ION CHANNELS

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

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

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

Psalmotoxin blocks ASIC1a, but has little effect upon ASIC1b, ASIC2a, ASIC3 or ASIC1a expressed as a heteromultimer with either ASIC2a, or ASIC3 (Escoubas *et al*., 2000). The pEC_{50} values for proton activation of ASIC1a, ASIC1b and ASIC3 are shifted to more acidic levels by increasing $[Ca^{2+}]_o$ (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). The 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). 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 proinflammatory mediators induce overexpression of ASIC-encoding genes and enhance ASIC currents (Mamet *et al*., 2002).

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

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Calcium channels (voltage-gated)

Overview: Calcium (Ca^{2+}) channels are voltage-gated ion channels present in the membrane of most excitable cells. The nomenclature for Ca^{2+} channels was proposed by Ertel *et al*. (2000) and approved by the NC-IUPHAR subcommittee on Ca^{2+} channels (Catterall *et al*., 2002; 2003). Ca^{2+} channels form hetero-oligomeric complexes. The α1 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 α1 subunit has four homologous repeats (I–IV), each repeat having six TM domains and a pore-forming region between TM 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 α1-subunit genes give rise to alternatively spliced products. At least for high voltage-activated channels, it is likely that native channels comprise coassemblies of α1, β and $\alpha2-\delta$ subunits. The γ subunits have not been proven to associate with channels other than α1s. The $\alpha2-\delta1$ and $\alpha2-\delta2$ 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, for example, nifedipine, diltiazem, verapamil, calciseptine	Dihydropyridine antagonists, for example, nifedipine, diltiazem, verapamil, calciseptine	Less sensitive to dihydropyridine antagonists, verapamil	less sensitive to dihydropyridine antagonists	ω-agatoxin IVA (P: IC_{50} ~1 nM) (Q: IC_{50} ~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	ENSG00000034827	ENSG00000006283	ENSG00000073761	—
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	Mibefradi, 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 –(GVDKAGCRYMFGGCSVNDDCCPRLGCHSLFSYCAWDLTFSD); **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 channels

Overview: Chloride channels are a functionally and structurally diverse group of anion selective channels involved in numerous processes that include 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 $GABA_A$ 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. There is no official recommendation 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 Valverde, 1999; Jentsch *et al*., 2002; Nilius & Droogmans, 2003) contains nine members that fall into three groups; ClC-1, ClC-2, hClC-Ka (rClC-K1) and hClC-Kb (rClC-K2); ClC-3 to ClC-5, and ClC-6 and -7. ClC-1 – to ClC-5 can be functionally expressed as plasma membrane chloride channels. Similarly, ClC-Ka and ClC-Kb (largely expressed in the kidney) form functional chloride channels in association with barttin (ENSG00000162399), a 320 amino-acid 2TM protein (Estévez *et al*., 2001). However, the location of several of these channels *in vivo* (i.e. ClC-3, ClC-4 and ClC-5) is likely to be predominantly intracellular. An intracellular location has been demonstrated for ClC-6 (ENSG00000011021) and ClC-7 (ENSG00000103249), also reviewed by Jentsch *et al.,* 1999 and Waldegger & Jentsch, 2000). Alternative splicing increases the structural diversity within the ClC family (e.g. for ClC-2, ClC-3 ClC-5 and ClC-6). The crystal structure of two bacterial ClC channels has recently been described (Dutzler *et al*., 2002). Each ClC subunit, with a complex topology of 18 membrane-associated α-helices, contributes a single pore to a dimeric 'double-barrelled' ClC channel that contains two independently gated pores, confirming the predictions of previous functional and structural investigations (reviewed by Estévez & Jentsch, 2002).

Nomenclature	**ClC-1**	**ClC-2**	**ClC-Ka**	**ClC-Kb**
Other names	Skeletal muscle Cl^- channel	—	ClC-K1 (rodent)	ClC-K2 (rodent)
Ensembl ID	ENSG00000186544	ENSG00000114859	ENSG00000186510	ENSG00000184908
Activators	—	PKA, arachidonic acid, amidation and acid-activated omeprazole	Constitutively active (when coexpressed with barttin)	Constitutively active (when coexpressed with barttin)
Blockers	*S*-(−)CPP, *S*-(−)CPB, 9-AC, Cd^{2+}, Zn^{2+}	DPC, Cd^{2+}, Zn^{2+}	Bis-phenoxy derivatives of CPP (Liantonio *et al*., 2002)	—
Functional characteristics	$\gamma = 1-2$ pS; voltage-activated (depolarization); inwardly rectifying; deactivation upon repolarization (by fast gating of single pores and a slower common gate)	$\gamma = \sim 3$ pS; voltage-activated (hyperpolarization), inward rectification (steady state currents); slow inactivation (seconds); activated by cell swelling and extracellular acidosis; inhibited by phosphorylation by p34(cdc2)/cyclin B	$\gamma = 1$ pS; slight outward rectification; largely time-independent currents; inhibited by extracellular acidosis; potentiated by extracellular Ca^{2+}	$\gamma = 1$ pS; slight outward rectification; largely time-independent currents; inhibitied by extracellular acidosis; potentiated by extracellular Ca^{2+}

