Epithelial sodium channel/degenerin family of ion channels: a variety of functions for a shared structure. *Physiol. Rev*., **82,** 735–767.

ROSSIER, B.C., PRADERVAND, S., SCHILD, L. & HUMMLER, E. (2002). Epithelial sodium channel and the control of sodium balance: interaction between genetic and environmental factors. *Annu. Rev. Physiol.,* **64,** 877–897.

SCHILD, L. (2004). The epithelial sodium channel: from molecule to disease. *Rev. Physiol. Biochem. Pharmacol*., **151,** 93–107.

References:

BARKER, P.M. *et al*. (1990). *J. Physiol*. **424,** 473–485.

CANESSA, C.M. *et al*. (1993). *Nature,* **361,** 467–470.

CANESSA, C.M. *et al*. (1994). *Nature,* **367,** 463–466.

FIRSOV, D. *et al*. (1998). *EMBO J.,* **17,** 344–352.

HUMMLER, E. *et al*. (1996). *Nature Genet*., **12,** 325–328.

KELLENBERGER, S. *et al*. (2003). *Mol. Pharmacol*., **64,** 848–856.

MORRIS, R.G. & SCHAFER, J.A. (2002). *J. Gen. Physiol*., **120,** 71–85.

ROTIN, D. (1994). *EMBO J.,* **13,** 4440–4450.

RICHARD, K. *et al*. (2004). *FEBS Lett*., **576,** 339–342.

SAYEGH, R. *et al*. (1999). *J. Biol. Chem*., **274,** 12431–12437.

STAUB, O. *et al*. (1996). *EMBO J.,* **15,** 2371–2380.

WALDMANN, R. *et al*. (1995). *J. Biol. Chem*., **270,** 27411–27414.

HCN (hyperpolarisation-activated, cyclic nucleotide-gated)

Overview: The hyperpolarisation-activated, cyclic nucleotide-gated (HCN) channels are cation channels that are activated by hyperpolarisation to voltages negative to ~ -50 mV (Gauss *et al*., 1998, Ludwig *et al*., 1998, Santoro *et al*., 1998). The cyclic nucleotides cAMP and cGMP directly activate the channels and shift the activation curves of HCN channels to more positive voltages, thereby enhancing channel activity (DiFrancesco & Tortora, 1991). HCN channels underlie pacemaker currents found in many excitable cells including cardiac cells and neurons (DiFrancesco, 1993; Pape, 1996). In native cells, these currents have a variety of names such as I_h, I_q and I_f. The four known HCN channels have 6 transmembrane domains and form tetramers. It is believed that the channels can form heteromers with each other, as has been shown for HCN1 and HCN4 (Altomare *et al*., 2003). A standardised nomenclature for HCN channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels (see Hofmann *et al*., 2002; 2003).

Nomenclature	**HCN1**	**HCN2**	**HCN3**	**HCN4**
Ensembl ID	ENSG00000164588	ENSG00000099822	ENSG00000143630	ENSG00000138622
Activators	cAMP > cGMP (both weak)	cAMP > cGMP	—	cAMP > cGMP
Inhibitors	Cs^+, ZD7288	Cs^+, ZD7288	Cs^+, ZD7288	Cs^+, ZD7288

HCN channels are permeable to both Na^+ and K^+ ions with a Na^+/K^+ permeability ratio of about 0.2. Functionally, they differ from each other in terms of time constant of activation with HCN1 fastest, HCN4 slowest and HCN2 & HCN3 intermediate. The compounds ZD7288 (BoSmith *et al*., 1993) and ivabradine (Bucchi *et al*., 2002) have proven useful in identifying and studying functional HCN channels in native cells.

Abbreviation: Ivabradine (S16257-2), (3-(3-{[((7S)-3,4-dimethoxybicyclo [4,2,0] octa-1,3,5-trien7-yl) methyl] methylamino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one hydrochloride; **ZD7288,** [4-(N-ethyl-N-phenyl-amino)-1,2-dimethyl-6-(methylamino)pyrimidinium chloride.

Further reading:

BIEL, M., LUDWIG, A., ZONG, X., HOFMANN, F. (1999). Hyperpolarisation-activated cation channels: a multi-gene family. *Rev. Physiol. Biochem. Pharmacol*., **136,** 165–181.

BIEL, M., SCHNEIDER, A. & WAHL, C. (2002). Cardiac HCN channels: Structure, function and modulation. *Trends in Cardiovasc. Med*., **12,** 206–213.

DIFRANCESCO, D. (1993). Pacemaker mechanisms in cardiac tissue. *Ann. Rev. Physiol*., **55,** 455–472.

DIFRANCESCO, D. & CAMM, J.A. (2004). Heart rate lowering by specific and selective I-f current inhibition with ivabradine – A new therapeutic perspective in cardiovascular disease. *Drugs*, **64,** 1757–1765.

HOFMANN, F., BIEL, M. & KAUPP, U.B. (2002). Cyclic nucleotide-modulated channels. In: *The IUPHAR compendium of voltage-gated ion channels* (Catterall, W.A., Chandy, K.G. & Gutman, G.A. Ed.) pp 191–206.

HOFMANN, F., BIEL, M. & KAUPP, U.B. (2003) International Union of Pharmacology. XLII. Compendium of Voltage-Gated Ion Channels: Cyclic Nucleotide-Modulated Channels. *Pharmac. Rev*., **55,** 587–589.

KAUPP, U.B. & SEIFERT, R. (2001). Molecular diversity of pacemaker ion channels. *Ann. Rev. Physiol*., **63,** 235–257.

PAPE, H.C. (1996) Queer current and pacemaker: the hyperpolarisation-activated cation current in neurons. *Ann. Rev. Physiol*., **58,** 299–327.

References:

ALTOMARE, C. *et al*. (2003). *J. Physiol*., **549,** 347–359.

BOSMITH, R.E. *et al*. (1993). *Br. J. Pharmacol*., **110,** 343–349.

BUCCHI, A. *et al*. (2002). *J. Gen. Physiol*., **120,** 1–13.

DIFRANCESCO, D. & TORTORA, P. (1991). *Nature*, **351,** 145–147.

GAUSS, R. *et al*. (1998). *Nature*, **393,** 583–587.

LUDWIG, A. *et al*. (1998). *Nature*, **393,** 587–591.

SANTORO, B. *et al*. (1998). *Cell*, **93,** 717–729.

IP_3 receptor

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

Nomenclature	**IP_3R1**	**IP_3R2**	**IP_3R3**
Other names	INSP3R1	INSP3R2	INSP3R3
Ensembl ID	ENSG00000150995	ENSG00000123104	ENSG00000096433
Endogenous activators	$Ins(1,4,5)P_3$ (nM – μM), cytosolic Ca^{2+} (<750 μM), cytosolic ATP (<mM)	$Ins(1,4,5)P_3$ (nM – μM), cytosolic Ca^{2+} (nM)	$Ins(1,4,5)P_3$ (nM-μM), cytosolic Ca^{2+} (nM)
Pharmacological activators	$InsP_3$ analogues including $Ins(2,4,5)P_3$, adenophostin A (nM)	$InsP_3$ analogues including $Ins(2,4,5)P_3$, adenophostin A (nM)	—
Antagonists	Xestospongin C (μM), phosphatidylinositol 4,5-bisphosphate (μM), caffeine (mM), heparin (μg/ml), decavanadate (μM), calmodulin at high cytosolic Ca^{2+}	Heparin (μg/ml), decavanadate (μM)	Heparin (µg/ml), decavanadate (μM)
Functional characteristics	Ca^{2+}: ($P_{Ba}/P_K \sim 6$) single channel conductance ~ 70 pS (50 mM Ca^{2+})	Ca^{2+}: single channel conductance ~ 70 pS (50 mM Ca^{2+}), ~ 390 pS (220 mM Cs^+)	Ca^{2+}: single channel conductance ~ 88 pS (55 mM Ba^{2+})

The absence of a modulator of a particular isoform of receptor indicates that the action of that modulator has not been determined, not that it is without effect. A region of IP_3R1 likely to be involved in ion translocation and selection has been identified (Ramos-Franco *et al*., 1999) and information on subunit oligomerization and topology are also available (Galvan *et al*., 1999).

Abbreviation: FKBP, FK506 binding protein

Further reading:

BERRIDGE, M.J., LIPP, P. & BOOTMAN, M.D. (2000). The versatility and universality of calcium signalling. *Nature Rev. Mol. Cell Biol*., **1,** 11 – 21.

BEZPROZVANNY, I. & EHRLICH, B.E. (1995). The inositol 1,4,5-trisphospate (Insp (3)) receptor. *J. Memb. Biol*., **145,** 205 – 216.

BOOTMAN, M.D., BERRIDGE, M.J. & RODERICK, H.L. (2002). Calcium signalling: More messengers, more channels, more complexity. *Curr. Biol*., **12,** R563 – 565.

BULTYNCK, G., SIENAERT, I., PARYS, J.B., CALLEWAERT, G., DE SMEDT, H., BOENS, N., DEHAEN, W. & MISSIAEN, L. (2003). Pharmacology of inositol trisphosphate receptors. *Pflügers Archiv*, **445,** 629 – 642.

EHRLICH, B.E. (1995). Function properties of intracellular calcium release channels. *Curr. Op. Neurobiol*., **5,** 304 – 309.

FURUICHI, T. & MIKOSHIBA, K. (1995). Inositol 1,4,5-trisphosphate receptor-mediated Ca^{2+} signaling in the brain. *J. Neurochem*., **64,** 953 – 960.

JOSEPH, S.K. (1996). The inositol trisphosphate receptor family. *Cellular Signalling*, **8,** 1 – 7.

MIKOSHIBA, K. (1997). The $InsP_3$ receptor and intracellular Ca^{2+} signalling. *Curr. Op. Neurobiol*., **7,** 339 – 345.

PATEL, S., JOSEPH, S.K. & THOMAS, A.P. (1999). Molecular properties of inositol 1,4,5-trisphosphate receptors. *Cell Calcium*, **25,** 247 – 264.

TAYLOR, C.W. & TRAYNOR, D. (1995). Calcium and inositol trisphosphate receptors. *J. Memb. Biol*., **145,** 109 – 118.

TAYLOR, C.W. & BROAD, L.M. (1998). Pharmacological analysis of intracellular Ca^{2+} signalling: problems and pitfalls. *Trends Pharmacol. Sci*., **19,** 370 – 375.

