Acid-sensing (proton-gated) (ASICs)

Overview: Acid-sensing ion channels (ASICs, provisional nomenclature; see Wemmie *et al*., 2006; Lingueglia *et al*., 2007) are members of a Na^+ channel superfamily that includes the epithelial Na channel (ENaC), the FMRF-amide activated channel (FaNaC) of invertebrates, the degenerins (DEG) of *Caenorhabitis elegans,* channels in *Drosophila melanogaster* 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-trimers (Jasti *et al*., 2007) to form proton-gated, voltage-insensitive, Na^+ permeable, channels. Splice variants of ASIC1 [provisionally termed ASIC1a (ASIC, ASICα, BNaC2α) (Waldmann *et al*. 1997a), ASIC1b (ASICβ, BNaC2β) (Chen *et al*., 1998) and ASIC1b2 (ASICβ2) (Ugawa *et al*., 2001); note that ASIC1a is also permeable to Ca^{2+}] and ASIC2 [provisionally termed ASIC2a (MDEG1, BNaC1α, BNC1a) (Price *et al*., 1996; Waldmann *et al*., 1996; Garcia-Anoveros *et al*., 1997) and ASIC2b (MDEG2, BNaC1β) (Lingueglia *et al*., 1997)] have been cloned. Unlike ASIC2a (listed in table), heterologous expression of ASIC2b alone does not support H^+-gated currents. A third member, ASIC3 (DRASIC, TNaC1) (Waldmann *et al*., 1997b), has been identified. 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), whereas one zebrafish orthologue (zASIC4.1) is functional as a homomer (Paukert *et al*., 2004) but a second (zASIC4.2) is not (Chen *et al*., 2007). ASIC channels are expressed in central and peripheral neurons including nociceptors where they participate in neuronal sensitivity to acidosis. The activation of ASIC1a within the brain contributes to neuronal injury caused by focal ischemia (Xiong *et al*., 2007). Further proposed roles for centrally and peripherally located ASICs are reviewed in Wemmie *et al*. (2006) and Lingueglia (2007). 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, 2006; Lingueglia *et al*., 2006; 2007, Diochot *et al*., 2004, 2007). Heterologously expressed heteromultimers form ion channels with altered kinetics, ion selectivity, pH- sensitivity and sensitivity to blockers (Lingueglia *et al*., 1997; Babinski *et al*., 2000, Escoubas *et al*., 2000) that resemble some of the native proton activated currents recorded from neurones.

Nomenclature	ASIC1	ASIC2	ASIC3
Other names	ASIC; BNaC2	BNC1; BNaC1; MDEG	DRASIC, TNaC1
Ensembl ID	ENSG00000110881	ENSG00000108684	OTTHUMG00000023710
Endogenous activators	Extracellular H^+ (ASIC1a, pEC_{50} ≈6.2–6.8; ASIC1b, pEC_{50} ≈5.1–6.2)	Extracellular H^+ (pEC_{50} ≈4.1–5.0)	Extracellular H^+ (transient component pEC_{50} ≈6.2 -6.7) (sustained component pEC_{50} ≈3.5–4.3)
Blockers (IC_{50})	ASIC1a: Psalmotoxin 1 (PcTx1) (0.9 nM), Zn^{2+} (7 ~ nM), Pb^{2+} (~4 μM), Ni^{2+} (~0.6 mM), amiloride (10 μM), EIPA, benzamil (10 μM), ibuprofen/flurbiprofen (350 μM), ASIC1b: Amiloride (21-23 μM); Pb^{2+} (~1.5 μM)	Amiloride (28 μM), Cd^{2+} (~1 mM)	APETx2 (63 nM) (transient component only), amiloride (16–63 μM) (transient component only—sustained component enhanced by 200 μM amiloride), aspirin/ diclofenac (92 μM—sustained component), salicylic acid (260 μM—sustained component), Gd^{3+} 40 μM
Functional characteristics	ASIC1a: γ ~14pS; $P_{Na}/P_K = 5–13$, $P_{Na}/P_{Ca} = 2.5$; rapid activation rate (5.8–13.7 ms) rapid inactivation rate (1.2–4 s) @ pH 6.0 ASIC1b: $P_{Na}/P_k = 14.0$; $P_{Na} \gg P_{Ca}$; rapid activation rate (9.9 ms); rapid inactivation rate (0.9–1.7 s) @ pH 6.0	γ ~10.4–13.4 pS; $P_{Na}/P_K = 10$, $P_{Na}/P_{Ca} = 20$; rapid activation rate, moderate inactivation rate (3.3–5.5 s) @ pH 5	γ ~13-15 pS; biphasic response consisting of rapidly inactivating transient and sustained components; very rapid activation (<5 ms) and inactivation (0.4 s); transient component partially inactivated at pH 7.2
Probes	[^{125}I]-PcTx1 (ASIC1a $K_D = 213$ pM)		