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

ClC channels other than ClC-3 display the permeability sequence $Cl^- > Br^{2-} > I^-$ (at physiological pH); for ClC-3, $I^- > Cl^-$. ClC-1 has significant opening probability at resting membrane potential, accounting for 75% of the membrane conductance at rest in skeletal muscle, and is important for repolarization and for stabilization of the membrane potential. *S*-(−)CPP and 9-AC act intracellularly and exhibit a strongly voltage-dependent block with strong inhibition at negative voltages and relief of block at depolarized potentials (reviewed by Pusch *et al*., 2002). Mutations in the ClC-1 gene result in myotonia congenita that can be either autosomal dominant (Thomsen's disease) or recessive (Becker myotonia) depending on the functional effect of the mutation (shift in voltage-dependence *versus* loss –of function). Although ClC-2 can be activated by cell swelling, its anion selectivity, voltage-dependence and rectification pattern argue against ClC-2 being the VRAC channel (see below). Alternative potential physiological functions of ClC-2 are reviewed by Strange (2002). Disruption of the ClC-2 gene in mice is associated with the degeneration of male germ cells and photoreceptors (Bösl *et al*., 2001). Functional expression of human ClC-Ka and ClC-Kb requires the presence of barttin (Estévez *et al*., 2001). The rodent homologue (ClC-K1) of ClC-Ka demonstrates limited expression as a homomer, but its function is enhanced by barttin (Estévez *et al*., 2001). Knock out of the ClC-K1 channel induces nephrogenic diabetes insipidus (Matsumura *et al*., 1999). Classic (type III) Bartter's syndrome and Gitelman's variant of Bartter's syndrome are associated with mutations of the ClC-Kb chloride channel (Simon *et al*., 1996; 1997). 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) is controversial. Activation of heterologously expressed ClC-3 by cell swelling in response to hypotonic solutions has been disputed as have 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 knockout mice, volume-regulated anion currents persist (Srobrawa *et al*., 2001; Arreola *et al*., 2002), indicating that ClC-3 is not indispensable for such regulation. However, ClC-3 antisense is reported to reduce VRAC function in HeLa cells and *Xenopus laevis* oocytes (Hermoso *et al*., 2002). A novel 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 knockout mice suggest an endosomal/synaptic vesicle location for the channel and a role, *via* the dissipation of electrical potential, in the acidification of vesicles. Mice lacking ClC-3 display total degeneration of the hippocampus and retinal degeneration (Srobrawa *et al*., 2001). Loss of function mutations of ClC-5 are associated with proteinuria, hypercalciuria and kidney stone formation (Dent's disease). A ClC 5 knockout provides a mouse model of this disease (Piwon *et al*., 2000). Disruption of the ClC-7 gene leads to osteopetrosis in mice due to the ablation of ClC-7 from endosomes that are important for the function of osteoclasts (Kornak *et al*., 2001).

CFTR. CFTR, a 12TM, ABC type protein, is a cAMP-regulated epithelial cell membrane Cl^- channel involved in normal fluid transport across various epithelia. The most common mutation in CFTR (i.e. the deletion mutant, Δ508) results in impaired trafficking of CFTR and reduces its incorporation into the plasma membrane causing cystic fibrosis. In addition to acting as an anion channel *per se*, CFTR may act as a regulator of several other conductances that include the epithelial Na channel (ENaC), the renal outer medullary potassium channel (ROMK), the outwardly rectifying chloride channel (ORCC), calcium-activated chloride channels (CaCC) and the volume-regulated anion channel (VRAC) (reviewed by Schwiebert *et al*., 1999, Nilius & Droogmans, 2003).

Nomenclature	**CFTR**
Ensemble ID	ENSG00000001626
Activators	Flavones (UCCF-339, UCCF-029, apigenin, genistein), benzimidazolones (UCCF-853, NS004), psoralens (8-methoxypsoralen)
Blockers	$CFTR_{inh}-172$, glibenclamide
Functional characteristics	$\gamma = 6-10$ pS; permeability sequence = $Br \geqslant Cl > I > F$, ($P_{Na}/P_{Cl} = 0.1-0.03$); slight outward rectification; phosphorylation necessary for activation by ATP binding at binding nucleotide-binding domains (NBD)1 and 2; positively regulated by PKC and PKGII (tissue specific); regulated by several interacting proteins like syntaxin, Munc18 and PDZ domain proteins such as NHERF and CAP70

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

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

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

Blockade of $I_{Cl(Ca)}$ by niflumic acid, 9-AC, NPA and Ins(3,4,5,6)P_4 is voltage dependent, whereas block by DIDS, mibefradil and NPPB is voltage independent. Extracellular niflumic acid and DCDPC (but not DIDS) exert a complex effect upon $I_{Cl(Ca)}$ in vascular smooth muscle, enhancing and inhibiting inwardly and outwardly directed currents in a manner dependent upon $[Ca^{2+}]_I$ (Piper *et al*., 2002). CaMKII modulates CaCC in a tissue-dependent manner. CaMKII inhibitors block activation of $I_{Cl(Ca)}$ in T_{84} cells, but have no effect in parotid acinar cells (reviewed by Jentsch *et al*., 2002). In tracheal and arterial smooth muscle cells, but not portal vein myocytes, inhibition of CaMKII reduces inactivation of $I_{Cl(Ca)}$. Intracellular Ins(3,4,5,6)P_4 may act as an endogenous negative regulator of CaCC channels activated by Ca^{2+}, or CaMKII.