WILCOX, R.A., PRIMROSE, W.U., NAHOSRSKI, S.R. & CHALLISS, R.A.J. (1998). New developments in the molecular pharmacology of the *myo*-inositol 1,4,5-trisphosphate receptor. *Trends Pharmacol. Sci*., **19,** 467 – 475.

VERKHRATSKY, A. (2002). The endoplasmic reticulum and neuronal calcium signalling. *Cell Calcium*, **32,** 393 – 404.

References:

GALVAN, D.L. *et al*. (1999). *J. Biol. Chem*., **274,** 29483 – 29492.

RAMOS-FRANCO, J. *et al*. (1999). *J. Gen. Physiol*., **114,** 243 – 250.

Potassium

Overview: Potassium channels are fundamental regulators of excitability. They control the frequency and the shape of action potential waveform, the secretion of hormones and neurotransmitters and cell membrane potential. Their activity may be regulated by voltage, calcium and neurotransmitters (and the signalling pathways they stimulate). They consist of a primary pore-forming α subunit often associated with auxiliary regulatory subunits. Since there are over 70 different genes encoding K channels α subunits in the human genome, it is beyond the scope of this guide to treat each subunit individually. Instead, channels have been grouped into families and subfamilies based on their structural and functional properties. The relevant Ensembl family references (rather than gene references) are given for each subfamily group. The three main families are the 2TM (2 transmembrane domain), 4TM and 6TM families. A standardised nomenclature for potassium channels has been proposed by the NC-IUPHAR subcommittees on potassium channels (see Gutman & Chandy, 2002; Gutman *et al*., 2003).

The 2TM family of K channels

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

Subfamily Group	**$K_{IR}1.x$**	**$K_{IR}2.x$**	**$K_{IR}3.x$**	**$K_{IR}4.x$**
Subtypes	$K_{IR}1.1$ (ROMK1)	$K_{IR}2.1-2.4$ (IRK1–4)	$K_{IR}3.1-3.4$ (GIRK1–4)	$K_{IR}4.1-4.2$
Ensembl family	ENSF00000000293	ENSF00000000293	ENSF00000000293	ENSF00000000293
Activators	—	—	PIP_2, $G\beta\gamma$	—
Inhibitors	—	$[Mg^{2+}]_i$, polyamines (internal)	—	—
Functional characteristic	Inward–rectifier current	IK_1 in heart, 'strong' inward–rectifier current	G-protein activated inward-rectifier current	Inward–rectifier current

Subfamily Group	**$K_{IR}5.x$**	**$K_{IR}6.x$**	**$K_{IR}7.x$**
Subtypes	$K_{IR}5.1$	$K_{IR}6.1-6.2$ (K_{ATP})	$K_{IR}7.1$
Ensembl family	ENSF00000000293	ENSF00000000293	ENSF00000000293
Activators	—	minoxidil, cromakalim, diazoxide, nicorandil	—
Inhibitors	—	Tolbutamide, glibenclamide	—
Functional characteristic	Inward–rectifier current	ATP-sensitive, inward–rectifier current	Inward–rectifier current
Associated subunits	—	SUR1, SUR2A, SUR2B	—

The 4TM family of K channels

The 4TM family of K channels are thought to underlie many leak currents in native cells. They are open at all voltages and regulated by a wide array of neurotransmitters and biochemical mediators. The primary pore-forming α subunit contains 2 pore domains (indeed, they are often referred to as 2-pore domain K channels or K2P) and so it is envisaged that they form functional dimers rather than the usual K channel tetramers. There is some evidence that they can form heterodimers within subfamilies (e.g. TASK1 with TASK3). There is no clear, current, consensus on nomenclature of 4TM K channels, nor on the division into subfamilies (see Gutman & Chandy, 2002; Gutman *et al*., 2003). The suggested division into subfamilies, below, is based on similarities in both structural and functional properties within subfamilies.

Subfamily Group	**TWIK**	**TREK**	**TASK**	**TALK**	**THIK**	**TRESK**
Subtypes	TWIK1 (KCNK1), TWIK2 (KCNK6), KNCK7	TREK1 (KCNK2), TREK2 (KCNK10), TRAAK (KCNK4)	TASK1 (KCNK3), TASK3 (KCNK9), TASK5 (KCNK15)	TALK1 (KCNK16), TASK2 (KCNK5), TASK4 (KCNK17)	THIK1 (KCNK13), THIK2 (KCNK12)	TRESK1, TRESK2
Ensembl family	ENSF00000000523	ENSF00000000523	ENSF00000001613	ENSF00000000523	ENSF00000002896	ENSF00000011494
Activators	—	Halothane (not TRAAK), riluzole stretch, heat, arachidonic acid, acid pH_I	Halothane	Alkaline pH_O	—	—
Inhibitors	Acid pH_I	—	Anandamide (TASK1), ruthenium red (TASK3), acid pH_O	—	Halothane	Arachidonic acid
Functional characteristic	Background current	Background current	Background current	Background current	Background current	Background current

The KCNK7, TASK5 and THIK2 subtypes, when expressed in isolation, are non-functional. All 4TM channels are insensitive to the classical potassium channel blockers TEA and 4-AP but are blocked to varying degrees by Ba^{2+} ions.

The 6TM family of K channels

The 6TM family of K channels comprises the voltage-gated K_V subfamilies, the KCNQ subfamily the EAG subfamily (which includes herg channels), the Ca^{2+}-activated Slo subfamily (actually with 7TM) and the Ca^{2+}-activated SK subfamily. As for the 2TM family, the pore-forming α subunits form tetramers and heteromeric channels may be formed within subfamilies (e.g. $K_V1.1$ with $K_V1.2$; KCNQ2 with KCNQ3).

Subfamily Group	**$K_V1.x$**	**$K_V2.x$**	**$K_V3.x$**	**$K_V4.x$**
Subtypes	$K_V1.1-K_V1.8$, Shaker-related	$K_V2.1-2.2$, Shab-related	$K_V3.1-3.4$, Shal-related	$K_V4.1-4.3$, Shaw-related
Ensembl family	ENSF00000000160	ENSF00000000160	ENSF00000000160	ENSF00000000160
Inhibitors	TEA potent (1.1), TEA moderate (1.3, 1.6), 4-AP potent (1.4), α-dendrotoxin (1.1, 1.2, 1.6), margatoxin (1.1, 1.2, 1.3), noxiustoxin (1.2, 1.3)	TEA moderate	TEA potent, 4-AP potent (3.1, 3.2), BDS-1 (3.4)	—
Functional characteristics	K_V (1.1–1.3, 1.5–1.8), K_A (1.4)	K_V (2.1)	K_V (3.1, 3.2), K_A (3.3, 3.4)	K_A
Associated subunits	$K_V\beta_1$, $K_V\beta_2$	$K_V5.1$, $K_V6.1-6.3$, $K_V8.1$, $K_V9.1-9.3$	MiRP2 ($K_V3.4$)	KChIP, KChAP

Subfamily Group	KCNQ	EAG	Slo	SK
Subtypes	KCNQ1-5	eag1-2, elk1-3, erg1-3 (herg 1-3)	Slo (BK), Slack, Slick	SK1 – SK3; SK4, (IK)
Ensembl family	ENSF00000000405	ENSF00000000391	ENSF00000000916	ENSF00000000793
Activators	Retigabine (KCNQ2-5)	—	NS004, NS1619	—
Inhibitors	TEA (KCNQ2, 4), XE991 (KCNQ1,2,4,5), linopirdine	E-4031 (erg1), astemizole (erg1), terfenadine (erg1)	TEA, charybdotoxin, iberiotoxin	charybdotoxin (SK4), apamin (SK1-3)
Functional characteristic	KCNQ1 – cardiac IK_S KCNQ2/3 –M current	(h)erg1 – cardiac IK_R	Maxi K_{Ca} K_{Na} (slack & slick)	SK_{Ca} (SK1-3) IK_{Ca} (SK4)
Associated subunits	minK, MiRP2 (KCNQ1)	minK, MiRP1 (erg1)	—	—

Abbreviations: **4-AP,** 4-aminopyridine; **BDS-1,** blood depressing substance 1; **E4031,** 1-(2-(6-methyl-2-pyridyl)ethyl)-4-(4-methylsulphonyl aminobenzoyl)piperidine; **NS004,** 1-(2-hydroxy-5-chlorophenyl)-5-trifluromethyl-2-benzimidazolone; **NS1619,** 1-(2′-hydroxy-5′-trifluromethylphenyl)-5-trifluro-methyl-2(3*H*)benzimidazolone; **PIP_2,** phosphatidylinositol 4,5, bisphosphate; **TEA,** tetraethylammonium; **XE991**, 10,10-bis(4-pyridinylmethyl)-9(10*H*)-anthracene

Further reading:

ABRAHAM, M.R., JAHANGIR, A., ALEKSEEV, A.E. & TERZIX, A. (1999). Channelopathies of inwardly rectifying potassium channels. *FASEB J.,* **13,** 1901–1999.

AGUILAR-BRYAN, L., CLEMENT, J.P., GONZALEZ, G., KUNJILWAR, K., BABENKO, A. & BRYAN, J. (1998). Toward understanding the assembly and structure of K_{ATP} channels. *Physiol. Rev.,* **78,** 227–245

ASHCROFT, F.M. & GRIBBLE, F.M. (1998). Correlating structure and function in ATP-sensitive K^+ channels. *Trends Neurosci.,* **21,** 288–294.

BAUER, C.K., SCHWARTZ, J.R. (2001). Physiology of EAG channels. *J. Membrane Biol*., **182,** 1–15.

BEZANILLA, F. (2000). The voltage sensor in voltage-dependent ion channels. *Physiol. Rev*., **80,** 555–592.

CHANDY, K.G. & GUTMAN, G.A (1995). Voltage-gated potassium channel genes. In; *Handbook of Receptors and Channels; Ligand and Voltage-gated Ion Channels* (North, R.A. Ed.) pp1–71. CRC Press.

COETZEE, W.A., *et al*. (1999). Molecular diversity of K^+ channels. *Ann. NY Acad. Sci*., **868,** 233–285.

GOLDSTEIN, S.A.N., BOCKENHAUER, D., O'KELLY, I. & ZILBERBERG, N. (2001). Potassium leak channels and the KCNK family of two-P domain subunits. *Nature Rev. Neurosci*., **2,** 175–184.

GUTMAN, G.A. & CHANDY, K.G. (2002). Potassium channels. In: *The IUPHAR compendium of voltage-gated ion channels* (Catterall, W.A., Chandy, K.G. & Gutman, G.A. Ed.) pp 58 –189.