Psalmotoxin 1 (PcTx1) inhibits ASIC1a by modifying activation and desensitization by H^+, but has little effect upon ASIC1b, ASIC2a, ASIC3, or ASIC1a expressed as a heteromultimer with either ASIC2a, or ASIC3 (Escoubas *et al*., 2000; Diochot *et al*., 2007). Blockade of ASIC1a by PcTx1 results in the activation of the endogenous enkephalin pathway and has very potent analgesic effects in rodents (Mazzuca *et al*., 2007). APETx2 most potently blocks homomeric ASIC3 channels, but also ASIC2b + ASIC3, ASIC1b + ASIC3, and ASIC1a + ASIC3 heteromeric channels with IC_{50} values of 117 nM, 900 nM and 2 μM, respectively. APETx2 has no effect on ASIC1a, ASIC1b, ASIC2a, or ASIC2a + ASIC3 (Diochot *et al*., 2004, 2007). A-317567 blocks ASIC channels native to dorsal root ganglion neurones with an IC_{50} within the range 2–30 μM (Dube *et al*., 2005). The pEC_{50} values for proton activation of ASIC channels are influenced by numerous factors including extracellular di- and poly-valent ions, Zn^{2+}, protein kinase C and serine proteases (Lingueglia *et al*., 2006). Rapid acidification is required for activation of ASIC1 and ASIC3 due to fast inactivation/desensitization. pEC_{50} values for H^+-activation of either transient, or sustained, currents mediated by ASIC3 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 selective for Na^+ (Waldmann *et al*., 1997b); for hASIC3 the transient component is Na^+ selective ($P_{Na}/P_K > 10$) whereas the sustained current appears non-selective ($P_{Na}/P_K = 1.6$) (de Weille *et al*., 1998; Babinski *et al*., 1999). Non-steroidal anti-inflammatory drugs (NSAIDs) are direct blockers of ASIC currents within the therapeutic range of concentrations (reviewed by Voilley, 2004). 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 chealation 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). Ammonium activates ASIC channels (most likely ASIC1a) in midbrain dopaminergic neurones which may be relevant to neuronal disorders that are associated with hyperammonemia (Pidoplichko and Dani, 2006). The positive modulation of homomeric, heteromeric and native ASIC channels by the peptide FMRFamide and related substances, such as neuropeptides FF and SF, is reviewed in detail by Lingueglia *et al*. (2006). Inflammatory conditions and particular pro-inflammatory mediators induce overexpression of ASIC-encoding genes, enhance ASIC currents (Mamet *et al*., 2002), and in the case of arachidonic acid directly activate the channel (Smith *et al*., 2007).

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

Further Reading

Diochot S, Salinas M, Baron A, Escoubas P, Lazdunski M (2007). Peptides inhibitors of acid-sensing ion channels. *Toxicon* **49**: 271–284.
Kress M, Waldmann R (2006). Acid sensing ionic channels. *Curr Top Membr* **57**: 241–276.
Krishtal O (2003). The ASICs: Signaling molecules? Modulators? *Trends Neurosci* **26**: 477–483.
Lingueglia E (2007). Acid-sensing ion channels in sensory perception. *J Biol Chem* **282**: 17325–17329.
Lingueglia E, Deval E, Lazdunski M (2006). FMRFamide-gated sodium channel and ASIC channels: a new class of ionotropic receptors for FMRFamide and related peptides. *Peptides* **27**: 1138–1152.
Reeh PW, Kress M (2001). Molecular physiology of proton transduction in nociceptors. *Curr Opin Pharmacol* **1**: 45–51.
Sutherland SP, Cook SP, McCleskey EW (2000). Chemical mediators of pain due to tissue damage and ischemia. *Prog Brain Res* **129**: 21–38.
Voilley N (2004). Acid-sensing ion channels (ASICs): new targets for the analgesic effects of non-steroid anti-inflammatory drugs (NSAIDs). *Curr Drug Targets Inflamm Allerg* **3**: 71–79.
Waldmann R (2001). Proton-gated cation channels-neuronal acid sensors in the central and peripheral nervous system. *Adv Exp Med Biol* **502**: 293–304.
Waldmann R, Lazdunski M (1998). H^+-gated cation channels: neuronal acid sensors in the NaC/DEG family of ion channels. *Curr Opin Neurobiol* **8**: 418–424.
Wemmie JA, Price MP, Welsh MJ (2006). Acid-sensing ion channels: advances, questions and therapeutic opportunities. *Trends Neurosci* **29**: 578–586.
Xiong ZG, Chu XP, Simon RP (2007). Acid sensing ion channels–novel therapeutic targets for ischemic brain injury. *Front Biosci* **12**: 1376–1386.
Xiong ZG, Pignataro G, Li M, Chang SY, Simon RP (2007). Acid-sensing ion channels as pharmacological targets for neurodegenerative diseases. *Curr Opin Pharmacol* Oct 16 [E-pub ahead of print].
Xu TL, Xiong ZG (2007). Dynamic regulation of acid-sensing ion channels by extracellular and intracellular modulators. *Curr Med Chem* **14**: 1753–1763.

