Acid-sensing ion channels

Overview: Acid-sensing ion channels (ASICs, provisional nomenclature) are members of an 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; Lingueglia *et al*., 2006) 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 ASIC1b2 (Ugawa *et al*., 2001)) and ASIC2 (provisionally termed ASIC2a (MDEG1) and ASIC2b (MDEG2); Lingueglia *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 mammalian 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), but the zebrafish orthologue (zASIC4.1) is functional as a homomer (Paukert *et al*., 2004). 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; Lingueglia *et al*., 2006). Heterologously expressed heteromultimers 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; Lingueglia *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 nonselective 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	ENSG00000197150
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)	APETx2 (63 nM), 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). APETx2 most potently blocks homomeric ASIC3 channels, but also ASIC2b + ASIC3, ASIC1b + ASIC3, and ASIC1a + ASIC3 heterometric channels, with IC_{50} values of 117 nM, 900 nM and 2 μM, respectively (Diochot *et al*., 2004). APETx2 has no effect on ASIC1a, ASIC1b, ASIC2a, or ASIC2a + ASIC3. A-317567 blocks ASIC channels native to dorsal root ganglion neurones with an IC_{50} within the range 2 to 30 μM (Dube *et al*., 2005). The pEC_{50} values for proton activation of ASIC1a, ASIC1b, and ASIC3 are shifted to more acidic levels by increasing $[Ca^{2+}]_o$ (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 nonselective ($P_{Na}/P_K = 1.6$) (de Weille *et al*., 1998; Babinski *et al*., 1999). Nonsteroidal 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). However, removal of contaminating Zn^{2+} by chelation reveals a high-affinity block of homomeric ASIC1a and heteromeric ASIC1a + ASIC2 channels by Zn^{2+}, indicating complex biphasic actions of the divalent (Chu *et al*., 2004). 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: **A-317567**, C-{6-[2-(1-Isopropyl-2-methyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-cyclopropyl]-naphthalen-2-yl}-methanediamine, **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

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Aquaporins

Overview: Aquaporins and aquaglyceroporins are membrane channels that allow the permeation of water and certain other small solutes across the cell membrane. Since the isolation and cloning of the first aquaporin (AQP1) (Preston *et al*., 1992), 12 additional members of the family have been identified, although little is known about the functional properties of two of these (AQP11 (ENSG00000178301) and AQP12 (ENSG00000184945)). The other 11 aquaporins can be divided into two families (aquaporins and aquaglyceroporins) depending on whether they are permeable to glycerol (King *et al*., 2004). One or more members of this family of proteins have been found to be expressed in almost all tissues of the body. Individual AQP subunits have six transmembrane domains with an inverted symmetry between the first three and last three domains (Castle, 2005). Functional AQPs exist as tetramers but, unusually, each subunit contains a separate pore, so each channel has four pores.

Nomenclature	**AQP0**	**AQP1**	**AQP2**	**AQP3**
Ensembl ID	ENSG00000135517	ENSG00000106125	ENSG00000167580	ENSG00000165272
Activators	—	cGMP	—	—
Inhibitors	Hg^{2+}	Hg^{2+}, TEA, Ag^{+}	Hg^{2+}	Hg^{2+} acid pH
Permeability	Water (low)	Water (high)	Water (high)	Water (high), glycerol

Nomenclature	**AQP4**	**AQP5**	**AQP6**	**AQP7**
Ensembl ID	ENSG00000171885	ENSG00000161798	ENSG00000086159	ENSG00000165269
Activators	—	—	Acid pH	—
Inhibitors	PKC activation	Hg^{2+}	Hg^{2+}	Hg^{2+}
Permeability	Water (high)	Water (high)	Water (low), anions	Water (high), glycerol

Nomenclature	**AQP8**	**AQP9**	**AQP10**
Ensembl ID	ENSG00000103375	ENSG00000103569	ENSG00000143595
Activators	—	—	—
Inhibitors	Hg^{2+}	Hg^{2+}, phloretin	Hg^{2+}
Permeability	Water (high)	Water (low), glycerol	Water (low), glycerol

AQP6 is an intracellular channel permeable to anions as well as water (Yasui *et al*. 1999).