GUTMAN, G.A., *et al*. (2003). International Union of Pharmacology. XLI. Compendium of Voltage-Gated Ion Channels: Potassium Channels. *Pharmacol. Rev*., **55,** 583–586

JAN, L.Y. & JAN, Y.N. (1997). Voltage-gated and inwardly rectifying potassium channels. *J. Physiol.,* **505,** 267–282.

KACZOROWSKI, G.J. & GARCIA, M.L. (1999). Pharmacology of voltage-gated and calcium-activated potassium channels. *Curr. Opin. Chem. Biol*., **3,** 448–458.

LEWIS, R.J. & GARCIA, M.L. (2003). Therapeutic potential of venom peptides. *Nature Rev. Drug Discov*., **2,** 790–802.

LESAGE, F. (2003). Pharmacology of neuronal background potassium channels. *Neuropharmacol*., **44,** 1–7.

LESAGE, F. & LAZDUNSKI, M. (2000). Molecular and functional properties of two-pore-domain potassium channels. *Am. J. Physiol. Renal Physiol.,* **279,** F793–F801.

MATHIE, A., CLARKE, C.E., RANATUNGA, K.M. & VEALE, E.L. (2003). What are the roles of the many different types of potassium channel expressed in cerebellar granule cells? *Cerebellum*, **2,** 11–25.

MILLER, C. (1995). The charybdotoxin family of K^+ channel-blocking peptides. *Neuron*, **15,** 5–10.

MILLER, C. (2003). A charged view of voltage-gated ion channels. *Nature Struct. Biol*., **10,** 422–424.NICHOLS, C.G. & LOPATIN, A.N. (1997). Inwardly rectifying potassium channels. *Ann. Rev. Physiol*., **59,** 171–191.

O'CONNELL, A.D., MORTON, M.J. & HUNTER, M. (2002). Two-pore domain K^+ channels – molecular sensors. *Biochem. Biophys. Acta – Biomemb*., **1566,** 152–161.

PATEL, A.J. & HONORE. E. (2001). Properties and modulation of mammalian 2P domain K^+ channels. *Trends in Neurosci*., **24,** 339–346.

REIMANN, F. & ASHCROFT, F.M. (1999). Inwardly rectifying potassium channels. *Curr. Opin. Cell Biol.,* **11,** 503–508.

ROBBINS, J. (2001). KCNQ potassium channels: physiology, pathophysiology and pharmacology. *Pharmacol. Therapeut*., **90,** 1–19.

SANGUINETTI, M.C. (2000). Maximal function of minimal K^+ channel subunits. *Trends. Pharmacol. Sci.,* **21,** 199–201.

SANGUINETTI, M.C. & SPECTOR, P.S. (1997). Potassium channelopathies. *Neuropharmacol*., **36,** 755–762.

SEINO, S. & MIKI, T. (2003). Physiological and pathophysiological roles of ATP-sensitive K^+ channels. *Prog. Biophys. Mol. Biol*., **81,** 133–176.

STANFIELD, P.R., NAKAJIMA, S. & NAKAJIMA, Y. (2002). Constitutively active and G-protein coupled inward rectifier K^+ channels: Kir2.0 and Kir3.0. *Rev. Physiol., Biochem. Pharmacol*., **145,** 47–179.

STOCKER, M. (2004). Ca^{2+}-activated K^+ channels: molecular determinants and function of the SK family. *Nature Rev. Neurosci*., **5,** 758–770.

TRIMMER, J.S. & RHODES, K.J. (2004). Localisation of voltage-gated ion channels in mammalian brain. *Ann. Rev. Physiol*., **66,** 477–519.

YAMADA, M., INANOBE, A. & KURACHI, Y. (1998). G Protein regulation of potassium ion channels. *Pharmac. Rev.,* **50,** 723–757.

YELLEN, G. (2002). The voltage-gated potassium channels and their relatives. *Nature*, **419,** 35–42.

Ryanodine receptor

Overview: The ryanodine receptors (RyRs) are found on intracellular Ca^{2+} storage/release organelles. The family of RyR genes encodes three highly related Ca^{2+} release channels: RyR1, RyR2 and RyR3, which assemble as large tetrameric structures. These RyR channels are ubiquitously expressed in many types of cells and participate in a variety of important Ca^{2+} signaling phenomena (neurotransmission, secretion, etc.). In addition to the three mammalian isoforms described below, various non-mammalian isoforms of the ryanodine receptor have been identified and these are discussed in Sutko & Airey (1996). The function of the ryanodine receptor channels may also be influenced by closely associated proteins such as the tacrolimus (FK506) binding protein, calmodulin (Yamaguchi *et al*., 2003), triadin, calsequestrin, junctin and sorcin and by protein kinases and phosphatases.

Nomenclature	**RyR1**	**RyR2**	**RyR3**
Ensembl ID	ENSG00000196218	ENSG00000198626	ENSG00000196765
Endogenous activators	Depolarisation via DHP receptor, cytosolic Ca^{2+} (μM), cytosolic ATP (mM), luminal Ca^{2+}, calmodulin at low cytosolic Ca^{2+}, CaM Kinase, PKA	Cytosolic Ca^{2+} (μM), cytosolic ATP (mM), luminal Ca^{2+}, CaM Kinase, PKA	Cytosolic Ca^{2+} (μM), cytosolic ATP (mM), calmodulin at low cytosolic Ca^{2+}
Pharmacological activators	Ryanodine (nM–μM), caffeine (mM), suramin (μM)	Ryanodine (nM–μM), caffeine (mM), suramin (μM)	Ryanodine (nM–μM), caffeine (mM)
Antagonists	Cytosolic Ca^{2+}(>100μM), cytosolic Mg^{2+} (mM), calmodulin at high cytosolic Ca^{2+} dantrolene	Cytosolic Ca^{2+}(>1mM), cytosolic Mg^{2+} (mM), calmodulin at high cytosolic Ca^{2+}	Cytosolic Ca^{2+}(>1 mM), cytosolic Mg^{2+} (mM), calmodulin at high cytosolic Ca^{2+}, dantrolene
Channel blockers	Ryanodine (>100 μM), ruthenium red, procaine	Ryanodine (>100 μM), ruthenium red, procaine	Ruthenium red
Functional characteristics	Ca^{2+}: ($P_{Ca}/P_K \sim 6$) single-channel conductance: ~90 pS (50mM Ca^{2+}), 770 pS (200 mM K^+)	Ca^{2+}: ($P_{Ca}/P_K \sim 6$) single-channel conductance: ~90 pS (50 mM Ca^{2+}), 720 pS (210 mM K^+)	Ca^{2+}: ($P_{Ca}/P_K \sim 6$) single-channel conductance: ~140 pS (250 mM Ca^{2+}), 777 pS (250 mM K^+)

The modulators of channel function included in this table are those most commonly used to identify ryanodine-sensitive Ca^{2+} release pathways. Numerous other modulators of ryanodine receptor/channel function can be found in the reviews listed below. The absence of a modulator of a particular isoform of receptor indicates that the action of that modulator has not been determined, not that it is without effect. The potential role of cyclic ADP ribose as an endogenous regulator of ryanodine receptor channels is controversial (see Sitsapesan *et al*., 1995). A region of RyR likely to be involved in ion translocation and selection has been identified (Zhao *et al*., 1999, Gao *et al*., 2000). RyR channel-mediated elementary Ca^{2+} release events may be monitored in intact, Fluo-3 loaded, cells using confocal imaging (see Cannell & Soeller, 1998).

Further reading:

BERRIDGE, M.J., BOOTMAN, M.D. & RODERICK, H.L. (2003). Calcium signalling: dynamics, homeostasis and remodelling. *Nature Rev. Mol. Cell Biol*., **4,** 517–529.

BERRIDGE, M.J., LIPP, P. & BOOTMAN, M.D. (2000). The versatility and universality of calcium signalling. *Nature Rev. Mol. Cell Biol*., **1,** 11–21.

BOUCHARD, R., PATTARINI, R. & GEIGER, J.D. (2003). Presence and functional significance of presynaptic ryanodine receptors. *Prog. Neurobiol*., **69,** 391–418.

CANNELL, M.B. & SOELLER, C. (1998). Sparks of interest in cardiac excitation-contraction coupling. *Trends Pharmacol. Sci*., **19,** 16–20.

EHRLICH, B.E. (1995). Function properties of intracellular calcium release channels. *Curr. Opin. Neurobiol*., **5,** 304–309.

FILL, M. & COPELLO, J.A. (2002). Ryanodine receptor calcium release channels. *Physiol. Rev*., **82,** 893–922.

ROSS, D. & SORRENTINO, V. (2002). Molecular genetics of ryanodine receptors Ca^{2+} release channels. *Cell Calcium*, **32,** 307–319.

SHOSHAN-BARMATZ, V. & ASHLEY, R.H. (1998). The structure, function and cellular regulation of ryanodine-sensitive Ca^{2+}-release channels. *Int. Rev. Cytol.,* **183,** 185–270.

SITSAPESAN, R., MCGARRY, S.J. & WILLIAMS, A.J. (1995). Cyclic ADP-ribose, the ryanodine receptor and Ca^{2+} release. *Trends Pharmacol. Sci*., **16,** 386–391.

SITSAPESAN, R. & WILLIAMS, A.J. eds. (1998). The structure and function of ryanodine receptors. *Imperial College Press*.

SUTKO, J.L. & AIREY, J.A. (1996). Ryanodine Ca^{2+} release channels: does diversity in form equal diversity in function? *Physiol. Rev*., **76,** 1027–1071.

SUTKO, J.L., AIREY, J.A., WELCH, W. & RUEST, L. (1997). The pharmacology of ryanodine and related compounds. *Pharmac. Rev*., **49,** 53–98.

ZUCCHI, R. & RONCA-TESTONI, S. (1997). The sarcoplasmic reticulum Ca^{2+} channel/ryanodine receptor: modulation by endogenous effectors, drugs and disease states. *Pharmac. Rev*., **49,** 1–51.

References:

GAO, L. *et al*. (2000). *Biophys. J*., **79,** 828–840.

YAMAGUCHI, N. *et al*. (2003). *J. Biol. Chem*., **278,** 23480–23486.

ZHAO, M.C. *et al*. (1999). *J. Biol. Chem.,* **274,** 25971–25974.