References

Akopian AN *et al.* (2000). *Neuroreport* **11**: 2217–2222.
Babinski K *et al.* (1999). *J Neurochem* **72**: 51–57.
Babinski K *et al.* (2000). *J Biol Chem* **37**: 28519–28525.
Baron A *et al.* (2001). *J Biol Chem* **276**: 35361–35367.
Chen C-C *et al.* (1998). *Proc Natl Acad Sci USA* **95**: 10240–10245.
Chen X *et al.* (2007). *J Biol Chem* **282**: 30406–30416.
Chu X-P *et al.* (2004). *J Neurosci* **24**: 8678–8689.
De Weille JR *et al.* (1998). *FEBS Lett* **433**: 257–260.
Diochot S *et al.* (2004). *EMBO J* **23**: 1516–1525.
Dube GR *et al.* (2005). *Pain* **117**: 88–96.
Escoubas P *et al.* (2000). *J Biol Chem* **275**: 25116–25121.
Garcia-Anoveros J *et al.* (1997). *Proc Natl Acad Sci USA* **94**: 1459–1464.
Grunder S *et al.* (2000). *Neuroreport* **11**: 1607–1611.
Jasti J *et al.* (2007). *Nature* **449**: 316–323.
Lingueglia E *et al.* (1997). *J Biol Chem* **272**: 29778–29783.
Mamet J *et al.* (2002). *J Neurosci* **22**: 10662–10670.
Mazzuca M *et al.* (2007). *Nat Neurosci* **10**: 943–945.
Paukert M *et al.* (2004). *J Biol Chem* **279**: 18733–18791.
Pidoplichko VI, Dani JA (2006). *Proc Natl Acad Sci USA* **103**: 11376–11380.
Price MP *et al.* (1996). *J Biol Chem* **271**: 7879–7882.
Sakai H *et al.* (1999). *J Physiol (Lond)* **519**: 323–333.
Schaefer L *et al.* (2000). *FEBS Lett* **471**: 205–210.
Smith ES *et al.* (2007). *Neuroscience* **145**: 686–698.
Sutherland SP *et al.* (2001). *Proc Natl Acad Sci USA* **98**: 711–716.
Ugawa S *et al.* (2001). *Neuroreport* **12**: 2865–2869.
Waldmann R *et al.* (1996). *J Biol Chem* **271**: 10433–10436.
Waldmann R *et al.* (1997a). *Nature* **386**: 173–177.
Waldmann R *et al.* (1997b). *J Biol Chem* **272**: 20975–20978.
Wemmie JA *et al.* (2002). *Neuron* **34**: 463–477.
Wemmie JA *et al.* (2003). *J Neurosci* **23**: 5496–5502.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

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).

Further Reading

Agre P (2006). The aquaporin water channels. *Proc Am Thoroc Soc* **3**: 5–13.
Agre P, King LS, Yasui M, Guggino WB, Ottersen OP, Fujiyoshi Y *et al*. (2002). Aquaporin water channels: from atomic structure to clinical medicine. *J Physiol* **542**: 3–16.
Amiry-Moghaddam M, Ottersen OP (2003). The molecular basis of water transport in the brain. *Nat Rev Neurosci* **4**: 991–1001.
Castle NA (2005). Aquaporins as targets for drug discovery. *Drug Discov Today* **10**: 485–493.
De Groot BL, Grubmuller H (2005). The dynamics and energetics of water permeation and proton exclusion in aquaporins. *Curr Opin Struct Biol* **15**: 176–183.
Frigeri A, Nicchia GP, Svelto M (2007). Aquaporins as targets for drug discovery. *Curr Pharm Des* **13**: 2421–2427.
Jeyaseelan K, Sepramaniam S, Armugam A, Wintour EM (2006). Aquaporins: a promising target for drug development. *Expert Opin Ther Targets* **10**: 889–909.
Kimelberg HK (2004). Water homeostasis in the brain: basic concepts. *Neuroscience* **129**: 851–860.
King KL, Kozono D, Agre P (2004). From structure to disease: the evolving tale of aquaporin biology. *Nat Rev Mol Cell Biol* **5**: 687–698.
Wang F, Feng XC, Li YM, Yang H, Ma TH (2006). Aquaporins as potential drug targets. *Acta Pharmacol Sin* **27**: 395–401.

References

Preston GM *et al*. (1992). *Science* **256**: 385–387.
Yasui M *et al*. (1999). *Nature* **402**: 184–187.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

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.*, 2005). 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 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 α1-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 α1, β and α2–δ subunits. The γ subunits have not been proven to associate with channels other than α1 s. The α2–δ1 and α2–δ2 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-(GVDKAGCRYMFGGCSVNDDCCPRLGCHSLFSYCAWDLTFSD); **SZ(+)-(S)-202-791**, isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridinecarboxylate

Further Reading

Catterall WA (2000). Structure and regulation of voltage-gated Ca^{2+} channels. *Annu Rev Cell Dev Biol* **16**: 521–555.