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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; 2005). 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 10 cloned α-subunits can be grouped into three families: (1) the high-voltage activated dihydropyridine-sensitive (L-type, $Ca_V1.x$) channels; (2) the high-voltage activated dihydropyridine-insensitive ($Ca_V2.x$) channels and (3) the low-voltage-activated (T-type, $Ca_V3.x$) channels. Each $\alpha 1$ 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 $\alpha 2-\delta$ 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	Less sensitive to dihydropyridine antagonists verapamil	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-pyridinecarboxylate

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Chloride

Overview: Chloride channels are a functionally and structurally diverse group of anion selective channels involved in processes including the regulation of the excitability of neurones, skeletal, cardiac and smooth muscle, cell volume regulation, transepithelial salt transport, the acidification of internal and extracellular compartments, the cell cycle and apoptosis (reviewed by Nilius & 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; 2005a,b; Nilius & Droogmans, 2003; Dutzler, 2004; Chen, 2005) contains nine members that fall into three groups; ClC-1, ClC-2, hClC-Ka (rClC-K1) and hClC-Kb (rClC-K2); ClC-3 -5, and ClC-6, -7. ClC-1 and ClC-2 are plasma membrane chloride channels as are ClC-Ka and ClC-Kb (largely expressed in the kidney) when associated with barttin (ENSG00000162399), a 320-amino-acid 2TM protein (Estévez *et al*., 2001). The localisation of CIC-3, ClC-4 and ClC-5 is likely to be predominantly intracellular and recent reports indicate that ClC-4 and ClC-5 (and by inference ClC-3) function as Cl^-/H^+ antiporters, rather than classical Cl^- channels (Picollo & Pusch, 2005; Scheel *et al*., 2005; reviewed by Miller, 2006 & Pusch *et al*., 2006). An intracellular location has been demonstrated for ClC-6 (ENSG00000011021) and ClC-7 (ENSG00000103249) also (reviewed by Jentsch *et al*., 2005b). 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 17 intramembrane 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; Chen, 2005). As found for ClC-4 and ClC-5, the prokaryotic ClC homologue functions as an H^+/Cl^- antiporter, rather than as an ion channel (Accardi & Miller, 2004).

Nomenclature	**ClC-1**	**ClC-2**	**ClC-Ka**	**ClC-Kb**
Other names	Skeletal muscle Cl^- channel	—	ClC-K1 (rodent)	ClC-K2 (rodent)
Ensembl ID	ENSG00000188037	ENSG00000114859	ENSG00000186510	ENSG00000184908
Activators	Constitutively active	Arachidonic acid, amidation, acid-activated omeprazole, lubiprostone (SPI-0211)	Constitutively active (when co-expressed with barttin)	Constitutively active (when co-expressed with barttin)
Blockers	*S*-(−)CPP, S-(−)CPB, 9-AC, Cd^{2+}, Zn^{2+}	DPC, Cd^{2+}, Zn^{2+}	3-phenyl-CPP, DIDS	3-phenyl-CPP, DIDS
Functional characteristics	$\gamma = 1-1.5$ pS; Voltage-activated (depolarization); inwardly rectifying; deactivation upon repolarization (by fast gating of single protopores and a slower common gate); inhibited by ATP binding to cytoplasmic CBS domains	$\gamma = 2-3$ pS; voltage-activated (hyperpolarization), inward rectification (steady-state currents); slow inactivation (seconds); activated by cell swelling, PKA and weak extracellular acidosis; inhibited by phosphorylation by p34(cdc2)/cyclin B	Slight outward rectification; largely time-independent currents; inhibited by extracellular acidosis; potentiated by extracellular Ca^{2+} and niflumic acid (10 – 1000 μM)	Slight outward rectification; largely time-independent currents; inhibited by extracellular acidosis; potentiated by extracellular Ca^{2+} and niflumic acid (10 – 1000 μM)

Nomenclature	**ClC-3**	**ClC-4**	**ClC-5**
Ensembl 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	Cl^-/H^+ antiporter (Picollo & Pusch, 2005; Scheel *et al*., 2005); extreme outward rectification; largely time-independent currents; inhibited by extracellular acidosis; ATP hydrolysis required for full activity	Cl^-/H^+ antiporter (Picollo & Pusch, 2005; Scheel *et al*., 2005); 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's myotonia). 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 Jentsch *et al*. (2005b). Disruption of the *ClC-2* gene in mice is associated with testicular and retinal degeneration. 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). Knockout of the ClC-K1 channel induces nephrogenic diabetes insipidus and classic (type III) Bartter's syndrome and Gitelman's variant of Bartter's syndrome are associated with mutations of the ClC-Kb chloride channel (reviewed by Jentsch *et al*., 2005b; Uchida Sasaki, 2005). ClC-Ka is approximately 5–6-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 and further complicated by the inference that ClC-3 is a Cl^-/H^+ exchanger, rather than an ion channel (Picollo & Pusch, 2005). 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 in to 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; Jentsch *et al*., 2005b). 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 in mice leads to osteopetrosis, blindness and lysosomal dysfunction (Kornak *et al*., 2001, Jentsch *et al*., 2005b).

CFTR. CFTR, a 12TM, ABC type protein, is a cAMP-regulated epithelial cell membrane Cl- channel involved in normal fluid transport across various epithelia. The most common mutation in CFTR (i.e. the deletion mutant, ΔF508) results in impaired trafficking of CFTR and reduces its incorporation into the plasma membrane causing cystic fibrosis. 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 SCL26 transporters, an effect facilitated by PKA-mediated phosphorylation of the R domain of CFTR (Ko *et al*., 2004).