Sodium (voltage-gated)

Overview: Sodium channels are voltage-gated sodium-selective ion channels present in the membrane of most excitable cells. Sodium channels comprise of one pore-forming α-subunit, which may be associated with either one or two β subunits (Isom, 2001). α-subunits consist of four homologous domains (I–IV), each containing six TM segments (S1–S6) and a pore forming loop. The positively charged fourth TM segment (S4) acts as a voltage-sensor and is involved in channel gating. Auxiliary β1, β2, β3 and β4 (Yu *et al*., 2003) subunits consist of a large extracellular N-terminal domain, a single TM segment and a shorter cytoplasmic domain.

The nomenclature for sodium channels was proposed by Goldin *et al*. (2000) and approved by the NC-IUPHAR subcommittee on sodium channels (Catterall *et al*., 2002; 2003). With the exception of $Na_v1.8\alpha1.9$, all channels are known to be activated by veratridine and baltrachotoxin.

Nomenclature	**$Na_V1.1$**	**$Na_V1.2$**	**$Na_V1.3$**	**$Na_V1.4$**	**$Na_V1.5$**
Alternative names	Brain type I	Brain type II	Brain type III	μ1, SkM1	h1, SkM II, cardiac
Ensembl ID	ENSG00000144285	ENSG00000136531	ENSG00000153253	ENSG00000007314	ENSG00000183873
Blockers	Tetrodotoxin (10 nM), saxitoxin	Tetrodotoxin (10 nM), saxitoxin	Tetrodotoxin (2–15 nM), saxitoxin	μ-conotoxin GIIIA, tetrodotoxin (5 nM) saxitoxin	Tetrodotoxin (2 μM)
Functional characteristic	fast inactivation (0.7 ms)	fast inactivation (0.8 ms)	fast inactivation (0.8 ms)	fast inactivation (0.6 ms)	fast inactivation (1 ms)

Nomenclature	**$Na_V1.6$**	**$Na_V1.7$**	**$Na_V1.8$**	**$Na_V1.9$**
Alternative names	PN4, NaCH6	PN1, NaS	SNS, PN3	NaN, SNS2
Ensembl ID	ENSG00000196876	ENSG00000169432	ENSG00000185313	ENSG00000168356
Blockers	Tetrodotoxin (6 nM), saxitoxin	Tetrodotoxin (4 nM), saxitoxin	Tetrodotoxin (60 μM)	Tetrodotoxin (40 μM)
Functional characteristic	fast inactivation (1 ms)	fast inactivation (0.5 ms)	slow inactivation (6 ms)	slow inactivation (16 ms)

Sodium channels are also blocked by local anaesthetic agents, antiarrythmic drugs and antiepileptic drugs. There are two clear functional fingerprints for distinguishing different subtypes. These are sensitivity to tetrodotoxin ($Na_V1.5$, $Na_V1.8$ & $Na_V1.9$ are much less sensitive to block) and rate of inactivation ($Na_V1.8$ & particularly $Na_V1.9$ inactivate more slowly).

Further reading:

BAKER, M.D. & WOOD, J.N. (2001). Involvement of Na^+ channels in pain pathways. *Trends Pharmacol. Sci*., **22,** 27–31.

CANTRELL, A.R. & CATTERALL, W.A. (2001). Neuromodulation of Na^+ channels: An unexpected form of cellular plasticity. *Nat. Rev. Neurosci*., **2,** 397–407.

CATTERALL, W.A. (1995). Structure and function of voltage-gated ion channels. *Ann. Rev. Biochem*., **64,** 493–531.

CATTERALL, W.A., GOLDIN, A.L. & WAXMAN, S.G. (2002). Voltage-gated sodium channels. In: *The IUPHAR compendium of voltage-gated ion channels* (Catterall, W.A., Chandy, K.G. & Gutman, G.A. Ed.) pp 9–30.

CATTERALL, W.A., GOLDIN, A.L. & WAXMAN, S.G. (2003). International Union of Pharmacology. XXXIX. Compendium of Voltage-Gated Ion Channels: Sodium Channels. *Pharmacol. Rev*., **55,** 575–578.

CATTERALL W.A. (2000). From ionic currents to molecular mechanisms.: the structure and function of voltage-gated sodium channels. *Neuron*, **26,** 13–25.

FOZZARD, H.A. & HANCK, D.A. (1996). Structure and function of voltage-dependent sodium channels–comparison of brain-II and cardiac isoforms. *Physiol. Rev*., **76,** 887–926.

GOLDIN, A.L. (1995). Voltage-gated sodium channels. In: *Handbook of Receptors and Channels; Ligand and Voltage-gated Ion Channels* (North, R.A. Ed.) pp. 73–111. CRC Press.

GOLDIN, A.L. (1999). Diversity of mammalian voltage-gated sodium channels. In: *Molecular and Functional Diversity of Ion Channels and Receptors* (Rudy, B. and Seeburg, P. Eds.) *Ann. NY Acad. Sci.,* **868,** 38–50.

GOLDIN, A.L. *et al*. (2000). Nomenclature of voltage-gated sodium channels. *Neuron,* **28,** 365–368.

GOLDIN, A.L. (2001). Resurgence of sodium channel research. *Ann. Rev. Physiol.,* **63,** 874–894.

ISOM, L.L. (2001). Sodium channel beta subunits: anything but auxiliary. *Neuroscientist*, **7,** 42–54.

LAI, J., PORRECA, F., HUNTER, J.C. & GOLD, M.S. (2004). Voltage-gated sodium channels and hyperalgesia. *Ann. Rev. Pharmacol. Toxicol*., **44,** 371–397.

LEWIS, R.J. & GARCIA, M.L. (2003). Therapeutic potential of venom peptides. *Nature Rev. Drug Discov*., **2,** 790–802.

MARBAN, E., YAMAGISHI, T. & TOMASELLI, G.F. (1998). Structure and function of voltage-activated sodium channels. *J. Physiol.,* **508**, 647–659.

PLUMMER, N.W. & MEISLER, M.H. (1999). Evolution and diversity of mammalian sodium channel genes. *Genomics*, **57,** 323–331.

RAGSDALE, D.S. & AVOLI, M. (1998). Sodium channels as molecular targets for antiepileptic drugs. *Brain Res. Rev.,* **26,** 16–28.

TERLAU, H. & OLIVERA, B.M. (2004). Conus venoms: A rich source of novel ion channel-targeted peptides. *Physiol. Rev*., **84,** 41–68.

TRIMMER, J.S. & RHODES, K.J. (2004). Localisation of voltage-gated ion channels in mammalian brain. *Ann. Rev. Physiol*., **66**, 477–519.

Reference:

YU, F.H. *et al*. (2003). *J. Neurosci*., **23,** 7577–7585.

Transient receptor potential (TRP) cation

Overview: The TRP superfamily of cation channels (nomenclature agreed by NC-IUPHAR; Clapham *et al*., 2003), whose founder member is the *Drosophila* Trp channel, can be divided, in mammals, into six families; TRPC, TRPM, TRPV, TRPA, TRPP and TRPML based on amino acid homologies (see Montell *et al*., 2002; Corey, 2003, Clapham, 2003; Delmas *et al*., 2004; Moran *et al*., 2004). TRP subunits contain six putative transmembrane domains and probably assemble as homo- or hetero-tetramers to form cation selective channels. The TRP**C** ('**C**anonical') and TRP**M** ('**M**elastatin') subfamilies consist of seven and eight different channels, respectively (*i.e*., TRPC1-TRPC7 and TRPM1-TRPM8). The TRP**V** ('**V**anilloid') subfamily presently comprises six members (TRPV1-TRPV6) whereas the most recently proposed subfamily, TRP**A,** (**A**nkyrin) has only one mammalian member (TRPA1). The TRP**P** ('**P**olycystin') and TRP**ML** ('**M**ucol**i**pin') families are not fully characterised, and the tables below are thus incomplete. The established, or potential, physiological functions of the individual members of the TRP families are discussed in detail in the recommended reviews and are briefly mentioned here.

TRPC family: Members of the TRPC subfamily, on the basis of sequence homology and similarities in function, fall into four subfamilies: TRPC1, TRPC2, TRPC3/6/7 and TRPC4/5. TRPC2 (not tabulated) is a pseudogene in man but, in rodents, is involved in pheromone detection by the vomeronasal organ and Ca^{2+} signalling in spermatozoa (reviewed by Clapham *et al*., 2001). All TRPC channels have been proposed to act as store-operated channels (SOCs), activated by depletion of intracellular calcium stores (see reviews by Clapham *et al*., 2001; Vennekens *et al*., 2002; Venkatachalam *et al*, 2002; Nilius, 2003a; see also www.stke.org/cgi/content/full/sigtrans;2004/243). However, there is conflicting evidence that TRPC4/5 and TRPC3/6/7 can function as receptor-operated channels that are mostly insensitive to store depletion (reviewed by Plant & Schaefer, 2003; Trebak *et al*., 2003a). In heterologous systems, the level of TRPC expression may contribute to such discrepancies (Treback *et al*., 2003b). TRPC4$^{-/-}$ mice demonstrate an impaired store-operated calcium current in vascular endothelial cells, suggesting that this protein forms, or is an essential component of, a store-operated Ca^{2+} channel (SOC) *in vivo* (Freichel *et al*., 2001; Tiruppathi *et al*., 2002). The relationship of other TRPC channels to endogenous SOCs is less clear at present, although TRPC1 and TRPC5 appear to be components of a cation channel within the CNS (Strübing *et al*., 2001). TRPC6 is essential for the function of a cation channel-mediated entry of Ca^{2+} into vascular smooth muscle cells subsequent to α-adrenoceptor activation (Inoue *et al*., 2001).