Catterall WA, Perez-Reyes E, Snutch TP, Striessing J (2005). International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. *Pharmacol Rev* **57**: 411–425.

Davies A, Hendrich J, Van Minh AT, Wratten J, Douglas L, Dolphin AC (2007). Functional biology of the alpha(2)delta subunits of voltage-gated calcium channels. *Trends Pharmacol Sci* **28**: 220–228.

Dolphin AC (2003). G protein modulation of voltage-gated calcium channels. *Pharmacol Rev* **55**: 607–627.

Elmslie KS (2004). Calcium channel blockers in the treatment of disease. *J Neurosci Res* **75**: 733–741.

Ertel EA, Campbell KP, Harpold MM, Hofmann F, Mori Y, Perez-Reyes E *et al.* (2000). Nomenclature of voltage-gated calcium channels. *Neuron* **25**: 533–535.

Hofmann F, Lacinova L, Klugbauer N (1999). Voltage-dependent calcium channels; from structure to function. *Rev Physiol Biochem Pharmacol* **139**: 35–87.

Kochegarov AA (2003). Pharmacological modulators of voltage-gated calcium channels and their therapeutic application. *Cell Calcium* **33**: 145–162.

Lewis RJ, Garcia ML (2003). Therapeutic potential of venom peptides. *Nat Rev Drug Discov* **2**: 790–802.

Lory P, Chemin J (2007). Towards the discovery of novel T-type calcium channel blockers. *Expert Opin Ther Targets* **11**: 717–722.

Nelson MT, Todorovic SM, Perez-Reyes E (2006). The role of T-type calcium channels in epilepsy and pain. *Curr Pharm Des* **12**: 2189–2197.

Perez-Reyes E (2003). Molecular physiology of low-voltage-activated T-type calcium channels. *Physiol Rev* **83**: 117–161.

Taylor CP, Anelotti T, Fauman E (2007). Pharmacology and mechanism of action of pregabalin; the calcium channel alpha2-delta subunit as a target for antiepileptic drug discovery. *Epilepsy Res* **73**: 137–150.
Terlau H, Olivera BM (2004). Conus venoms: a rich source of novel ion channel-targeted peptides. *Physiol Rev* **84**: 41–68.
Triggle DJ (2006). L-type calcium channels. *Curr Pharm Des* **12**: 443–457.
Triggle DJ (2007). Calcium channel antagonists: clinical uses – past, present and future. *Biochem Pharmacol* **74**: 1–9.
Trimmer JS, Rhodes KJ (2004). Localisation of voltage-gated ion channels in mammalian brain. *Annu Rev Physiol* **66**: 477–519.
Yu FH, Catterall WA (2004). The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* **2004** (253): re15.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

CatSper

Overview: CatSper channels (CatSper1-4; nomenclature as agreed by NC-IUPHAR, Clapham and Garbers, 2005) are putative 6TM, voltage-gated, calcium permeant channels that are presumed to assemble as a tetramer of α-like subunits and mediate the current $I_{CatSper}$. In mammals, CatSper subunits are structurally most closely related to individual domains of voltage-activated calcium channels (Ca_v) (Ren *et al*., 2001). CatSper1 (Ren *et al*., 2001), CatSper2 (Quill *et al*., 2001) and CatSpers 3 and 4 (Lobley *et al*., 2003; Lin *et al*., 2005; Qi *et al*., 2007), in common with a recently identified putative 2TM auxiliary CatSperβ protein (Liu *et al*., 2007), are restricted to the testis and localised to the principle piece of sperm tail.

Nomenclature	CatSper1	CatSper2	CatSper3	CatSper4
Ensembl ID	ENSG00000175294	ENSG00000166762	ENSG00000152705	ENSG00000188782
Activators	Constitutively active, weakly facilitated by membrane depolarisation, strongly augmented by intracellular alkalinisation	—	—	—
Blockers	Cd^{2+} (200 μM), Ni^{2+} (300 μM), ruthenium red (10 μM)	—	—	—
Functional characteristics	Calcium selective ion channel ($Ba^{2+} > Ca^{2+} \gg Mg^{2+} \gg Na^{+}$); quasilinear monovalent cation current in the absence of extracellular divalent cations; alkalinization shifts the voltage-dependence of activation towards negative potentials ($V_{1/2}$ @ pH 6.0 = +87 mV; $V_{1/2}$ @ pH 7.5 = +11 mV)	Required for $I_{CatSper}$	Required for $I_{CatSper}$	Required for $I_{CatSper}$