Nomenclature	**CFTR**
Other names	ABCC7
Ensembl ID	ENSG00000001626
Activators	Flavones (e.g. UCCF-339, UCCF-029, apigenin, genistein), benzimidazolones (e.g. UCCF-853, NS004), benzoquinolines (e.g. CBIQ), psoralens (8-methoxypsoralen), 1,4-dihydropyridines (e.g. felopidine, nimodipine), capsaicin
Blockers	GlyH-101, $CFTR_{inh}$-172, glibenclamide
Functional characteristics	$\gamma = 6-10$ pS; permeability sequence = $Br^- \geq Cl^- > I^- > F^-$, ($P_{Na}/P_{Cl} = 0.1 - 0.03$); 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 including syntaxin 1A, Munc18 and PDZ domain proteins such as NHERF (EBP50) and CAP70

CFTR contains two cytoplasmic nucleotide-binding domains (NBDs) that bind ATP. A single open–closing cycle is hypothesised to involve, in sequence: binding of ATP at the N-terminal NBD1, ATP binding to the C-terminal NBD2 leading to the formation of an intramolecular NBD1–NBD2 dimer associated with the open state, and subsequent ATP hydrolysis at NBD2 facilitating dissociation of the dimmer and channel closing (Vergani *et al*. 2005). Phosphorylation by PKA at sites within a cytoplasmic regulatory (R) domain are required for the binding of ATP to gate CFTR (Gadsby *et al*., 2006). PKC (and PKGII within intestinal epithelial cells *via* guanylin-stimulated cGMP formation) positively regulates CFTR activity.

Calcium activated chloride channel: Chloride channels activated by intracellular calcium (CaCC) are widely expressed in excitable and nonexcitable cells, where they perform diverse functions (Hartzell *et al*., 2005). The molecular nature of CaCC is unclear. Numerous putative calcium-activated chloride channel proteins (the CLCA family) have been cloned from human, murine, bovine and porcine species (reviewed by Loewen & Forsyth, 2005), but their relationship to endogenous CaCC is controversial (reviewed by Jentsch *et al*., 2002; Eggermont, 2004). 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 ascite 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; Eggermont *et al*., 2004). CLCA members and native CaCC also differ in that the former are inhibited by dithiothreitol, whereas the latter are not (Eggermont, 2004). However, a recent report raises the possibility that the properties of CLCA isoforms may be 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 been shown to be an anion-selective channel, activated by physiological concentrations of intracellular Ca^{2+}, in heterologous expression system (Qu *et al*., 2003; 2004).

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

Blockade of $I_{Cl(Ca)}$ by niflumic acid, DIDS and 9-AC is voltage-dependent, whereas block by NPPB is voltage-independent (Hartzell *et al*., 2005). Extracellular niflumic acid 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 (reviewed by Hartzell *et al*., 2005). 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, macula densa cells of the kidney 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 similar channel mediates ATP release from macula densa cells within the thick ascending of the loop of Henle in response to changes in luminal NaCl concentration (Bell *et al*., 2003). A family of human-high conductance Cl^- channels (TTYH1–3) that resemble Maxi Cl^- channels has 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-oestrogens (tamoxifen, toremifine), extracellular chlorpromazine and triflupromazine, cell swelling
Blockers	SITS, DIDS, NPPB, DPC, intracellular arachidonic acid, extracellular Zn^{2+} and Gd^{3+}
Functional characteristics	$\gamma = 280-430$ 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 shutdown ($K_d = 4-5\,\mu$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-estrogens in whole cell recordings requires the presence of intracellular nucleotides and is prevented by pre-treatment with 17β-estradiol, 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 & 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 knockout 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 of 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	NS3728, DCPIB, 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). A proton-activated, outwardly rectifying anion channel has also recently been described (Lambert & Oberwinkler, 2005).

Abbreviations: **9-AC**, anthracene-9-carboxylic acid; **CBIQ**, 4-chlorobenzo[F]isoquinoline; **$CFTR_{inh}$-172**, 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; ***S*-(−)CPB**, *S*-(−)2-(4-chlorophenoxy)butyric acid; ***S*-(−)CPP**, *S*-(−)2-(4-chlorophenoxy)propionic 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**, 4,4́-diisothiocyanostilbene-2,2́-disulphonic acid; **DNDS**, 4,4́-dinitrostilbene-2,2́-disulphonic acid; **GlyH-101**, *N*-(2-naphthalenyl)-[(3,5-dibromo-2,4-dihydroxyphenyl)methylene]glycine hydrazide; **NDGA**, nordihydroguiaretic acid; **DPC**, diphenylamine carboxylic acid; **DPDPC**, dichloro-diphenylamine 2-carboxylic 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; **NS3728**, *N*-[3,5-bis(trifluromethyl)-phenyl]-*N*′[4-bromo-2-(1*H*-tetrazol-5yl)-phenyl]urea; **SITS**, 4́-isothiocyanostilbene-2,2́-disulphonic acid; **UCCF-029**, 2-(4-pyridinium)benzo[*h*]4*H*-chromen-4-one bisulphate; **UCCF-180**, 3-(3-butynyl)-5-methoxy-1-phenylpyrazole-4-carbaldehyde; **UCCF-853**, 1-(3-chlorophenyl)-5-trifluoromethyl-3-hydroxy-benzimidazol-2-one