Maxi chloride channel. Maxi Cl^- channels are high-conductance, anion-selective, channels initially characterised in skeletal muscle and subsequently found in many cell types including neurones, glia, cardiac muscle, lymphocytes, secreting and absorbing epithelia and human placenta syncytiotrophoblasts. The physiological significance of the maxi Cl^- channel is uncertain, but roles in cell volume regulation and apoptosis have been claimed. Recent evidence suggests a role for maxi Cl^- channels as a conductive pathway in the swelling-induced release of ATP from mouse mammary C127i cells that may be important for autocrine and paracrine signalling by purines (Sabirov *et al*., 2001; Dutta *et al*., 2002).

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 antioestrogens (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

Differing ionic conditions may contribute to variable estimates of γ reported in the literature ($K_m = 120$ mM in symmetrical Cl^-). Inhibition by arachinonic acid (and *cis*-unsaturated fatty acids) is voltage independent, occurs at an intracellular site, and involves both channel shut down ($K_d = 4-5$ μM) and a reduction of γ ($K_d = 13-14$ μM). Blockade of channel activity by SITS, DIDS, Gd^{3+} and arachidonic acid is paralleled by decreased swelling-induced release of ATP (Sabirov *et al*., 2001; Dutta *et al*., 2002). Channel activation by antioestrogens in whole cell recordings requires the presence of intracellular nucleotides and is prevented by pretreatment with 17β-oestradiol, dibutryl cAMP or intracellular dialysis with GDPβS (Diaz *et al*., 2001). Activation by tamoxifen is suppressed by low concentrations of okadaic acid, suggesting that a dephosphorylation event by protein phosphatase PP2A occurs in the activation pathway (Diaz *et al*., 2001). In contrast, 17β-estradiol and tamoxifen appear to directly inhibit the maxi Cl^- channel of human placenta reconstituted into giant liposomes and recorded in excised patches (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). 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 an anti-ClC-3 antibody. However, the specificity of the antibody employed 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*., 1997; 1999; Okada, 1997; Strange, 1998; Jentsch *et al*., 2002; Nilius & Droogmans, 2003).

Nomenclature	**VRAC** (volume-regulated anion channel), **VSOAC** (volume-sensitive organic osmolyte/anion channel), **VRC** (volume-regulated channel), **VSOR** (volume expansion-sensing outwardly rectifying anion channel)
Activators	Cell swelling; low intracellular ionic strength; GTPγS
Blockers	DCPIB (most selective agent available), clomiphene, nafoxidine, mefloquine, tamoxifen, gossypol, arachidonic acid, mibefradil, NPPB, quinine, quinidine, chromones NDGA, 9-AC, DIDS, 1,9-dideoxyforskolin, oxalon dye (diBA-(5)-C4), extracellular nucleotides, nucleoside analogues, intracellular Mg^{2+}
Functional characteristics	$\gamma = 10-20$ pS (negative potentials), 50–90 pS (positive potentials); permeability sequence $SCN > I > NO^{3-} > Br^- > Cl^- > F^- >$ gluconate; outward rectifcation due to voltage dependence of γ; inactivates at positive potentials in many, but not all, cell types; time-dependent inactivation at positive potentials; intracellular ionic strength modulates sensitivity to cell swelling and rate of channel activation; rate of swelling-induced activation is modulated by intracellular ATP concentration; ATP dependence is independent of hydrolysis and modulated by rate of cell swelling; inhibited by increased intracellular free Mg^{2+} concentration; tyrosine phosphorylation step(s) may modulate channel activation; swelling-induced activation of VRAC requires a functional Rho-Rho kinase MLCK phosphorylation pathway, but not activation of the pathway (i.e. a permissive effect)

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).