Nomenclature	**TRPC1**	**TRPC3**	**TRPC4**
Other names	TRP1	TRP3	TRP4, CCE1
Ensembl ID	ENSG00000144935	ENSG00000138741	ENSG00000100991
Activators	Metabotropic glutamate receptor mGlu1, OAG (weak and only in divalent-free extracellular solution), PLCγ stimulation, intracellular $Ins(1,4,5)P_3$ (disputed), thapsigargin (disputed)	$G_{q/11}$-coupled receptors, OAG (independent of PKC), PLCγ stimulation, $Ins(1,4,5)P_3$, (disputed) and thapsigargin (disputed), probably activated by Ca^{2+} (disputed)	$G_{q/11}$-coupled receptors, GTPγS (requires extracellular Ca^{2+}), $Ins(1,4,5)P_3$ (disputed) and thapsigargin (disputed), activated by F2v peptide and calmidazolium by antagonism of Ca^{2+}-calmodulin
Blockers	Gd^{3+}, La^{3+}, 2-APB, SKF96365, Ca^{2+}- calmodulin inhibits	Gd^{3+}, La^{3+}, 2-APB, SKF96365	La^{3+} (at mM concentrations – augments in μM range), 2-APB
Functional characteristics	$\gamma = 16$ pS (estimated by fluctuation analysis); conducts mono- and di-valent cations non-selectively; monovalent cation current suppressed by extracellular Ca^{2+}; non-rectifying, or mildly inwardly rectifying; non-inactivating; physically associates *via* Homer with IP_3 receptors, also associates with TRPC4, calmodulin, TRPP1, IP_3 receptors, caveolin and plasma membrane Ca^{2+}-ATPase	$\gamma = 66$ pS; conducts mono- and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 1.6$); monovalent cation current suppressed by extracellular Ca^{2+}; dual (inward and outward) rectification; relieved of inhibition by Ca^{2+}-calmodulin by IP_3 receptors, IP_3 receptor derived peptide (F2v) and calmidazolium; inhibited by PKG-mediated phosphorylation; associates with TRPC1 in embryonic tissue; also associates with IP_3 receptors, SERCA, caveolin-1 and calmodulin	$\gamma = 30-41$ pS, conducts mono- and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 1.1-7.7$); dual (inward and outward) rectification; physically associates *via* a PDZ binding domain on NHERF with phospholipase C isoforms; also associates with TRPC1 and 5, IP_3 receptors and calmodulin

Nomenclature	**TRPC5**	**TRPC6**	**TRPC7**
Other names	TRP5, CCE2	TRP6	TRP7
Ensemble ID	ENSG00000072315	ENSG00000137672	ENSG00000069018
Activators	$G_{q/11}$-coupled receptors, $Ins(1,4,5)P_3$, GTPγS (potentiated by extracellular Ca^{2+}), adenophostin A and thapsigargin (disputed), La^{3+} (10 μM), Gd^{3+} (0.1 mM), elevated $[Ca^{2+}]_o$ (5–20 mM)	$G_{q/11}$-coupled receptors, AlF_4^-, GTPγS (but not $Ins(1,4,5)P_3$), 20-HETE, OAG (independent of PKC) and inhibition of DAG lipase with RHC80267, synergistic stimulation by $G_{q/11}$-coupled receptors and OAG, activated by Ca^{2+} (disputed), AlF_4, flufenamate	$G_{q/11}$-coupled receptors. OAG (independent of PKC), thapsigargin (disputed), $[Ca^{2+}]_i$
Blockers	La^{3+} (at mM concentrations – augments in μM range), SKF96365	La^{3+} ($IC_{50} \cong 6$ μM), Gd^{3+}, amiloride, SKF96365, 2-APB	La^{3+}, SKF96365, amiloride
Functional characteristics	$\gamma = 63$ pS; conducts mono-and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 1.8$); dual rectification (inward and outward) as a homomer, outwardly rectifying when expressed with TRPC1 or TRPC4; inhibited by xestospongin C; physically associates *via* a PDZ binding domain on NHERF with phospholipase C isoforms,	$\gamma = 28-37$ pS; conducts mono- and divalent cations with a preference for divalents ($P_{Ca}/P_{Na} = 4.5-5.0$; dual rectification (inward and outward), or inward rectification, enhanced by flufenamate; positively modulated by phosphorylation mediated by Src protein tyrosine kinases; associates with TRPC3 and 7 and calmodulin	Conducts mono and divalent cations with a preference for divalents ($P_{Ca}/P_{Cs} = 5.9$); modest outward rectification (monovalent cation current recorded in the absence of extracellular divalents); monovalent cation current suppressed by extracellular Ca^{2+} and Mg^{2+}, associates with TRPC3 and 6 and calmodulin

The function and regulation of heterologously expressed TRPC1 has been controversial (see Clapham *et al*., 2001; Beech *et al*., 2003). However, there is evidence that TRPC1 is a component of a store-operated channel *in situ* (reviewed by Beech *et al*., 2003). Functional hetero-oligomers of TRPC1/TRPC4 and TRPC1/TRPC5 activated by receptors signalling *via* $G_{q/11}$ have been suggested from heterologous expression systems (Strübing *et al*., 2001). TRPC1 may physically couple to mGlu1 and activation of the latter stimulates cation flux through TRPC1 containing-channels to produce a slow e.p.s.p. *in vivo* (Kim *et al*., 2003). Association of TRPC1 with the IP_3 receptor *via* the adaptor protein, Homer, regulates channel activity (Yuan *et al*., 2003). For TRPC3, the stimulatory effect of $Ins(1,4,5)P_3$ on single channel

activity recorded from inside-out membrane patches is blocked by the IP_3 receptor antagonists, heparin and xestospongin C. One mode of activation of TRPC3 is postulated to involve a direct association of the channel with activated IP_3 receptors (reviewed by Treback *et al*., 2003; Zhu & Tang, 2004). In such a scheme, the N-terminal domain of the IP_3 receptor competes with Ca^{2+}-calmodulin (which inhibits TRPC3 activity) for a common binding site within the C-terminal domain of TRPC3 and thus relieves inhibition. A similar mechanism may apply to the gating of certain other members of the TRPC family (Tang *et al*., 2001). However, OAG also simulates TRPC3 channel activity independent of coupling to IP_3 receptors (Ventakatchalam *et al*., 2001) and Src kinase appears to play an obligatory role in such activation (Vazquez *et al*., 2004). Enhancement of currents mediated by TRPC3 and TRPC6 by activation of $G_{q/11}$-coupled receptors, and TRPC5 *via* stimulation of receptor tyrosine kinases, involves the exocytotic insertion of the channel into the plasma membrane (see Montell, 2004).

TRPM family: Members of the TRPM subfamily, on the basis of sequence homology, fall into four groups: TRPM1/3, TRPM2/8, TRPM4/5 and TRPM6/7. The properties of TRPM2 suggest that it may function as a sensor of redox status in cells (Hara *et al*., 2002). A splice variant of TRPM4 (*i.e*. TRPM4b) and TRPM5 are (unlike other TRP channels) inherently voltage sensitive and are molecular candidates for endogenous calcium-activated cation (CAN) channels (Launey *et al*., 2002; Hofmann *et al*. 2003; Nilius *et al*., 2003). In addition, TRPM5 in taste receptor cells of the tongue appears essential for the transduction of sweet, amino acid and bitter stimuli (Zhang *et al*., 2003). TRPM6 and 7 combine channel and enzymatic activities ('chanzymes') and are involved in Mg^{2+} homeostasis (Schmitz *et al*., 2003; reviewed by Montell, 2003; Voets *et al*., 2004a). TRPM8 is a channel activated by cooling and pharmacological agents evoking a 'cool' sensation.

Nomenclature	**TRPM1**	**TRPM2**	**TRPM3**
Other names	LTRPC1, Melastatin	(TRPC7, LTRPC2)	LTRPC3
Ensembl ID	ENSG00000134160	ENSG00000142185	ENSG00000083067
Activators	Constitutively active (disputed)	Intracellular ADP ribose; β-NAD^+ and agents producing reactive oxygen (e.g. H_2O_2) and nitrogen (e.g. GEA 3162) species (via elevated NAD^+); potentiated by arachidonic acid and, in the presence of ADP-ribose, intracellular Ca^{2+}	Constitutively active, stimulated by store depletion with thapsigargin, stimulated by cell swelling, activated by D-*erythro*-sphiongosine
Blockers	La^{3+}, Gd^{3+}	–	Gd^{3+}
Functional characteristics	Permeable to Ca^{2+} and Ba^{2+}; down regulated by a short splice variant of TRPM1	$\gamma = 52-60$ pS at negative potentials, 76 pS at positive potentials; conducts mono- and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 0.67$); non-rectifying; inactivation at negative potentials, modulation *via* PARP inhibitors (protecting from oxidative stress-induced cell death)	$\gamma = 83$ pS (Na^+ current), 65 pS (Ca^{2+} current); conducts mono- and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 1.57$); non-rectifying

Nomenclature	**TRPM4**	**TRPM5**	**TRPM6**
Other names	LTRPC4	TRP-T	—
Ensembl ID	ENSG00000130529	ENSG00000070985	ENSG00000119121
Activators	Whole cell current transiently activated by intracellular Ca^{2+} (EC_{50} 320–520 nM) and subsequently inactivated; patch excision (outside-out) reverses inactivation	$G_{q/11}$-coupled receptors, $Ins(1,4,5)P_3$, transiently activated by intracellular Ca^{2+} (EC_{50} 30 μM)	Constitutively active, activation by reduction of intracellular Mg^{2+},
Blockers	Intracellular nucleotides (ATP^{4-}, ADP, AMP, AMP-PNP) and adenosine; spermine, flufenamate	Flufenamate, spermine (not inhibited by ATP^{4-})	Ruthenium red (voltage dependent block, $IC_{50} = 100$ nM at -120 mV), Ca^{2+} and Mg^{2+} block
Functional characteristics	$\gamma = 25$ pS (within the range 60 to $+60$ mV); permeable to monovalent cations; impermeable to Ca^{2+}; strong outward rectification; slow activation at positive potentials, rapid deactivation at negative potentials, deactivation blocked by decavanadate; intrinsically voltage sensitive	$\gamma = 15-25$ pS; conducts monovalent cations selectively ($P_{Ca}/P_{Na} = 0.05$); strong outward rectification; slow activation at positive potentials, rapid inactivation at negative potentials; activated and subsequently desensitized by $[Ca^{2+}]_I$, desensitisation relieved by short chain synthetic $PtdIns(4,5)P_2$; intrinsically voltage-sensitive	Permeable to mono- and di-valent cations with a preference for divalents ($Mg^{2+} > Ca^{2+}$), strong outward rectification abolished by removal of extracellular divalents, inhibited by intracellular Mg^{2+}, associates with TRPM7