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Cyclic nucleotide-gated channels

Overview: Cyclic nucleotide-gated (CNG) channels are responsible for signalling in the primary sensory cells of the vertebrate visual and olfactory systems. A standardised nomenclature for CNG channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels (see Hofmann *et al*., 2002; 2003; 2005).

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 ($EC_{50} \approx 30\,\mu M$) > > cAMP	Intracellular cyclic nucleotides: cGMP ≈ cAMP ($EC_{50} \approx 1\,\mu M$)	Intracellular cyclic nucleotides: cGMP ($EC_{50} \approx 30\,\mu M$) > > 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).

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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), which has a wider tissue distribution. ENaC subunits contain two 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)**
Ensemble ID	Human α subunit, ENSG00000111319; human β subunit, ENSG00000168447; human γ subunit, ENSG00000166828; human δ subunit, ENSG00000162572
Blockers (IC_{50})	Amiloride (100–200 nM), benzamil (~10 nM), triamterene (~5 μM) (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* both serum and glucocorticoid-regulated kinases (SGK1, 2 and 3) (Debonneville *et al*., 2001; Friedrich *et al*., 2003) and *via* cAMP/PKA (Morris and Schafer, 2002). Recent data indicate that ENaC is also activated by membrane-bound serine proteases (Rossier, 2004) and is also regulated by phosphatidylinositides (Pochynyuk *et al*., 2006).

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 overexpression or underexpression 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). Regulation of ENaC by phosphoionositides may underlie insulin-evoked renal Na^+ retention that can complicate the clinical management of type 2 diabetes using insulin-sensitizing thiazolidinedione drugs (Guan *et al*. 2005).

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Hyperpolarisation-activated, cyclic nucleotide-gate (HCN)

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 six transmembrane domains and form tetramers. It is believed that the channels can form heteromers with each other, as has been shown for HCN1 and HCN4 (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; 2005).

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 the fastest, HCN4 the slowest and HCN2 and 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.

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

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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 and 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).

Abbreviations: **FKBP**, FK506-binding protein

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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 (note that these family references may alter with Ensembl release. The numbers quoted here are for Ensembl release 4I, October 2006). The three main families are the 2TM (two transmembrane domain), 4TM and 6TM families. A standardised nomenclature for potassium channels has been proposed by the NC-IUPHAR subcommittees on potassium channels (see Gutman & Chandy, 2002, Gutman *et al.*, 2003, Yu & Catterall, 2004; Goldstein *et al.*, 2005; Gutman *et al.*, 2005; Kubo *et al.*, 2005; Wei *et al.*, 2005).

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	ENSF00000000218	ENSF00000000218	ENSF00000000218	ENSF00000000218
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	ENSF00000000218	ENSF00000000218	ENSF00000000218
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 two pore domains (indeed, they are often referred to as two-pore domain K channels or K2P) and so it is envisaged that they form functional dimers rather than the usual K channel tetramers. There is some evidence that they can form heterodimers within subfamilies (e.g. $K_{2P}3.1$ with $K_{2P}9.1$). There is no current, clear, consensus on nomenclature of 4TM K channels, nor on the division into subfamilies (see Gutman & Chandy, 2002, Gutman *et al.,* 2003, Goldstein *et al.,* 2005). 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	$K_{2P}1.1$ (TWIK1) $K_{2P}6.1$ (TWIK2) $K_{2P}7.1$ (KNCK7)	$K_{2P}2.1$ (TREK1) $K_{2P}10.1$ (TREK2) $K_{2P}4.1$ (TRAAK)	$K_{2P}3.1$ (TASK1) $K_{2P}9.1$ (TASK3) $K_{2P}15.1$ (TASK5)	$K_{2P}16.1$ (TALK1) $K_{2P}5.1$ (TASK2) $K_{2P}17.1$ (TASK4)	$K_{2P}13.1$ (THIK1) $K_{2P}12.1$ (THIK2)	$K_{2P}18.1$ (TRESK1)
Ensembl family	ENSF00000000468	ENSF00000000468	ENSF00000002737	ENSF00000000468	ENSF00000004306	ENSF00000004883
Activators	—	Halothane (not TRAAK), riluzole stretch, heat, arachidonic acid, acid pH_i	Halothane alkaline pH_o ($K_{2P}3.1$)	Alkaline pH_O	—	—
Inhibitors	Acid pH_i	—	Anandamide ($K_{2P}3.1$, $K_{2P}9.1$) ruthenium red ($K_{2P}9.1$) acid pH_O	—	Halothane	Arachidonic acid
Functional characteristic	Background current	Background current	Background current	Background current	Background current	