CatSper channel subunits expressed singly, or in combination, fail to functionally express in heterologous expression systems (Quill *et al*., 2001; Ren *et al*., 2001). The properties of CatSper1 tabulated above are derived from whole cell voltage-clamp recordings comparing currents endogenous to spermatozoa isolated from the *corpus epididymis* of wild-type and *Catsper1*$^{(-/-)}$ mice (Kirichok *et al*., 2006). $I_{CatSper}$ is also undetectable in the spermatozoa of *Catsper2*$^{(-/-)}$, *Catsper3*$^{(-/-)}$, or *Catsper4*$^{(-/-)}$ mice and CatSper 1 associates with CatSper 2, 3, or 4 in heterologous expression systems (Qi *et al*., 2007). Moreover, targeted disruption of *Catsper1*, *2*, *3*, or *4* genes results in an identical phenotype in which spermatozoa fail to exhibit the hyperactive movement (whip-like flagellar beats) necessary for penetration of the egg *cumulus* and *zona pellucida* and subsequent fertilization. Such disruptions are associated with a deficit in alkalinization and depolarization-evoked Ca^{2+} entry into spermatozoa (Carlson *et al*., 2003, 2005; Qi *et al*., 2007). Thus, it is likely that the CatSper pore is formed by a heterotetramer of CatSpers1-4 (Qi *et al*., 2007). The driving force for Ca^{2+} entry is principally determined by a mildly outwardly rectifying K^{+} channel (KSper) that, like CatSpers, is activated by intracellular alkalinization (Navarro *et al*., 2007). KSper is not yet identified, but its properties are most consistent with mSlo3, a protein detected only in testis (Navarro *et al*., 2007).

Further Reading

Clapham DE, Garbers DL (2005). International Union of Pharmacology. L. Nomenclature and structure-function relationships of CatSper and two-pore channels. *Pharmacol Rev* **57**: 451–454.
Quill TA, Wang D, Garbers DL (2006). Insights into sperm cell motility through sNHE and the CatSpers. *Mol Cell Endocrinol* **250**: 84–92.
Zhang D, Gopalakrishnan M (2005). Sperm ion channels: molecular targets for the next generation of contraceptive medicines? *J Androl* **26**: 643–653.

References

Carlson AE *et al.* (2005). *J Biol Chem* **280**: 32238–32244.
Carlson AE *et al.* (2003). *Proc Natl Acad Sci USA* **100**: 14864–14868.
Kirichok Y *et al.* (2006). *Nature* **439**: 737–740.
Lin J-L *et al.* (2005). *Biol Reprod* **73**: 1235–1242.
Liu J *et al.* (2007). *J Biol Chem* **282**: 18945–18952.
Lobley A *et al.* (2003). *Reprod Biol Endocrinol* **1**: 53.
Navarro B *et al.* (2007). *Proc Natl Acad Sci USA* **104**: 7688–7692.
Qi H *et al.* (2007). *Proc Natl Acad Sci USA* **104**: 1219–1223.
Quill TA *et al.* (2001). *Proc Natl Acad Sci USA* **98**: 12527–12531.
Ren D *et al.* (2001). *Nature* **413**: 603–609.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

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 and Droogmans, 2003). Excluding the transmitter-gated GABA and glycine receptors (see separate tables), well characterised chloride channels can be classified as the voltage-sensitive ClC subfamily, calcium-activated channels, high (maxi) conductance channels, the cystic fibrosis transmembrane conductance regulator (CFTR) and volume regulated channels. No official recommendation exists regarding the classification of chloride channels. Functional chloride channels that have been cloned from, or characterised within, mammalian tissues are listed.

ClC-family: The mammalian ClC family (reviewed by Jentsch *et al*., 2002; Nilius and Droogmans, 2003; Chen, 2005; Jentsch *et al*., 2005a, b; Dutzler, 2006) contains 9 members that fall into three groups; ClC-1, ClC-2, hClC-Ka (rClC-K1) and hClC-Kb (rClC-K2); ClC-3 to ClC-5, and ClC-6 and -7. ClC-1 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 ClC-3 (ENSG00000109572), ClC-4 (ENSG00000073464) and ClC-5 (ENSG00000171365) 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 and 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 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 and Jentsch, 2002; Babini and Pusch, 2004; Chen, 2005; Dutzler, 2006). 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 and Miller, 2004).

Nomenclature	ClC-1	ClC-2	ClC-Ka	ClC-Kb
Other names	Skeletal muscle Cl^- channel	—	ClC-K1 (rodent)	ClC-K2 (rodent)
Ensembl ID	ENSG00000186544	ENSG00000114859	ENSG00000186510	ENSG00000184908
Activators	Constitutively active	Arachidonic acid, amidation, acid-activated omeprazole, lubiprostone (SPI-0211)	Constitutively active (when co-expressed with barttin)	Constitutively active (when co-expressed with barttin)
Blockers	*S*-(−)CPP, S-(−)CPB, 9-AC, Cd^{2+}, Zn^{2+}, niflumic acid	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 cystathionine β-synthetase related (CBS) domains, inhibited by intracellular acidosis in the presence of ATP	$\gamma = 2$–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; cell surface expression and activity increased by association with Hsp90	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 A-9-C)	—	—
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 and 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 and 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, A-9-C and niflumic acid act intracellularly and exhibit a strongly voltage-dependent block with strong inhibition at negative voltages and relief of block at depolarized potentials (Liantonio *et al*., 2007 and reviewed by Pusch *et al*., 2002). Mutations in the ClC-1 gene result in myotonia congenita. 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; Scholl *et al*., 2006). The rodent homologue (ClC-K1) of ClC-Ka demonstrates limited expression as a homomer, but its function is enhanced by barttin which increases both channel opening probablility in the physiological range of potentials and single channel conductance (Estévez *et al*., 2001; Scholl *et al*., 2006). Knock out of the ClC-K1 channel induces nephrogenic diabetes insipidus. 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 and Sasaki, 2005). ClC-Ka is approximately 5 to 6-fold