Nomenclature	**TRPM7**	**TRPM8**
Other names	TRP-PLIK, Chak1, MagNum, MIC	CMR1, TRP-p8
Ensembl ID	ENSG00000092439	ENSG000000144481
Activators	G_s-coupled receptors *via* elevated cAMP and activation of PKA; potentiated by intracellular ATP	Depolarization ($V_{1/2} \cong +50$ mV at 15°C), cooling (<22–26°C), icilin (requires intracellular Ca^{2+} as a co-factor for full agonist activity), (−)-menthol; agonist activities are temperature dependent and potentiated by cooling
Blockers	Spermine (permeant blocker), La^{3+}	BCTC, capsazepine, 2-APB, La^{3+}, insensitive to ruthenium red
Functional characteristics	$\gamma = 105$ pS at positive potentials; conducts mono-and di-valent cations with a preference for monovalents ($P_{Ca}/P_{Na} = 0.34$); conducts trace elements, outward rectification, decreased by removal of extracellular divalent cations; inhibited by intracellular Mg^{2+}, Ba^{2+}, Sr+, Zn^{2+}, Mn^{2+} and Mg.ATP; inhibited by hydrolysis of $PtdIns(4,5)P_2$ (disputed); inhibited by G_i-coupled receptors; associates with TRPM6, Gq-PLCβ and TK(EGF)-PLCγ; kinase domain phosphorylates annexin1	$\gamma = 83$ pS at positive potentials; conducts mono- and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 1\text{-}.0-3.3$); pronounced outward rectification; demonstrates densensitization to chemical agonists and adaptation to a cold stimulus in the presence of Ca^{2+}; intrinsically voltage-sensitive

TRPM1 is decreased in melanoma cells with an inverse correlation with melanoma progression. TRPM2 possesses an ADP ribose hydrolase activity associated with a NUDT9 motif within an extended intracellular C-terminal domain of the channel (Perraud *et al*., 2001). Deletion of this domain abolishes activation by H_2O_2 (Hara *et al*., 2002). A truncated TRPM2 isoform (TRPM2-S) generated by alternative splicing prevents activation of the full-length protein (TRPM2-L) by H_2O_2 when co-expressed with the latter, which is important for apoptosis and cell death (Zhang *et al*., 2003). TRPM4 exists as two splice variants, TRPM4a and a longer protein TRPM4b (Launey *et al*., 2002) containing an additional 174 amino acids N-terminal to the predicted start of TRPM4a. Data listed are for TRPM4b. The sensitivity of TRPM4b to activation by $[Ca^{2+}]_i$ demonstrates a pronounced and time-dependent reduction following excision of inside-out membrane patches and high concentrations of the divalent cause inhibition (IC_{50} 9.3 mM). Fura2A ratiometric imaging suggests that Ca^{2+} and Ba^{2+} permeate TRPM4a in addition to monovalent cations. TRPM6 is important for Mg^{2+} homeostatis, mediating absorption and reabsorption of Mg^{2+} by the kidney intestine, respectively (Voets *et al*., 2004a) Loss-of-function mutations of TRPM6 result in hypomagnesaemia with secondary hypocalcaemia (HSH). TRPM7 embodies an atypical serine/threonine protein kinase within its C-terminal domain and is subject to autophosphorylation (Runnels *et al*., 2001; Schmitz *et al*., 2003). Intact kinase activity of TRPM7 has been claimed to be required for channel function (Runnells *et al*., 2001) although this is disputed (Nadler *et al*., 2001; Schmitz *et al*., 2003). The kinase activity of TRPM7 modulates sensitivity to inhibition by Mg^{2+} (Schmitz *et al*., 2003) and regulation by intracellular cAMP (Takezawa *et al*., 2004). TRPM7 plays a major role in anoxic neuronal cell death (Aarts *et al*., 2003). Activation of TRPM8 by depolarization is strongly temperature-dependent *via* a channel-closing rate that decreases with decreasing temperature. The potential for half maximal depolarisation ($V_{1/2}$) is shifted in the hyperpolarizing direction both by decreasing temperature and by exogenous agonists, such as menthol (Voets *et al*., 2004b). Intracellular pH modulates activation of TRPM8 by cold and icilin, but not menthol (Anderson *et al*., 2004). Icilin activates TRPA1 in addition to TRPM8 (Jordt *et al*., 2004). TRPM8 is up-regulated in a variety of primary tumours (*e.g.* prostate, breast, colon, lung, skin).

TRPV family: Members of the TRPV family (reviewed by Gunthorpe *et al*., 2002), on the basis of structure and function, comprise four groups: TRPV1/2, TRPV3, TRPV4 and TRPV5/6. TRPV1-4 are thermosensitive, non-selective cation channels that, in the case of TRPV1 and TRPV4, can also be activated by numerous additional stimuli (reviewed by Benham *et al*., 2003, Nilius *et al*., 2004). Members of the TRPV family function as tetrameric complexes. Under physiological conditions, TRPV5 and TRPV6 are calcium selective channels involved in the absorption and reabsorption of calcium across intestinal and kidney tubule epithelia (reviewed by den Dekker *et al*., 2003; Nijenhuis *et al*., 2003).

Nomenclature	**TRPV1**	**TRPV2**	**TRPV3**
Other names	VR1, vanilloid/capsaicin receptor, OTRPC1	VRL-1, OTRPC2, GRC	
Ensemble ID	ENSG00000043316	ENSG00000154039	ENSG00000167723
Activators	Depolarization ($V_{1/2} \cong 0$ mV at 35°C), noxious heat (>43°C at pH 7.4), extracellular protons ($pEC_{50} = 5.4$ at 37°C), capsaicin, resiniferatoxin, phenylacetylrivanil, olvanil, anandamide, some eicosanoids (*e.g.*12-(S)-HPETE, 15-(S)-HPETE, 5-(S)-HETE, leukotriene B_4), N-arachidonoyl-dopamine, 2-APB	Noxious heat (>53°C), 2-APB (disputed)	Heat (23°–39°C, temperature threshold influenced by 'thermal history' of the cell), 2-APB
Blockers	Ruthenium red, 5′-iodoresiniferatoxin, 6-iodo-*nor*dihydrocapsaicin, SB366791, SB452533, BCTC, capsazepine, DD161515, DD191515, JYL1421	Ruthenium red ($IC_{50} = 0.6\ \mu$M), SKF96365, La^{3+}	Ruthenium red ($IC_{50} < 1\ \mu$M)
Functional characteristics	$\gamma = 35$ pS at − 60 mV; 77 pS at + 60 mV, conducts mono- and di-valent cations with a selectivity for divalents ($P_{Ca}/P_{Na} = 9.6$); allows proton influx contributing to intracellular acidification in acidic media; voltage- and time-dependent outward rectification; potentiated by ethanol; activated/potentiated/upregulated by PKC stimulation; extracellular acidification facilitates activation by PKC; desensitisation inhibited by PKA; inhibited by $PtdIns(4,5)P_2$ and Ca^{2+}/calmodulin; cooling reduces vanilloid-evoked currents; associates with TRPV3, calmodulin, PLCγ, TrkA, PP2B, calcineurin/cyclosporin, synaptotagmin and synapsin	Conducts mono- and di-valent cations ($P_{Ca}/P_{Na} = 0.9–2.9$); dual (inward and outward) rectification; current increases upon repetitive activation by heat; translocates to cell surface in response to IGF-1 to induce a constitutively active conductance, translocates to the cell surface in response to membrane stretch; associates with PKA, AKAP (ACBD3), RGA (recombinase gene activator) and dystrophin-glycoprotein complex	$\gamma = 197$ pS at = +40 to +80 mV, 48 pS at negative potentials; conducts mono- and di-valent cations; outward rectification

Nomenclature	**TRPV4**	**TRPV5**	**TRPV6**
Other names	VRL-2, OTRPC4, VR-OAC, TRP12	ECaC, ECaC1, CaT2, OTRPC3	ECaC2, CaT1, CaT-L
Ensembl ID	ENSG00000111199	ENSG00000127412	ENSG00000165125
Activators	Constitutively active, heat (>24–32°C), cell swelling (not membrane stretch or reduced internal ionic strength), responses to heat increased in hypoosmotic solutions and *vice versa*, 4α-PDD, PMA, 5,6-epoxyeicosatrienoic acid; sensitized by PKC	Constitutively active (with strong buffering of intracellular Ca^{2+})	Constitutively active (with strong buffering of intracellular Ca^{2+}), potentiated by 2-APB
Blockers	Ruthenium red (voltage dependent block), La^{3+}, Gd^{3+}	Ruthenium red ($IC_{50} = 121$ nM), econazole, miconazole, $Pb^{2+} = Cu^{2+} = Gd^{3+} > Cd^{2+} > Zn^{2+} > La^{3+} > Co^{2+} > Fe^{2+}$; Mg^{2+}	Ruthenium red ($IC_{50} = 9\ \mu$M), Cd^{2+}, Mg^{2+}, La^{3+}
Functional characteristics	$\gamma = \sim 60$ pS at −60 mV, ~90–100 pS at +60 mV; conducts mono- and di-valent cations with a preference for divalents ($P_{Ca}/P_{Na} = 6–10$); dual (inward and outward) rectification; potentiated by intracellular Ca^{2+} *via* Ca^{2+}/calmodulin; inhibited by elevated intracellular Ca^{2+} *via* an unknown mechanism ($IC_{50} = 0.4\ \mu$M); potentiated by Src family tyrosine kinase; associates with MAP7 and calmodulin	$\gamma = 65–78$ pS for monovalent ions at negative potentials, conducts mono- and di-valents with high selectivity for divalents ($P_{Ca}/P_{Na} > 107$); voltage- and time-dependent inward rectification; inhibited by intracellular Ca^{2+} promoting fast inactivation and slow downregulation; feedback inhibition by Ca^{2+} reduced by calcium binding protein 80-K-H; inhibited by extracellular acidosis; upregulated by 1,25-dihydrovitamin D3; associates with TRPV6, S100A10 – annexin II, calmodulin, calbindin D_{28} and Rab11	$\gamma = 58–79$ pS for monovalent ions at negative potentials, conducts mono- and di-valents with high selectivity for divalents ($P_{Ca}/P_{Na} > 130$); voltage- and time-dependent inward rectification; inhibited by intracellular Ca^{2+} promoting fast and slow inactivation; gated by voltage-dependent channel blockade by intracellular Mg^{2+}; slow inactivation due to Ca^{2+}-dependent calmodulin binding; phosphorylation by PKC inhibits Ca^{2+}-calmodulin binding and slow inactivation; upregulated by 1,25-dihydroxyvitamin D3; associates with TRPV5