Abbreviations: **9-AC**, anthracene-9-carboxylic acid; **CFTR$_{inh}$-172**, 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; ***S*-(−)CPP**, *S*-(−)2-(4-chlorophenoxy)propionic acid; ***S*-(−)CPB**, *S*-(−)2-(4-chlorophenoxy)butyric acid; **DCPIB**, 4-(2-butyl-6,7-dichlor-2-cyclopentyl-indan-1-on-5-yl) oxybutyric acid; **diBA-(5)-C4**, bis-(1,3-dibutylbarbituric acid)pentamethine oxanol; **DIDS**, 4,4′-di-isothiocyanostilbene-2,2′-disulphonic acid; **DNDS**, 4,4′-dinitrostilbene-2,2′-disulphonic acid; **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-2H-benzimidazole-2-one; **SITS**, 4′-isothiocyanostilbene-2,2′-disulphonic acid; **UCCF-029**, 2-(4-pyridinium)benzo[*h*]4H-chromen-4-one bisulphate; **UCCF-180**, 3-(3-butynyl)-5-methoxy-1-phenylpyrazole-4-carbaldehyde; **UCCF-853**, 1-(3-chlorophenyl)-5-trifluoromethyl-3-hydroxybenzimidazol-2-one

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Cyclic nucleotide-gated (CNG) channels

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

CNG channels are voltage-independent cation channels formed as tetramers. Each subunit has 6TM with the pore-forming domain between TM5 and TM6. CNG channels were first found in rod photoreceptors (Fesenko *et al*., 1985; Kaupp *et al*., 1989), where light signals through rhodopsin and transducin to stimulate phosphodiesterase and reduce intracellular cGMP levels. 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	ENSG00000170455	ENSG00000183862	ENSG00000144191
Activators	Intracellular cyclic nucleotides: cGMP (EC_{50} $\approx$30 μM) > > cAMP	Intracellular cyclic nucleotides: cGMP $\approx$ cAMP (EC_{50} $\approx$1 μM)	Intracellular cyclic nucleotides: cGMP (EC_{50} $\approx$30 μM) > > cAMP
Inhibitors	L-*cis* diltiazem	—	L-*cis* diltiazem
Functional characteristics	γ = 25–30 pS P_{Ca}/P_{Na} 3.1	γ = 35 pS P_{Ca}/P_{Na} 6.8	γ = 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: $CNGA3_3$/CNGB3; olfactory neurons: $CNGA2_2$/CNGA4/CNGB1b (Weitz *et al*., 2002; Zheng *et al*., 2002; Zhong *et al*., 2002).

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Epithelial sodium channels (ENaC)

Overview: ENaC 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 and vasopressin, and is one of the essential mechanisms in the regulation of sodium balance, blood volume and blood pressure. The sodium reabsorption is suppressed by the 'potassium-sparing' diuretics amiloride and triamterene. The first ENaC subunit (α) was isolated by expression cloning from a rat colon cDNA library, as a current sensitive to inhibition by amiloride (Canessa *et al*., 1993). Two further subunits (β and γ) were identified by functional complementation of the α subunit (Canessa *et al*., 1994). A related δ subunit was later identified (Waldmann *et al*., 1995) that has a wider tissue distribution. ENaC subunits contain two putative TM domains. The stoichiometry of the epithelial sodium channel in the kidney and related epithelia is thought to be predominantly a heterotetramer of $2\alpha:1\beta:1\gamma$ 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	Amiloride (100 nM), benzamil (10 nM) (Canessa *et al*., 1994)
Functional characteristics	$\gamma \approx 5$ pS, $P_{Na}/P_K > 10$; tonically open at rest; expression and ion flux regulated by circulating aldosterone and aldosterone-mediated changes in gene transcription, action of aldosterone competitively antagonised by spironolactone and its more active metabolite, canrenone

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).

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HCN (hyperpolarisation-activated, cyclic nucleotide-gated) channels

Overview: The 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 do not directly activate the channels but shift the activation curves of HCN channels to more positive voltages, thereby enhancing channel activity. HCN channels underlie pacemaker currents found in many excitable cells including cardiac cells and neurons (Di Francesco, 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 TM domains and form tetramers. It is not known whether they can form heteromers with each other. A standardised nomenclature for HCN channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels (see Hofmann *et al*., 2002; 2003).

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

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

Abbreviation: ZD7288, 4-(*N*-ethyl-*N*-phenyl-amino)-1,2-dimethyl-6-(methylamino)pyrimidinium chloride.

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IP_3 receptor channels

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

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

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

Abbreviation: FKBP, FK506 binding protein

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Potassium channels

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

The 2TM family of K channels

The 2TM domain family of K channels are also known as the inward-rectifier K channel family. This family includes the strong inward-rectifier K channels ($K_{IR}2.x$), the G-protein-activated inward-rectifier K channels ($K_{IR}3.x$) and the ATP-sensitive K channels ($K_{IR}6.x$ that 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	ENSF00000000219	ENSF00000000219	ENSF00000000219	ENSF00000000219
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	ENSF00000000219	ENSF00000000219	ENSF00000000219
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) and so it is envisaged that they form functional dimers rather than the usual K channel tetramers. There is some evidence that they can form heterodimers within subfamilies (e.g. TASK1 with TASK3). There is no clear, current, consensus on nomenclature of 4TM K channels, nor on the division into subfamilies (see Gutman & Chandy 2002; Gutman *et al*., 2003). The suggested division into subfamilies, below, is based on similarities in both structural and functional properties within subfamilies.