more sensitive to block by 3-phenyl-CPP and DIDS than ClC-Kb (Liantonio *et al*., 2002). The biophysical and pharmacological properties of ClC-3, and the relationship of the protein to the endogenous volume-regulated anion channel(s) VRAC (see Guan *et al*., 2006 and below) are controversial and further complicated by the inference that ClC-3 is a Cl^-/H^+ exchanger, rather than an ion channel (Picollo and 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 (Stobrawa *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 (Stobrawa *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. Disruption of the ClC-7 gene in mice leads to osteopetrosis, blindness and lysosomal dysfunction (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, Δ508) results in impaired trafficking of CFTR and reduces its incorporation into the plasma membrane causing cystic fibrosis. In addition to acting as an anion channel *per se*, CFTR may act as a regulator of several other conductances including inhibition of the epithelial Na channel (ENaC), calcium activated chloride channels (CaCC) and volume regulated anion channel (VRAC), activation of the outwardly rectifying chloride channel (ORCC), and enhancement of the sulphonylurea sensitivity of the renal outer medullary potassium channel (ROMK2), (reviewed by Nilius and 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, phenylglycines (e.g. 2-[(2-1*H*-indol-3-yl-acetyl)-methylamino]-*N*-(4-isopropylphenyl)-2-phenylacetamide), sulfonamides (e.g. 6-(ethylphenylsulfamoyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid cycloheptylamide)
Blockers	GlyH-101, $CFTR_{inh}$-172, glibenclamide
Functional characteristics	$\gamma = 6$–10 pS; permeability sequence $= Br^- \geqslant Cl^- > I^- > F^-$, ($P_I/P_{Cl} = 0.1$–$0.85$); slight outward rectification; phosphorylation necessary for activation by ATP binding at binding nucleotide binding domains (NBD)1 and 2; positively regulated by PKC and PKGII (tissue specific); regulated by several interacting proteins including syntaxin 1A, Munc18 and PDZ domain proteins such as NHERF (EBP50) and CAP70

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 dimer and channel closing, and the initiation of a new gating cycle (Vergani *et al*., 2005; Aleksandrov *et al*., 2007). Phosphorylation by PKA at sites within a cytoplasmic regulatory (R) domain are required for the binding ATP to gate CFTR (Gadsby *et al*., 2006). PKC (and PKGII within intestinal epithelial cells *via* guanylin-stimulated cGMP formation) positively regulate CFTR activity.

Calcium activated chloride channel: Chloride channels activated by intracellular calcium (CaCC) are widely expressed in excitable and non-excitable cells where they perform diverse functions (Hartzell *et al*., 2005). The molecular nature of CaCC is unclear. Members of the initial putative calcium-activated chloride channel proteins (the CLCA family) have been cloned from human, murine, bovine and porcine species (reviewed by Loewen and Forsyth, 2005), but their similarity to endogenous CaCC is slim (e.g. Britton *et al*., 2002; Eggermont, 2004) and doubt has been cast on their existence as ion channels (e.g. Gibson *et al*., 2005). CLCAs now appear to function as cell adhesion proteins, or are secreted proteins but the properties of CLCA isoforms may be modified by auxillary subunits (Greenwood *et al*., 2002). More recently the Best gene family (hbest1-4) have been identified whose expression products (bestrophins) have a topology more consistent with ion channels (see Hartzell *et al*., 2005). Moreover, mutation of amino acids in the theoretical pore region affects anion conductance and the channels are activated by physiological concentrations of intracellular Ca^{2+} in a 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, DCDPC, DIDS, SITS, NPPB, A-9-C, $Ins(3,4,5,6)P_4$, mibefradil, fluoxetine
Functional characteristics	$\gamma = 0.5$–5 pS; permeability sequence, $SCN^- > NO_3^- > I^- > Br^- > Cl^- > F^-$; relative permeability of SCN^-:$Cl^- \sim 8$. I^-:$Cl^- \sim 3$, aspartate:$Cl^- \sim 0.15$, outward rectification (decreased by increasing $[Ca^{2+}]_i$); sensitivity to activation by $[Ca^{2+}]_i$ decreased at hyperpolarized potentials; slow activation at positive potentials (accelerated by increasing $[Ca^{2+}]_i$); rapid deactivation at negative potentials, deactivation kinetics modulated by anions binding to an external site; modulated by redox status