The $K_{2P}7.1$, $K_{2P}15.1$ and $K_{2P}12.1$ subtypes, when expressed in isolation, are nonfunctional. All 4TM channels are insensitive to the classical potassium channel blockers 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	ENSF00000000586	ENSF00000000387	ENSF00000001015	ENSF00000001600
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	**K_V7.x ('KCNQ')**	**K_V10.x, K_V11.x, K_V12.x ('EAG')**	**K_{Ca}1.x, K_{Ca}4.x, K_{Ca}5.x ('Slo')**	**K_{Ca}2.x, K_{Ca}3.x ('SK')**
Subtypes	K_V.7.1–7.5 (KCNQ1-5)	K_V10.1–10.2 (eag1–2) K_V11.1–11.3 (erg1-3, herg 1–3) K_V12.1–12.3 (elk1-3)	K_{Ca}1.1, K_{Ca}4.1–4.2, K_{Ca}5.1 Slo (BK), Slack, Slick	K_{Ca}2.1–2.3 (SK1–SK3) K_{Ca}3.1 (SK4, IK)
Ensembl family	ENSF00000000511	ENSF00000000404	ENSF00000001057/1504	ENSF00000000967
Activators	Retigabine (K_V.7.2,–5)	—	NS004, NS1619	—
Inhibitors	TEA (K_V.7.2, 7.4), XE991 (K_V.7.1, 7.2, 7.4, 7.5), linopirdine	E-4031 (K_V11.1), astemizole (K_V11.1), terfenadine (K_V11.1)	TEA, charybdotoxin, iberiotoxin	Charybdotoxin (K_{Ca}3.1), apamin (K_{Ca}2.1–2.3)
Functional characteristic	K_V7.1 – cardiac IK_S K_V7.2/7.3–M current	K_V11.1 – cardiac IK_R	Maxi K_{Ca} K_{Na} (slack & slick)	SK_{Ca} (K_{Ca}2.1–2.3) IK_{Ca} (K_{Ca}3.1)
Associated subunits	minK, MiRP2 (K_V.7.1)	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

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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 nonmammalian 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	ENSG00000198838
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+}(>100 μM), cytosolic Mg^{2+} (mM), calmodulin at high cytosolic Ca^{2+} dantrolene	Cytosolic Ca^{2+}(>1 mM), 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 (50 mM 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).

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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 transmembrane segments (S1–S6) and a pore-forming loop. The positively charged fourth transmembrane segment (S4) acts as a voltage sensor and is involved in channel gating. Auxiliary β1, β2, β3 and now β4 (Yu *et al*., 2003) subunits consist of a large extracellular N-terminal domain, a single transmembrane segment and a shorter cytoplasmic domain.

The nomenclature for sodium channels was proposed by Goldin *et al.,* (2000) and approved by the NC-IUPHAR subcommittee on sodium channels (Catterall *et al*., 2002; 2003; 2005).

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
Activators	Veratridine, batrachotoxin	Veratridine, batrachotoxin	Veratridine, batrachotoxin	Veratridine, batrachotoxin	Veratridine, batrachotoxin
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
Activators	Veratridine, batrachotoxin	Veratridine, batrachotoxin	—	—
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 ($Na_V1.5$, $Na_V1.8$ and $Na_V1.9$ are much less sensitive to block) and rate of inactivation ($Na_V1.8$ and particularly $Na_V1.9$ inactivate more slowly).

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Transient receptor potential (TRP)

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 Clapham, 2003; Delmas *et al*., 2004; Moran *et al*., 2004; Montell, 2005, Nilius & Voets, 2005; Pedersen *et al*., 2005; Voets *et al*., 2005; Ramsey *et al*., 2006). TRP subunits contain six putative transmembrane domains and assemble as homo- or hetero-tetramers to form cation selective channels with varied permeation properties (reviewed by Owsianik *et al*., 2006). The TRP**C** ('Canonical') and TRP**M** ('Melastatin') subfamilies consist of seven and eight different channels, respectively (i.e., TRPC1–TRPC7 and TRPM1–TRPM8). The TRP**V** ('Vanilloid') subfamily comprises six members (TRPV1–TRPV6), whereas the TRP**A** (Ankyrin) subfamily has only one mammalian member (TRPA1). The TRP**P** ('Polycystin') and TRP**ML** ('Mucolipin') families are not fully characterised, and the tables below are thus incomplete. Established, or potential, physiological functions of the individual members of the TRP families are discussed in detail in the recommended reviews and are only briefly mentioned here.