Activation of TRPV1 by depolarisation is strongly temperature-dependent *via* a channel opening rate that increases with increasing temperature. The potential for half maximal depolarisation ($V_{1/2}$) is shifted in the hyperpolarizing direction both by increasing temperature and by exogenous agonists (Voets *et al*., 2004). Capsaicin, resiniferatoxin and olvanil are exogenous agonists of TRPV1 that possess a vanilloid group, but the receptor is also activated by endogenous lipids that lack a vanilloid moiety (see van der Stelt & Di Marzo, 2004). Adenosine has recently been proposed to be an endogenous antagonist of TRPV1 (Puntambekar *et al*., 2004). Blockade of TRPV1 by capsazepine, 6-iodo-*nor*dihydrocapsaicin, BCTC, JYL1421 and SB366791 is competitive; all other antagonists listed act by non- or uncompetitive antagonism. [^{3}H]-Resiniferatoxin and [^{125}I]-resiniferatoxin are radioligands for TRPV1. Capsaicin, resiniferatoxin or low extracellular pH (4.0–5.0) do not activate TRPV2, or TRPV3. TRPV2 likely plays a role in skeletal muscle and cardiac muscle degeneration and the pain pathway. TRPV3 can co-assemble with TRPV1 to form a functional hetero-oligomer. The sensitivity of TRPV4 to heat, but not 4α-PDD, is lost upon patch excision. TRPV4 is activated by anandamide and arachidonic acid following P450 epoxygenase-dependent metabolism to 5,6-epoxyeicosatrienoic acid (reviewed by Nilius *et al*., 2004). Activation of TRPV4 by cell swelling, but not heat, or phorbol esters, is mediated *via* the formation of 5,6-epoxyeicosatrienoic acid. Phorbol esters bind directly to TRPV4. TRPV5 preferentially conducts Ca^{2+} under physiological conditions, but in the absence of extracellular Ca^{2+}, conducts monovalent cations. Single channel conductances listed for TRPV5 and TRPV6 were determined in divalent cation-free extracellular solution. Ca^{2+}-induced inactivation occurs at hyperpolarized potentials when Ca^{2+} is present extracellularly. Single channel events cannot be resolved (probably due to greatly reduced conductance) in the presence of extracellular divalent cations. Measurements of P_{Ca}/P_{Na} for TRPV5 and TRPV6 are dependent upon ionic conditions due to anomalous mole fraction behaviour. Blockade of TRPV5 and TRPV6 by extracellular Mg^{2+} is voltage-dependent. Intracellular Mg^{2+} also exerts a voltage dependent block that is alleviated by hyperpolarization and contributes to the time-dependent activation and deactivation of TRPV6 mediated monovalent cation currents. TRPV5 and TRPV6 differ in their kinetics of Ca^{2+}-dependent inactivation and recovery from inactivation. TRPV5 and TRPV6 function as homo- and hetero-tetramers. TRPV6 is up-regulated in prostate cancer. TRPV5 and TRPV6 are essential for the re-absorption and absorption of Ca^{2+} in the kidney and intestine, respectively.

TRPA family: The TRPA family currently comprises one mammalian member, TRPA1, which in some (Story *et al*., 2003; Bandell *et al*., 2004), but not other (Jordt *et al*., 2004), studies is activated by noxious cold. Additionally, TRPA1 has recent been proposed to be a component of a mechanosensitive transduction channel of vertebrate hair cells (Corey *et al*., 2004). TRPA1 presents the unusual structural feature of 14 ankyrin repeats within the intracellular N-terminal domain.

Nomenclature	**TRPA1**
Other names	ANKTM1, p120, TRPN1
Ensembl ID	ENSG00000104321
Activators	Cooling ($<17^{\circ}$C) (disputed), isothiocyanates, THC, cinnamaldehyde, bradykinin (insensitive to menthol and capsaicin)
Blockers	Ruthenium red (IC_{50} $<1\,\mu$M)
Functional characteristics	Conducts mono- and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 0.84$); outward rectification; inactivates in response to prolonged cooling; sensitises in response to repeated applications of cinnamaldehyde; activated by OAG and arachidonic acid downstream of receptor-mediated PLC stimulation

Icilin activates TRPM8 in addition to TRPA1 (Jordt *et al*., 2004).

TRPML family: The TRPML family consists of three mammalian members (TRPML1-3). TRPML channels are probably restricted to intracellular vesicles and mutations in the gene (*MCOLN1*) encoding TRPML1 (mucolipin 1) are the cause of mucolipidosis type IV (MLIV) in man, a lysosomal storage disorder. TRPML1 is important for sorting/transport of endosomes in the late endocytotic pathway. TRPML2 (MCLN2, ENSG00000153898) and TRPML3 (ENSG00000055732) remain to be functionally characterised and are excluded from the table. TRPML3 is important for hair cell maturation, stereocilia maturation and intracellular vesicle transport.

Nomenclature	**TRPML1**
Other names	MCLN1, mucolipin-1 (ML1)
Ensembl ID	ENSG00000090674
Activators	Constitutively active, probably activated by $[Ca^{2+}]_I$
Blockers	Amiloride (1 mM)
Functional characteristics	$\gamma = 46$ pS (main state in the presence of a K^+ gradient), multiple conductance states may correspond to complexes with variable channel numbers; conducts mono- and di-valent cations; channel opening decreased at negative potentials; channel opening blocked by 'intravesicular' acidification; loop between TM1 and TM2 is a lipase

Data in the table are for *in vitro* transcribed/translated TRPML1 incorporated into liposomes (Raychowdhury *et al*., 2004).

TRPP family: The TRPP family (reviewed by Delmas *et al*., 2004) subsumes the polycystins that are structurally divided into two groups, polycystic kidney disease 1-like (PKD1-like) and polycystic kidney disease 2-like (PKD2-like). Members of the PKD1-like group, in mammals, include PKD1 (recently reclassified as TRPP1), PDKREJ, PKD1L1, PKD1L2 and PKD1L3. The PKD2-like members comprise PKD2, PKD2L1 and PKD2L2, which have been renamed TRPP2, TRPP3 and TRPP5, respectively (Moran *et al*., 2004). PKDREJ (ENSG00000130943), PKD1L1 (ENSG00000158683), PKD1L2 (ENSMUS00000034416), PKD1L3 (ENSG00000187008) and TRPP5 (ENSG00000078795) are not listed in the table due to lack of functional data. Similarly, TRPP1 (ENSG00000008710) is also omitted because, although one recent study (Babich *et al*., 2004) has reported the induction of a cation conductance in CHO cells transfected with TRPP1, there is no unequivocal evidence that TRPP1 is a channel *per se* and in other studies (*e.g*. Hanaoka *et al*., 2000; Delmas *et al*., 2004) TRPP1 is incapable of producing currents. Conversely, TRPP1 has been demonstrated to activate G-proteins constitutively and subsequently c-Jun N-terminal kinase. Unlike other TRP channels, TRPP1 contains 11 putative transmembrane domains and an extremely large and complex extracellular N-terminal domain that contains several adhesive domains. There is good evidence that TRPP1 and TRPP2 physically couple to act as a signalling complex (Delmas, 2004). The association of TRPP1 and TRPP2 suppresses the G-protein stimulating activity of TRPP1 and also the constitutive channel activity of TRPP2. Antibodies directed against the REJ domain of TRPP1 alleviate such mutual inhibition, simultaneously enhancing TRPP2 channel gating and the activation of G-proteins by TRPP1.

Nomenclature	**TRPP2**	**TRPP3**
Other names	Polycystin-2 (PC2), polycystic kidney disease 2 (PKD2)	Polycystic kidney disease 2-like 1 protein (PKD2L1)
Ensembl ID	ENSG00000118762	ENSG00000107593
Activators	Constitutive activity, suppressed by co-expression of TRPP1	Low constitutive activity
Blockers	La^{3+}, Gd^{3+}, amiloride	La^{3+}, Gd^{3+-}, flufenamate
Functional characteristics	$\gamma = 123$–177 pS (with K^+ as charge carrier); $P_{Na}/P_K = 0.14$–1.1; conducts both mono- and di-valent cations; probably associates with TRPV4; also associates with cortactin and cadherin *via* TRPP1	$\gamma = 137$ pS (within the range -50 to $+50$ mV), conducts mono- and di-valent cations with a preference for divalents ($P_{Ca}/P_{Na} = 4.3$); slight inward rectification; activated and subsequently inactivated by intracellular Ca^{2+}; inhibited by extracellular acidosis

Data in the table are extracted from Delmas *et al*. (2004a). Broadly similar single channel conductance, mono- and di-valent cation selectivity and sensitivity to blockers are observed for TRPP2 co-expressed with TRPP1 (Delmas, 2004b). TRPP2 is important for cilia movement, development of the heart, skeletal muscle and kidney. TRPP2 is also likely to act as an intracellular Ca^{2+}-release channel. Single channel conductance quoted for TRPP3 with $[Na^+]$ set at 100 mM; conductance in the presence of symmetrical K^+ solutions (100 mM) is substantially larger and demonstrates slight inward rectification. Ca^{2+}, Ba^{2+} and Sr^{2+} permeate TRPP3, but reduce inward currents carried by Na^+. Mg^{2+} is largely impermeant and exerts a voltage dependent inhibition that increases with hyperpolarization. TRPP3 plays a role in retinal development.

Abbreviations: **2-APB**, 2-amino ethoxyphenylborate; **4α-PDD**, 4α-phorbol 12,13-didecanoate; **5-(*S*)-HETE**, 5-(*S*)-hydroxyeicosatetraenoic acid; **12-(*S*)-HPETE and 15-(*S*)-HPETE**, 12- and 15-(*S*)-hydroperoxyeicosatetraenoic acids; **20-HETE**, 20-hydroxyeicosatetraenoic acid; **BCTC**; *N*-(4-tertiarybutylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2 *H*)-carbox-amide; **DD161515**, *N*-[2-(2-(*N*-methylpyrrolidinyl)ethyl)glycyl]-[*N*-[2,4-dichlorophenethyl]glycyl]-*N*-(2,4-dichlorophenethyl)-glycinanmide; **DD191515**, *N*-[3-(*N*-*N*-diethylamino)propyl]glycyl]-*N*-[2,4-dichlorophenethyl]glycyl]-*N*-(2,4-dichlorophenethyl)glycinanmide, **GEA3162**, 1,2,3,4-oxatriazolium-5-amino-3-(3,4-dichlorophenyl)-chloride; **JYL1421**, *N*-(4-tert-butylbenzyl)-*N*′-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea; **OAG**, 1-oleoyl-2-acetyl-*sn*-glycerol; **PMA**, phorbol 12 myristate 13-acetate; **RHC80267**, 1,6-di[O-(carbamoyl)cyclohexanone oxime]hexane; **SB366791**, *N*-(3-methoxyphenyl)-4-chlorocinnamide; **SDZ249665**, 1-[4-(2-amino-ethoxy)-3-methoxy-benzyl]-3-(4-tert-butyl-benzyl)-urea; **SKF96265**, 1-(β-(3-(4-methoxyphenyl)propoxy)-4-methoxyphenethyl)-1H-imidazole hydrochloride; **THC**, Δ^9-tetrahydrocannabinol

Further reading:

BEECH, D.J., XU, S.Z., MCHUGH, D. & FLEMMING, R. (2003). TRPC1 store-operated cationic channel subunit. *Cell Calcium*, **33,** 433–440.