Blockade of $I_{Cl(Ca)}$ by niflumic acid, DIDS and 9-AC is voltage-dependent whereas block by NPPB is voltage-independent (Hartzell *et al*., 2005). Extracellular niflumic acid; DCDPC and A-9-C (but not DIDS) exert a complex effect upon $I_{Cl(Ca)}$ in vascular smooth muscle, enhancing and inhibiting inwardly and outwardly directed currents in a manner dependent upon $[Ca^{2+}]_i$ (see Leblanc *et al*., 2005 for summary). Considerable crossover in pharmacology with large conductance Ca^{2+}-activated K^+ channels also exists (see Greenwood and Leblanc, 2007 for overview). CaMKII modulates CaCC in a tissue dependent manner (reviewed by Hartzell *et al*., 2005; Leblanc *et al*., 2005). CaMKII inhibitors block activation of $I_{Cl(Ca)}$ in T_{84} cells but have no effect in parotid acinar cells. In tracheal and arterial smooth muscle cells, but not portal vein myocytes, inhibition of CaMKII reduces inactivation of $I_{Cl(Ca)}$. Intracellular Ins(3,4,5,6)P_4 may act as an endogenous negative regulator of CaCC channels activated by Ca^{2+}, or CaMKII. Smooth muscle CaCC are also regulated positively by Ca^{2+}-dependent phosphatase, calcineurin (see Leblanc *et al*., 2005 for summary).

Maxi chloride channel: Maxi Cl^- channels are high conductance, anion selective, channels initially 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. Evidence suggests a role for maxi Cl^- channels as a conductive pathway in the swelling-induced release of ATP from mouse mammary C127i cells that may be important for autocrine and paracrine signalling by purines (Sabirov *et al*., 2001; Dutta *et al*., 2002). A similar channel mediates ATP release from macula densa cells within the thick ascending of the loop of Henle in response to changes in luminal NaCl concentration (Bell *et al*., 2003). A family of human high conductance Cl^- channels (TTYH1-3) that resemble Maxi Cl^- channels has been cloned (Suzuki and Mizuno, 2004), but alternatively, Maxi Cl^- channels have also been suggested to correspond to the voltage-dependent anion channel, VDAC, expressed at the plasma membrane (Bahamonde *et al*., 2003; Okada *et al*., 2004).

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

Differing ionic conditions may contribute to variable estimates of 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 anti-oestrogens in whole cell recordings requires the presence of intracellular nucleotides and is prevented by pre-treatment with 17β-oestradiol, dibutryl cAMP, or intracellular dialysis with GDPβS (Diaz *et al*., 2001). Activation by tamoxifen is suppressed by low concentrations of okadaic acid, suggesting that a dephosphorylation event by protein phosphatase PP2A occurs in the activation pathway (Diaz *et al*., 2001). In contrast, 17β-estradiol and tamoxifen appear to directly inhibit the maxi Cl^- channel of human placenta reconstituted into giant liposomes and recorded in excised patches (Riquelme, 2006).

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 and Droogmans, 2003; Okada *et al*., 2004, Mulligan and MacVicar, 2006). 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. See the discussion above for the role of CLC-3 in VRAC. In addition to CLC-3 expression products several former VRAC candidates including *MDR1* P-glycoprotein, Icln, Band 3 anion exchanger and phospholemman are also no longer considered likely to fulfil this function (see reviews by Jentsch *et al*., 2002; d'Angelmont de Tassigny *et al*., 2003; Nilius and Droogmans, 2003; Sardini *et al*., 2003, Okada, 2006).

Nomenclature	VRAC (volume regulated anion channel), VSOAC (volume-sensitive organic osmolyte/anion channel), VRC (volume regulated channel), VSOR (volume expansion-sensing outwardly rectifying anion channel)
Activators	Cell swelling; low intracellular ionic strength; GTPγS
Blockers	NS3728, DCPIB, clomiphene, nafoxidine, mefloquine, tamoxifen, gossypol, arachidonic acid, mibefradil, NPPB, quinine, quinidine, chromones NDGA, A-9-C, DIDS, 1,9-dideoxyforskolin, oxalon dye (diBA-(5)-C4), extracellular nucleotides, nucleoside analogues, intracellular Mg^{2+}
Functional characteristics	$\gamma = 10$–20 pS (negative potentials), 50–90 pS (positive potentials); permeability sequence $SCN^- > I^- > NO_3^- > Br^- > Cl^- > F^-$ > gluconate; outward rectification due to voltage dependence of γ; inactivates at positive potentials in many, but not all, cell types; time dependent inactivation at positive potentials; intracellular ionic strength modulates sensitivity to cell swelling and rate of channel activation; rate of swelling-induced activation is modulated by intracellular ATP concentration; ATP dependence is independent of hydrolysis and modulated by rate of cell swelling; inhibited by increased intracellular free Mg^{2+} concentration; 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). A Cl channel activated by cGMP with a dependence on raised intracellular Ca^{2+} has been recorded in various vascular smooth muscle cells types, which has a pharmacology very different from the 'conventional' CaCC (see Matchkov *et al*., 2004; Piper and Large, 2004). A proton-activated, outwardly rectifying anion channel has also recently been described (Lambert and Oberwinkler, 2005).