TRPC family: Members of the TRPC subfamily (reviewed by Vazquez *et al*., 2004; Freichel *et al*., 2005; Pedersen *et al*., 2005; Putney, 2005), 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. All TRPC channels have been proposed to act as store-operated channels (SOCs), activated by depletion of intracellular calcium stores (reviewed by Nilius, 2003a; Vazquez *et al*., 2004a; Pedersen *et al*., 2005; see also www.stke.org/cgi/content/full/sigtrans; 2004/243). However, there is conflicting evidence that TRPC1, TRPC4/5 and TRPC3/6/7 can function as receptor-operated channels that are mostly insensitive to store depletion (reviewed by Plant & Schaefer, 2003; Vazquez *et al*., 2004a). In heterologous systems, the level of TRPC expression may contribute to such discrepancies. 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 mGlu1 and orexin OX_1 receptors, membrane stretch, 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+}, Ni^{2+}, 2-APB, SKF96365	La^{3+} (at mM concentrations – augments in μM range), 2-APB
Functional characteristics	γ = 16 pS (estimated by fluctuation analysis); conducts mono- and divalent cations nonselectively; monovalent cation current suppressed by extracellular Ca^{2+}; nonrectifying, or mildly inwardly rectifying; noninactivating; physically associates *via* Homer with IP_3 receptors, also associates with TRPC4 and 5, calmodulin, TRPP1, IP_3 receptors, caveolin, enkurin and plasma membrane Ca^{2+}-ATPase	γ = 66 pS; conducts mono- and divalent cations nonselectively ($P_{Ca}/P_{Na} = 1.6$); 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 TRPC6 and 7; also associates with IP_3 receptors, ryanodine receptors, NXC1, caveolin-1 and calmodulin	γ = 30–41 pS, conducts mono- and divalent cations nonselectively ($P_{Ca}/P_{Na} = 1.1–7.7$); 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, calmodulin, and ZO-1

Nomenclature	**TRPC5**	**TRPC6**	**TRPC7**
Other names	TRP5, CCE2	TRP6	TRP7
Ensembl 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), 2-APB, SKF96365	La^{3+} ($IC_{50} \cong 6$ μM), Gd^{3+}, amiloride, SKF96365, 2-APB	La^{3+}, SKF96365, amiloride
Functional characteristics	γ = 63 pS; conducts mono- and divalent cations nonselectively ($P_{Ca}/P_{Na} = 1.8$); 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, in neurons associates with synaptotagmin and stathmin 2	γ = 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, calmodulin, Fyn and MxA	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 have been controversial. However, there is emerging evidence that TRPC1 is a component of a store-operated channel *in situ* (reviewed by Beech *et al*., 2005). Functional hetero-oligomers of TRPC1 and TRPC4 and TRPC1 and 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). Additional physiological functions involving TRPC1, including netrin-1 and BDNF-mediated growth cone guidance are reviewed in Beech (2005) and Pedersen *et al*. (2005). 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 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*., 2004b). 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 (reviewed by Fleig & Penner, 2004; Harteneck, 2005; Pedersen *et al*., 2005), 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 TRPM7 combine channel and enzymatic activities ('chanzymes') and are involved in Mg^{2+} homeostasis (Schmitz *et al*., 2003;. Voets *et al*., 2004a; reviewed by Montell, 2003). 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 (ADPR) and cyclic ADPR; agents producing reactive oxygen (e.g. H_2O_2) and nitrogen (e.g. GEA 3162) species; potentiated by arachidonic acid and, in the presence of ADP-ribose, intracellular Ca^{2+} ($EC_{50} = 340$ nM)	Constitutively active, stimulated by store depletion with thapsigargin, stimulated by cell swelling, activated by D-erythro-sphingosine and dihydrosphingosine
Blockers	La^{3+}, Gd^{3+}	Clotrimazole, econazole, flufenamic acid; activation by ADPR blocked by AMP ($IC_{50} = 70\ \mu$M)	La^{3+}, Gd^{3+}
Functional characteristics	Permeable to Ca^{2+} and Ba^{2+}; downregulated by a short splice variant of TRPM1, interacts with the short transcript	$\gamma = 52-60$ pS at negative potentials, 76 pS at positive potentials; conducts mono- and divalent cations nonselectively ($P_{Ca}/P_{Na} = 0.6-0.7$); nonrectifying; 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 divalent cations nonselectively ($P_{Ca}/P_{Na} = 1.6-1.9$); nonrectifying