Subfamily group	**TWIK**	**TREK**	**TASK**	**TALK**	**THIK**
Subtypes	TWIK1 (KCNK1), TWIK2 (KCNK6), KNCK7	TREK1 (KCNK2), TREK2 (KCNK10), TRAAK (KCNK4)	TASK1 (KCNK3), TASK3 (KCNK9), TASK5 (KCNK15)	TALK1 (KCNK16), TASK2 (KCNK5), TASK4 (KCNK17)	THIK1 (KCNK13), THIK2 (KCNK12)
Ensembl family	ENSF00000000669	ENSF00000000669	ENSF00000000937	ENSF00000000669	ENSF00000003131
Activators	—	Halothane (not TRAAK), riluzole, stretch, heat, arachidonic acid, acid pH_i	Halothane	Alkaline pH_O	—
Inhibitors	Acid pH_i		Anandamide (TASK1), Ruthenium red (TASK3), Acid pH_O	—	Halothane

The KCNK7, TASK5 and THIK2 subtypes, when expressed in isolation, are nonfunctional. A recently cloned novel member of this family (TRESK, ENSG00000186795, Sano *et al*., 2003) does not fit into any of the five subfamilies above and is highly localised to the spinal cord in humans. 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	ENSF00000000193	ENSF00000000193	ENSF00000000193	ENSF00000000193
Inhibitors	TEA potent (1.1), TEA moderate (1.3, 1.6), 4-AP potent (1.4), α-dendrotoxin (1.1, 1.2, 1.6), margatoxin (1.1, 1.2, 1.3), noxiustoxin (1.2, 1.3)	TEA moderate	TEA potent, 4-AP potent (3.1, 3.2), BDS-1 (3.4)	—
Functional characteristics	K_V (1.1–1.3, 1.5 -1.8) K_A (1.4)	K_V (2.1)	K_V (3.1, 3.2) K_A (3.3, 3.4)	K_A
Associated subunits	$K_V\beta_1$, $K_V\beta_2$	$K_V5.1$, $K_V6.1-6.3$, $K_V8.1$, $K_V9.1-9.3$	MiRP2 ($K_V3.4$)	KCHIP, KCHAP

Subfamily group	**KCNQ**	**EAG**	**Slo**	**SK**
Subtypes	KCNQ1–5	eag1-2, elk1-3, erg1-3 (herg 1-3)	Slo (BK), Slack	SK1–SK3; SK4 (IK)
Ensembl family	ENSF00000000476	ENSF00000000403	ENSF00000000871	ENSF00000000663
Activators	Retigabine (KCNQ2-5)		NS004, NS1619	
Inhibitors	TEA (KCNQ2, 4), XE991 (KCNQ1,2,4,5), linopirdine	E-4031 (erg1), astemizole (erg1), terfenadine (erg1)	TEA, charybdotoxin, iberiotoxin	Charybdotoxin (SK4), apamin (SK1-3)
Functional characteristic	KCNQ1 – cardiac IK_S, KCNQ2/3 – M current	(h)erg1 – cardiac IK_R	Maxi K_{Ca} K_{Na} (slack)	SK_{Ca} (SK1-3), IK_{Ca} (SK4)
Associated subunits	minK, MiRP2 (KCNQ1)	minK, MiRP1 (erg1)		—

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

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Ryanodine receptor channels

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

Nomenclature	**RyR1**	**RyR2**	**RyR3**
Ensembl ID	ENSG00000066598	ENSG00000133014	ENSG00000069895
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 $-\mu$M), caffeine (mM), suramin (μM)	Ryanodine (nM$-\mu$M), caffeine (mM), suramin (μM)	Ryanodine (nM$-\mu$M), caffeine (mM)
Antagonists	Cytosolic Ca^{2+} ($>100\,\mu$M), 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 ($>100\,\mu$M), ruthenium red, procaine	Ryanodine ($>100\,\mu$M), ruthenium red, procaine	Ruthenium red
Functional characteristics	$P_{Ca}/P_K \sim 6$, single-channel conductance: ~ 90 pS (50 mM Ca^{2+}), 770 pS (200 mM K^+)	$P_{Ca}/P_K \sim 6$, single-channel conductance: ~ 90 pS (50 mM Ca^{2+}), 720 pS (210 mM K^+)	$P_{Ca}/P_K \sim 6$, 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 channels (voltage-gated)

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

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

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	ENSG00000086117	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 ($Na_V1.5$, $Na_V1.8$ & $Na_V1.9$ 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) cation channels

Overview: The TRP superfamily of cation channels, whose founder member is the *Drosophila* Trp channel, can be divided into seven families; TRPC, TRPM, TRPN, TRPV, TRPA, TRPP and TRPML based on amino-acid homologies (see Montell *et al*., 2002; Clapham, 2003; Corey, 2003). TRP subunits contain six putative TM domains and probably assemble as homo- or heterotetramers to form cation-selective channels. The TRP**C** ('**C**anonical') subfamily presents seven different channels (TRPC1-TRPC7). TheTRP**M** ('**M**elastatin') subfamily contains eight members TRPM1-TRPM8, but TRPM6 has not been characterised in sufficient detail to permit its inclusion within the tables. The TRP**V** ('**V**anilloid') subfamily presently comprises six members (TRPV1-TRPV6), whereas the most recently proposed subfamily, TRP**A** (**A**NKTM1), has only one mammalian member (TRPA1; Story *et al*., 2003). The TRPP ('**P**olycystin') and TRPML ('**M**uco**l**ipin') families are presently not sufficiently characterised for inclusion within the tables below. The established, or potential, physiological functions of the individual members of the TRP families are discussed in the recommended reviews. The nomenclature used here is that proposed by the TRP Nomenclature committee (see Montell *et al*., 2002) and presently used by NC-IUPHAR (Clapham *et al*., 2003).