BEECH, D.J., MURAKI, K. & FLEMMING, R. (2004). Non-selective cationic channels of smooth muscle and the mammalian homologues of *Drosophila TRP*. *J. Physiol (Lond.)*. **559,** 685–706.

BENHAM, C.D., GUNTHORPE, M.J. & DAVIS, J.B. (2003). TRPV channels as temperature sensors. *Cell Calcium*, **33,** 479–487.

CANTIELLO, H.F. (2004). Regulation of calcium signalling by polycystin-2. *Am. J. Physiol*., **286,** F1012-F1029.

CATERINA, M.J. & JULIUS, D. (2001). The vanilloid receptor: a molecular gateway to the pain pathway. *Annu. Rev. Neurosci*., **24,** 487–517.

CLAPHAM, D.E. (2003). TRP channels as cellular sensors. *Nature*, **426,** 517–524.

CLAPHAM, D.E., MONTELL, C., SCHULTZ, G. & JULIUS, D. (2003). International Union of Pharmacology. XLIII. Compendium of Voltage-gated ion channels. Transient receptor potential channels. *Pharmacol. Rev*., **55,** 591–596.

CLAPHAM, D.E., RUNNELS, L.W. & STRÜBING, C. (2001). The TRP ion channel family. *Nat. Rev. Neurosci*., **2,** 387–396.

COREY, D.P. (2003). New TRP channels in hearing and mechanosensation. *Neuron*, **39,** 585–588.

DELMAS, P., PADILLA, F., OSORIO, N., COSTE, B., RAOUX, M. & CREST, M. (2004a). Polycystins, calcium signaling, and human diseases. *Biochem. Biophys. Res. Commun*., **322,** 1374–1383.

DEN DEKKER, E., HOENDEROP, J.G., NILIUS, B. & BINDELS, R.J. (2003). The epithelial calcium channels, TRPV5 & TRPV6: from identification towards regulation. *Cell Calcium*, **33,** 497–507.

GUNTHORPE, M.J., BENHAM, C.D., RANDALL, A. DAVIS, J.D. (2002). The diversity in the vanilloid (TRPV) receptor family of ion channels. *Trends Pharmacol. Sci*., **23,** 183–191.

JORDT, S.E., MCKEMY, D.D. & JULIUS, D. (2003). Lessons from peppers and peppermint: the molecular logic of thermosensation. *Curr. Opin. Neurobiol*., **13,** 487–492.

MONTELL, C. (2003). Mg^{2+} homeostasis: the Mg^{2+}nificent TRPM chanzymes. *Curr. Biol*., **13,** R799–R801.

MONTELL, C., BIRNBAUMER, L., FLOCKERZI, V., BINDELS, R.J., BRUFORD, E.A., CATERINA, M.J., CLAPHAM, D.E., HARTENECK, C., HELLER, S., JULIUS, D., KOJIMA, I., MORI, Y., PENNER, R., PRAWITT, D., SCHARENBERG, A.M., SCHULTZ, G., SHIMIZU, N. & ZHU, M.X. (2002). A unified nomenclature for the superfamily of TRP cation channels. *Mol. Cell*., **9,** 229–231.

MONTELL, C. (2004). Exciting trips for TRPs. *Nat. Cell Biol*., **6,** 690–692.

MORAN, M.M., XU, H. & CLAPHAM, D.E. (2004). TRP ion channels in the nervous system. *Curr. Opin. Neurobiol*., **14,** 362–369.

NIJENHUIS, T., HOENDEROP, J.G., NILIUS, B. & BINDELS, R.J. (2003). (Patho)physiological implications of the novel epithelial Ca^{2+} channels TRPV5 and TRPV6. *Pflugers Arch*., **446,** 401–409.

NILIUS, B. (2003a). From TRPs to SOCs, CCEs, and CRACs: consensus and controversies. *Cell Calcium*, **33,** 293–298.

NILIUS, B. (2003b). Calcium-impermeable monovalent cation channels: a TRP connection? *Br. J. Pharmacol*., **138,** 5–7.

NILIUS, B., DROOGMANS, G. & WONDERGEM, R. (2003). Transient receptor potential channels in endothelium: solving the calcium entry puzzle? *Endothelium*, **10,** 5–15.

NILIUS, B., VRIENS, J., PRENEN, J., DROOGMANS, G. & VOETS, T. (2004). TRPV4 calcium channel: a paradigm for gating diversity. *Am J. Physiol*., **286,** C195–C205.

PATAPOUTIAN, A., PEIER, A.P., STORY, G. & VISWANATH, V. (2003). ThermoTRPs and beyond: Mechanisms of temperature sensation. *Nat. Rev. Neurosci*., **4,** 529–539.

PLANT, T.D. & SCHAEFER, M. (2003). TRPC4 and TRPC5: receptor-operated Ca^{2+}-permeable non-selective cation channels. *Cell Calcium*, **33,** 441–450.

PUTNEY, J. (Ed.) (2004). Mammalian TRP Channels as Molecular Targets – Novartis Foundation Symposium No. 258, pp 1–286. Wiley, Europe.

SZALLASI, A. & BLUMBERG, P.M. (1999). Vanilloid (capsaicin) receptors and mechanisms. *Pharmacol. Rev*., **51,** 159–211.

SZALLASI, A. & DI MARZO, V. (2000). New perspectives on enigmatic vanilloid receptors. *Trends Neurosci*., **23,** 491–497.

TREBAK, M., VAZQEUZ, G., BIRD, G. & PUTNEY, J.W. (2003a). The TRPC3/6/7 subfamily of cation channels. *Cell Calcium*, **33,** 451–461.

VAN DER STELT, M. & DIMARZO (2004). Endovanilloids: putative endogenous ligands of transient receptor potential vanilloid 1 channels. *Eur. J. Biochem*., **271,** 1827–1834.

VENNEKENS, R., DROOGMANS, G. & NILIUS, B. (2001). Function properties of the epithelial Ca^{2+} channel, ECaC. *Gen. Physiol. Biophys*., **20,** 239–253.

VENNEKENS, R., VOETS, T., BINDELS, R.J., DROOGMANS, G. & NILIUS, B. (2002). Current understanding of mammalian TRP homologues. *Cell Calcium*, **31,** 253–264.

VENTAKATACHALAM, K., VAN ROSSUM, D.B., PATTERSON, R.L., MA, H.-T. & GILL, D.L. (2002). The cellular and Molecular basis of store-operated calcium entry. *Nature Cell Biol*., **4,** E263–E272.

VOETS, T. & NILIUS, B. (2003). TRPs make sense. *J. Membrane Biol*., **192,** 1–8.

ZU, M.X. & TANG, J. (2004). TRPC channel interactions with calmodulin and IP_3 receptors. *Novartis Found. Symp*., **258,** 44–58.

ZITT, C., HALASZOVICH, C.R. & LUCKHOFF, A. (2002) The TRP family of cation channels: probing and advancing the concepts on receptor-activated calcium entry. *Prog. Neurobiol*., **66,** 243–264.

References:

AARTS, M. *et al*. (2003). *Cell*, **115,** 863–877.
ANDERSON, D.A. *et al*. (2004). *J. Neurosci.*, **24,** 5364–5369.
BABICH, V. *et al*. (2004). *J. Biol. Chem*., **279,** 25582–25589.
BANDELL, M. *et al*. (2004). *Neuron*, **41,** 849–857.
COREY, D.P. *et al*. (2004). *Nature*, **432,** 723–730.
DELMAS, P. *et al*. (2004b). *FASEB J*., **18,** 740–742.
FREICHEL, M. *et al*. (2001). *Nature Cell Biol*., **3,** 121–127.
HANAOKA, K. *et al*. (2000). *Nature*, **408,** 990–994.
HARA, T. *et al*. (2002). *Mol. Cell*, **9,** 163–173.
HOFMANN, T. *et al*. (2003). *Curr. Biol*., **13,** 1153–1158.
INOUE, R. *et al*. (2001). *Circ. Res*., **88,** 325–332.
JORDT, S.E. *et al*. (2004). *Nature*, **427,** 260–265.
KIM, S.J. *et al*. (2003). *Nature*, **426,** 285–291.
LAUNAY, P. *et al*. (2002). *Cell*, **109,** 397–407.
NADLER, M.J.S. *et al*. (2001). *Nature*, **411,** 590–595.
NILIUS, B. *et al*. (2003). *J. Biol. Chem*., **278,** 30813–30820.
PUNTAMBEKAR, P *et al*. (2004). *J. Neurosci*., **24,** 3663–3671.
PERRAUD, A.L. *et al*. (2001). *Nature*, **411,** 595–599.
RUNNELS, L.W. *et al*. (2001). *Science*, **291,** 1043–1047.
SCHMITZ, C. *et al*. (2003). *Cell*, **114,** 191–200.
SMITH, G.D. *et al*. (2002). *Nature*, **418,** 186–190.
STORY, G.M. *et al*. (2003). *Cell*, **112,** 819–829.
STRÜBING, C. *et al*. (2001). *Neuron*, **29,** 645–655.
TAKEZAWA, R. *et al*. (2004). *Proc. Natl. Acad. Sci. USA*, **101,** 6009–6014.
TANG, J. *et al*. (2001). *J. Biol. Chem*., **276,** 21303–21310.
TIRUPPATHI, C. *et al*. (2002). *Circ. Res*., **91,** 70–76.
TREBAK, M. *et al*. (2003b). J. *Biol. Chem*., **278,** 16244–16252.
URBAN, L. *et al*. (2000). *Pain*, **89,** 65–74.
VAZQUEZ, G. *et al*. (2004). *J. Biol. Chem*. **279,** 40521–40528.
VENTAKATCHALAM, K. *et al*. (2001). *J. Biol. Chem*. **276,** 33980–33985.
VOETS, T. *et al*. (2004a). *J. Biol. Chem*. **279,** 19–25.
VOETS, T. *et al*. (2004b). *Nature*, **430,** 748–754.
YUAN, J.P. *et al*. (2003). *Cell*, **114,** 777–789.
ZHANG, Y. *et al*. (2003). *Cell*, **112,** 293–301.