Nomenclature	**TRPM4**	**TRPM5**	**TRPM6**
Other names	LTRPC4	TRP-T	—
Ensembl ID	ENSG00000130529	ENSG00000070985	ENSG00000119121
Activators	Decavanadate, whole-cell current transiently activated by intracellular Ca^{2+} (EC_{50} 15–20 μM), activated by membrane depolarisation in the presence of elevated $[Ca^{2+}]_i$, activated by $PtdIns(4,5)P_2$	$G_{q/11}$-coupled receptors, $Ins(1,4,5)P_3$, transiently activated by intracellular Ca^{2+} (EC_{50} 700–840 nM), stimulated by $PtdIns(4,5)P_2$	Constitutively active, activated by reduction of intracellular Mg^{2+}
Blockers	Intracellular nucleotides (ATP^{4-}, ADP, AMP, AMP-PNP) and adenosine; spermine ($IC_{50} = 35-61\ \mu$M), flufenamic acid ($IC_{50} = 2.8\ \mu$M)	Spermine ($IC_{50} = 37\ \mu$M), flufenamic acid ($IC_{50} = 24\ \mu$M), extracellular protons ($IC_{50} = 630$ nM), (not inhibited by ATP^{4-})	Ruthenium red (voltage-dependent block, $IC_{50} = 100$ nM at -120 mV), inward current mediated by monovalent cations blocked by Ca^{2+} ($IC_{50} = 4.8\ \mu$M) and Mg^{2+} ($IC_{50} = 1.1\ \mu$M)
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 decavanidate; intrinsically voltage sensitive; associates with calmodulin	$\gamma = 15-25$ 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 desensitised by $[Ca^{2+}]_i$, desensitisation relieved by short-chain synthetic $PtdIns(4,5)P_2$; intrinsically voltage-sensitive	$\gamma = 40$ pS; permeable to mono- and divalent cations with a preference for divalents ($Mg^{2+} > Ca^{2+}$; $P_{Ca}/P_{Na} = 6.9$), strong outward rectification abolished by removal of extracellular divalents; inhibited by intracellular Mg^{2+} ($IC_{50} = 0.5$ mM); 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; positively modulated by $PtdIns(4,5)P_2$	Depolarisation ($V_{1/2} \cong +50$ mV at 15°C), cooling (<22–26°C), $PtdIns(4,5)P_2$; 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+}, extracellular protons	BCTC, capsazepine, 2-APB, La^{3+}, insensitive to ruthenium red
Functional characteristics	$\gamma = 40-105$ pS at negative and positive potentials, respectively; conducts mono- and divalent 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 (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 divalent cations nonselectively ($P_{Ca}/P_{Na} = 1.0-3.3$); pronounced outward rectification; demonstrates densensitisation 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 (Nilius *et al*., 2005b). TRPM2 possesses an ADP ribose hydrolase activity associated with a NUDT9 motif within an extended intracellular C-terminal domain of the channel (see Kühn *et al*., 2005). Deletion of this domain abolishes activation by H_2O_2. A truncated TRPM2 isoform (TRPM2-S) generated by alternative splicing prevents activation of the full-length protein (TRPM2-L) by H_2O_2 when coexpressed 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 and TRPM5 to activation by $[Ca^{2+}]_i$ demonstrates a pronounced and time-dependent reduction following excision of inside-out membrane patches (Ullrich *et al*., 2005). Fura2A ratiometric imaging suggests that Ca^{2+} and Ba^{2+} permeate TRPM4a in addition to monovalent cations. TRPM6 is important for Mg^{2+} homeostasis, mediating absorption and reabsorption of Mg^{2+} by the kidney and intestine, respectively (Voets *et al*., 2004a). Loss-of-function mutations of TRPM6 result in hypomagnesaemia with secondary hypocalcaemia (HSH) (Nilius *et al*., 2005b). 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 regulation by intracellular cAMP (Takezawa *et al*., 2004), but whether sensitivity to inhibition by Mg^{2+} is similarly affected is disputed (Schmitz *et al*., 2003; Matsushita *et al*., 2005). TRPM7 plays a major role in anoxic neuronal cell death (Aarts & Tymianski, 2005). Activation of TRPM8 by depolarisation 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 hyperpolarising 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 upregulated 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, nonselective 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; Pedersen *et al*., 2005). 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	Depolarisation ($V_{1/2} \cong 0$ 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, camphor, allicin, 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), carvacrol, eugenol, thymol, camphor, menthol, 2-APB
Blockers	Ruthenium red, 5′-iodoresiniferatoxin, 6-iodo-nordihydrocapsaicin, 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 divalent 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 divalent cations ($P_{Ca}/P_{Na} = 0.9–2.9$); dual (inward and outward) rectification; current increases upon repetitive activation by heat; translocates to the 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 divalent 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*, bisandrographolide A, 4α-PDD, PMA, epoxyeicosatrieonic acids; sensitised 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 divalent 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, functionally associates with RyR2	$\gamma = 65–78$ pS for monovalent ions at negative potentials, conducts mono- and divalents 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 D_3; associates with TRPV6, S100A10 – annexin II, calmodulin, calbindin D_{28} and Rab11; activated by klotho *via* deglycosylation	$\gamma = 58–79$ pS for monovalent ions at negative potentials, conducts mono- and divalents 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 D_3; 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 hyperpolarising 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 (Nilius *et al*., 2005b). 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 epoxyeicosatrienoic acids (reviewed by Nilius *et al*., 2004). Activation of TRPV4 by cell swelling, but not heat, or phorbol esters, is mediated *via* the formation of epoxyeicosatrieonic acids. Phorbol esters bind directly to TRPV4. TRPV5 preferentially conducts Ca^{2+} under physiological conditions, but in the absence of extracellular Ca^{2+}, conducts monovalent cations. Single-channel conductances listed for TRPV5 and TRPV6 were determined in divalent cation-free extracellular solution. Ca^{2+}-induced inactivation occurs at hyperpolarised 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 hyperpolarisation 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 upregulated 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; Nagata *et al*., 2005), studies is activated by noxious cold. Additionally, TRPA1 has recently been proposed to be a component of a mechanosensitive transduction channel of vertebrate hair cells (Corey *et al*., 2004; Nagata *et al*., 2005 but TRPA$^{(-/-)}$ mice demonstrate no impairment in hearing, or vestibular function (Bautista *et al*., 2006; Kwan *et al*., 2006). 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, allicin, carvacrol (insensitive to capsaicin)
Blockers	Ruthenium red (IC_{50} $<1-3\,\mu$M), Gd^{3+}, menthol, gentamicin
Functional characteristics	$\gamma \approx 100$ pS; conducts mono- and divalent cations nonselectively ($P_{Ca}/P_{Na} = 0.84$); 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). Activation of TRPA1 by isothiocyanates occurs *via* covalent modification of cysteine residues within the cytoplasmic N terminus of the channel (Hinman *et al*., 2006) TRPA1 acts as a mechanosensor and nociceptor channel (Nagata *et al*., 2005).