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

Nomenclature	**TRPC1**	**TRPC3**	**TRPC4**
Other names	TRP1	TRP3	TRP4, CCE1
Ensembl ID	ENSG00000144935	ENSG00000138741	ENSG00000100991
Activators	Metabotropic glutamate receptor mGlu1, OAG (weak and only in divalent-free extracellular solution), PLCγ stimulation, intracellular $Ins(1,4,5)P_3$ (disputed), thapsigargin (disputed)	$G_{q/11}$-coupled receptors, OAG (independent of PKC), PLCγ stimulation, $Ins(1,4,5)P_3$, (disputed) and thapsigargin (disputed)	$G_{q/11}$-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	Gd^{3+}, La^{3+}, 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	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	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

Nomenclature	**TRPC5**	**TRPC6**	**TRPC7**
Other names	TRP5, CCE2	TRP6	TRP7
Ensemble ID	ENSG00000072315	ENSG00000137672	ENSG00000069018
Activators	$G_{q/11}$-coupled receptors, $Ins(1,4,5)P_3$, GTPγS (potentiated by extracellular Ca^{2+}), adenophostin A and thapsigargin (disputed)	$G_{q/11}$-coupled receptors, AlF_4^-, GTPγS (but not $Ins(1,4,5)P_3$), OAG (independent of PKC) and inhibition of DAG lipase with RHC80267	OAG (independent of PKC), thapsigargin (disputed)
Blockers	La^{3+} (at mM concentrations – augments in μM range), SKF96365	La^{3+}, Gd^{3+}, amiloride, SKF96365	La^{3+}, SKF96365, amiloride
Functional characteristics	γ = 63 pS; conducts mono-and divalent cations non-selectively (P_{Ca}/P_{Na} = 1.8); dual rectification (inward and outward); inhibited by xestospongin C; physically associates *via* a PDZ binding domain on NHERF with phospholipase C isoforms	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	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+}

The function and regulation of heterologously expressed TRPC1 has been controversial (see Clapham *et al*., 2001; Beech *et al*., 2003). However, there is evidence that TRPC1 is a component of a SOC *in situ* (reviewed by Beech *et al*., 2003). 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). Recent studies suggest that TRPC1 is physically coupled to mGlu1, and that activation of the latter stimulates cation flux through TRPC1-containing channels to produce a slow e.p.s.p. *in vivo* (Kim *et al*., 2003). Association of TRPC1 with the IP_3 receptor *via* the adaptor protein, Homer, regulates channel activity (Yuan *et al*., 2003). For TRPC3, the stimulatory effect of $Ins(1,4,5)P_3$ on single channel activity recorded from inside-out membrane patches is blocked by the IP_3 receptor antagonists, heparin and xestospongin C. One mode of activation of TRPC3 is postulated to involve a direct association of the channel with activated IP_3 receptors (reviewed by Treback *et al*., 2003). Gating of TRPC3 appears to involve an interaction between a sequence (termed F2r) downstream of the agonist binding N-terminal domain of the IP_3 receptor with a sequence (termed C7) within the C-terminal domain of TRPC3 (Boulay *et al*., 1999; Kiselyov *et al*., 1999) Two regions (F2q and F2g) within the IP_3 receptor sequence bind to the C7 domain of TRPC3 (Boulay *et al*., 1999). An 18 amino-acid synthetic peptide (F2v) representing a portion of the sequence of F2q activates TRPC3 by competing with Ca^{2+}-calmodulin (which inhibits TRPC3) for a site within C7 (Schaefer *et al*., 2002). 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).