TRPML family: The TRPML family (see Bach, 2005; Qian & Noben-Trauth, 2005; Cantiello *et al*., 2005) consists of three mammalian members (TRPML1–TRPML3). TRPML channels are probably restricted to intracellular vesicles and mutations in the gene (*MCOLN1*) encoding TRPML1 (mucolipin-1) are the cause of the neurodegenerative disorder mucolipidosis type IV (MLIV) in man. TRPML1 is a cation-selective ion channel that is important for sorting/transport of endosomes in the late endocytotic pathway and specifically fusion between late endosome–lysosome hybrid vesicles. TRPML2 (MCLN2, 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 divalent 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 and studied in a lipid bilayer system (Raychowdhury *et al*., 2004). Mutations in TRPML3 result in the varitint waddler mouse phenotype (reviewed by Nilius *et al*., 2005b; Qian & Noben-Trauth, 2005).

TRPP family: The TRPP family (reviewed by Delmas *et al*., 2004a; Delmas, 2005; Giamarchi *et al*., 2006) subsumes the polycystins that are divided into two structurally distinct groups, polycystic kidney disease 1-like (PKD1-like) and polycystic kidney disease 2-like (PKD2-like). Members of the PKD1-like group, in mammals, include PKD1 (recently reclassified as TRPP1), PKDREJ, 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*., 2004b), TRPP1 is incapable of producing currents. Conversely, TRPP1 has been demonstrated to constitutively activate G-proteins 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, 2004a). 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 divalent cations; probably associates with TRPV4; also associates with cortactin and cadherin *via* TRPP1; channel activity increased by association with α-actinin; interacts with several cytoskeletal proteins that determine subcellular distribution including CD2AP, AP-1, PACS-1 and 2, COPI and PIGEA-14	$\gamma = 137$ pS (within the range -50 to $+50$ mV), conducts mono- and divalent 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; possibly interacts with TRPA1

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 is quoted for TRPP3 with $[Na^+]_o$ 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 hyperpolarisation. TRPP3 plays a role in retinal development.

Abbreviations: **2-APB**, 2-amino ethoxyphenylborate; **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; **20-HETE**, 20-hydroxyeicosatetraenoic acid; **5-(*S*)-HETE**, 5-(*S*)-hydroxyeicosatetraenoic acid; **12-(*S*)-HPETE and 15-(*S*)-HPETE**, 12- and 15-(*S*)-hydroperoxyeicosatetraenoic acids; **JYL1421**, *N*-(4-tert-butylbenzyl)-*N*′-[3-fluoro-4-(methylsulphonylamino)benzyl]thiourea; **OAG**, 1-oleoyl-2-acetyl-*sn*-glycerol; **PMA**, phorbol 12 myristate 13-acetate; **4α-PDD**, 4α-phorbol 12,13-didecanoate; **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)-1*H*-imidazole hydrochloride; **THC**, Δ^9-tetrahydrocannabinol

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