TRPM family: Members of the TRPM subfamily, on the basis of sequence homology, fall into four groups: TRPM1/3, TRPM2/8, TRPM4/5 and TRPM6/7. The properties of TRPM2 suggest that it may function as a sensor of redox status in cells (Hara *et al*., 2002). A spice variant of TRPM4 (i.e. TRPM4b) and TRPM5 are inherently voltage sensitive and are molecular candidates for endogenous calcium-activated cation (CAN) channels (Launey *et al*., 2002; Hofmann *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). TRPM4 and TRPM5, unlike other TRP channels, display inherent voltage sensitivity. TRPM6 and 7 combine channel and enzymatic activities ('chanzymes') and are involved in Mg^{2+} homeostasis (Schmitz *et al*., 2003; Voets *et al*., 2003; 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; β-NAD^+ and agents producing reactive oxygen (e.g. H_2O_2) and nitrogen (e.g. GEA 3162) species (*via* elevated NAD^+); potentiated by arachidonic acid and, in the presence of ADP-ribose, intracellular Ca^{2+}	Constitutively active, stimulated by store depletion with thapsigargin, stimulated by cell swelling
Blockers	La^{3+}, Gd^{3+}	—	Gd^{3+}
Functional characteristics	Permeable to Ca^{2+} and Ba^{2+}; downregulated by a short splice variant of TRPM1, downregulated in metastatic melanomas	$\gamma = 52-60$ pS at negative potentials; 76 pS at positive potentials; conducts mono- and divalent cations nonselectively ($P_{Ca}/P_{Na} = 0.67$); nonrectifying; inactivation at negative potentials	$\gamma = 83$ pS (Na^+ current), 65 pS (Ca^{2+} current); conducts mono- and divalent cations nonselectively ($P_{Ca}/P_{Na} = 1.57$); nonrectifying

Nomenclature	**TRPM4**	**TRPM5**	**TRPM6**
Other names	LTRPC4	TRP-T	—
Ensembl ID	ENSG00000130529	ENSG00000070985	ENSG00000119121
Activators	Transiently activated by intracellular Ca^{2+} (EC_{50} 320–520 nM) and subsequently inactivated; patch excision (outside-out) reverses inactivation	$G_{q/11}$-coupled receptors, $Ins(1,4,5)P_3$, transiently activated by intracellular Ca^{2+} (EC_{50} 30 μM)	Constitutively active
Blockers	—	—	Ruthenium red (voltage-dependent block, $IC_{50} = 100$ nM at -120 mV)
Functional characteristics	$\gamma = 25$ pS (within the range 60 to $+60$ mV); permeable to monovalent cations; impermeable to Ca^{2+}; outward rectification; slow activation at positive potentials, rapid inactivation at negative potentials; intrinsically voltage sensitive	$\gamma = 23$ (at $+60$ mV); conducts monovalent cations selectively ($P_{Ca}/P_{Na} = 0.05$); outward rectification; slow activation at positive potentials, rapid inactivation at negative potentials; intrisically voltage sensitive	Permeable to mono- and divalent cations with a preference for divalents ($Mg^{2+} > Ca^{2+}$), strong outward rectification abolished by removal of extracellular divalents, inhibited by intracellular Mg^{2+}

Nomenclature	**TRPM7**	**TRPM8**
Other names	TRP-PLIK, Chak1, MagNum, MIC	CMR1, TRP-p8
Ensembl ID	ENSG00000092439	ENSG000000144481
Activators	Potentiated by intracellular ATP	Cooling ($<22-26$°C), icilin (requires the presence of extracellular Ca^{2+}), menthol (temperature dependent, potentiated by cooling)
Blockers	Spermine (permeant blocker), La^{3+}	Insensitive to ruthenium red
Functional characteristics	$\gamma = 105$ pS at positive potentials; 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+} and Mn^{2+}, inhibited by Mg.ATP and hydrolysis of $PtdIns(4,5)P_2$	$\gamma = 83$ pS at positive potentials; conducts mono- and divalent cations nonselectively ($P_{Ca}/P_{Na} = 1.0-3.3$); pronounced outward rectification; demonstrates densensitization to chemical agonists and adaptation to a cold stimulus

TRPM2 possesses an ADP ribose hydrolase activity associated with a NUDT9 motif within an extended intracellular C-terminal domain of the channel (Perraud *et al*., 2001). Deletion of this domain abolishes activation by H_2O_2 (Hara *et al*., 2002). A truncated TRPM2 isoform (TRPM2-S) generated by alternative splicing prevents activation of the full-length protein (TRPM2-L) by H_2O_2 when coexpressed with the latter (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. Fura2A ratiometric imaging suggests that Ca^{2+} and Ba^{2+} permeate TRPM4a in addition to monovalent cations. TRPM7 embodies an atypical serine/threonine protein kinase within its C-terminal domain and is subject to autophosphorylation (Runnels *et al*., 2001; Schmitz *et al*., 2003). Intact kinase activity of TRPM7 has been claimed to be required for channel function (Runnells *et al*., 2001) although this is disputed (Nadler *et al*., 2001; Schmitz *et al*., 2003). The kinase activity of TRPM7 modulates sensitivity to inhibition by Mg^{2+} (Schmitz *et al*., 2003).

TRPA family: The TRPA family currently comprises one mammalian member, TRPA1, which is activated by noxious cold (Story *et al*., 2003).

Nomenclature	**TRPA1**
Other names	ANKTM1, p120, TRPN1
Ensembl ID	ENSG00000104321
Activators	Cooling ($<17^{\circ}C$), icilin (insensitive to menthol and capsaicin)
Blockers	Ruthenium red ($IC_{50}<1\,\mu M$)
Functional characteristics	Conducts mono- and divalent cations nonselectively ($P_{Ca}/P_{Na}=0.84$); outward rectification; inactivates in response to prolonged cooling

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). 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).

	TRPV1	**TRPV2**	**TRPV3**
Nomenclature			
Other names	VR1, vanilloid/capsaicin receptor, OTRPC1	VRL-1, OTRPC2, GRC	—
Ensembl ID	ENSG00000043316	ENSG00000154039	ENSG00000167723
Activators	Noxious heat ($>43^{\circ}C$ at pH 7.4), extracellular protons ($pEC_{50}=5.4$ at $37^{\circ}C$), capsaicin, resiniferatoxin, olvanil, anandamide, some eicosanoids (e.g.12-(S)-HPETE, 15-(S)-HPETE, 5-(S)-HETE, leukotriene B_4), *N*-arachidonoyl-dopamine	Noxious heat ($>53^{\circ}C$)	Heat (23°–$39^{\circ}C$, temperature threshold influenced by 'thermal history' of the cell)
Blockers	Ruthenium red, iodoresiniferatoxin, SB366791, capsazepine, DD161515, DD191515	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 ($P_{Ca}/P_{Na}=9.6$); voltage- and time- dependent outward rectification; potentiated by ethanol; activated/potentiated by PKC stimulation; extracellular acidification facilitates activation by PKC; desensitisation inhibited by PKA; inhibited by $PtdIns(4,5)P_2$; cooling reduces vanilloid-evoked currents	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 cell surface in response to IGF-1 to induce a constitutively active conductance	$\gamma=197$ pS at $=+40$ to $+80$ mV, 48 pS at negative potentials; conducts mono- and divalent cations; outward rectification

	TRPV4	**TRPV5**	**TRPV6**
Nomenclature			
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–$32^{\circ}C$), cell swelling (not membrane stretch or reduced internal ionic strength), responses to heat increased in hypo-osmotic solutions and *vice versa*, 4α-PDD, PMA, 5′,6′-epoxyeicosatrieonic acid	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	$\gamma=\sim60$ 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 ($IC_{50}=0.4\,\mu M$)	$\gamma=65$–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; inhibited by extracellular acidosis, regulated by vitamin D	$\gamma=58$–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

Capsaicin, resiniferatoxin and olvanil are exogenous agonists of TRPV1 that possess a vanilloid group. The receptor is also activated by compounds lacking a vanilloid moiety (see Sterner and Szallasi, 1999) and by novel analogues of capsaicin (e.g. SDZ249665) that lack pungency. Blockade of TRPV1 by capsazepine and SB366791 is competitive; all other antagonists listed act by non- or uncompetitive antagonism. [^{3}H]-Resiniferatoxin and [^{125}I]-iodoresiniferatoxin are radioligands for TRPV1. Capsaicin, resiniferatoxin or low extracellular pH (4.0–5.0) do not activate TRPV2 or TRPV3. TRPV3 can coassemble with TRPV1 to form a functional hetero-oligomer. The sensitivity of TRPV4 to heat, but not 4α-PDD, is lost upon patch excision. TRPV4 is activated by anandamide and arachidonic acid following P450 epoxygenase-dependent metabolism to 5′,6′-epoxyeicosatrienoic acid (reviewed by Nilius *et al*., 2004). TRPV5 preferentially conducts Ca^{2+} under physiological conditions, but in the absence of extracellular Ca^{2+}, conducts monovalent cations. Single channel conductances listed for TRPV5 and TRPV6 were determined in divalent cation-free extracellular solution. Ca^{2+}-induced inactivation occurs at hyperpolarized potentials when Ca^{2+} is present extracellularly. Single channel events cannot be resolved (probably due to greatly reduced conductance) in the presence of extracellular divalent cations. Measurements of P_{Ca}/P_{Na} for TRPV5 and TRPV6 are dependent upon ionic conditions due to anomalous mole fraction behaviour. Blockade of TRPV5 and TRPV6 by extracellular Mg^{2+} is voltage dependent. Intracellular Mg^{2+} also exerts a voltage-dependent block that is alleviated by 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 heterotetramers.

Abbreviations: **2-APB**, 2-amino ethoxyphenylborate; **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; **OAG**, 1-oleoyl-2-acetyl-*sn*-glycerol; **PMA**, phorbol 12 myristate 13-acetate; **RHC80267**, 1,6-di[*O*-(carbamoyl)cyclohexanone oxime]hexane; **SB366791**, *N*-(3-methoxyphenyl)-4-chlorocinnamide; **SDZ249665**, 1-[4-(2-amino-ethoxy)-3-methoxy-benzyl]-3-(4-tert-butyl-benzyl)-urea; **SKF96265**, 1-(β-(3-(4-methoxyphenyl)propoxy)-4-methoxyphenethyl)-1H-imidazole hydrochloride; **4α-PDD**: 4α-phorbol 12,13-didecanoate; **12-(*S*)-HPETE and 15-(*S*)-HPETE**, 12- and 15-(*S*)-hydroperoxyeicosatetraenoic acids; **5-(*S*)-HETE**, 5-(*S*)-hydroeicosatetraenoic acid

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