Abbreviations: **A-9-C**, anthracene-9-carboxylic acid; **CBIQ**, 4-chlorobenzo[F]isoquinoline; **$CFTR_{inh}$-172**, 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; **DCPIB**, 4-(2-butyl-6,7-dichlor-2-cyclopentyl-indan-1-on-5-yl) oxybutyric acid; **diBA-(5)-C4**, bis-(1,3-dibutylbarbituric acid)pentamethine oxanol; **DIDS**, 4,4′-diisothiocyanostilbene-2,2′-disulphonic acid; **DNDS**, 4,4′-dinitrostilbene-2,2′-disulphonic acid; **DPC**, diphenylamine carboxylic acid; **DPDPC**, dichloro-diphenylamine 2-carboxylic acid; **GlyH-101**, *N*-(2-naphthalenyl)-[(3,5-dibromo-2,4-dihydroxyphenyl)methylene]glycine hydrazide; **NDGA**, nordihydroguiaretic 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; ***S*-(−)CPB**, *S*-(−)2-(4-chlorophenoxy)butyric acid; ***S*-(−)CPP**, *S*-(−)2-(4-chlorophenoxy)propionic acid; **SITS**, 4′-isothiocyanostilbene-2,2′-disulphonic acid; **UCCF-029**, 2-(4-pyridinium)benzo[*h*]4H-chromen-4-one bisulfate; **UCCF-180**, 3-(3-butynyl)-5-methoxy-1-phenylpyrazole-4-carbaldehyde; **UCCF-853**, 1-(3-chlorophenyl)-5-trifluoromethyl-3-hydroxybenzimidazol-2-one

Further Reading

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

Aromataris EC, Rychkov GY (2006). ClC-1 chloride channel: matching its properties to a role in skeletal muscle. *Clin Exp Pharmacol Physiol* **33**: 1118–1123.

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

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

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

Dutzler R (2006). The ClC family of chloride channels and transporters. *Curr Opin Struct Biol* **16**: 439–446.

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

Eggermont J (2004). Calcium activated chloride channels: (Un)known, (Un)loved? *Proc Am Thorac Soc* **1**: 22–27.

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

Estévez R, Jentsch TJ (2002). CLC chloride channels: correlating structure with function. *Curr Opin Struct Biol* **12**: 531–539.

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

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

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

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

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

Jentsch TJ, Neagoe I, Scheel O (2005a). CLC channels and transporters. *Curr Opin Neurobiol* **15**: 319–325.

Jentsch TJ, Poet M, Fuhrmann JC, Zdebik AA (2005b). Physiological functions of CLC Cl- channels gleaned from human genetic disease and mouse models. *Annu Rev Physiol* **67**: 779–807.

Jentsch TJ, Stein V, Weinreich F, Zdebik AA (2002). Molecular structure and physiological function of chloride channels. *Physiol Rev* **82**: 503–568.

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

Loewen ME, Forsyth GW (2005). Structure and function of CLCA proteins. *Physiol Rev* **85**: 1061–1092.

Miller C (2006). ClC chloride channels viewed through a transporter lens. *Nature* **440**: 484–489.

Mulligan SJ, MacVicar BA (2006). VRACs CARVe a path for novel mechanisms of communication in the CNS. *Sci STKE* **357**: pe42.

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

Nilius B, Eggermont J, Droogmans G (2000). The endothelial volume-regulated anion channel, VRAC. *Cell Physiol Biochem* **10**: 313–320.

Okada Y, Maeno E, Shimizu T, Manabe K, Mori S, Nabekura T (2004). Dual roles of plasmalemmal chloride channels in induction of cell death. *Pflügers Arch* **448**: 287–295.

Okada Y (2006). Cell-volume sensitive chloride channels: phenotypic properties and molecular identity. *Contrib Nephrol* **152**: 9–24.

Puljak L, Kilic G (2006). Emerging roles of chloride channels in human diseases. *Biochim Biopsy Acta* **1762**: 404–413.

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

Pusch M, Accardi A, Liantonio A, Guida P, Traverso S, Camerino DC *et al*. (2002). Mechanisms of block of muscle type CLC chloride channels. *Mol Membr Biol* **19**: 285–292.

Pusch M, Zifarelli G, Murgia AR, Picollo A, Babini E (2006). Channel or transporter? The CLC saga continues. *Exp Physiol* **91**: 149–152.

Riordan JR (2005). Assembly of functional CFTR chloride channels. *Annu Rev Physiol* **67**: 701–718.

Riquelme G (2006). Apical maxi-chloride channel from the human placenta: 12 years after the first electrophysiological recordings. *Biol Res* **39**: 437–445.

Sardini A, Amey JS, Weylandt KH, Nobles M, Valverde MA, Higgins CF (2003). Cell volume regulation and swelling-activated chloride channels. *Biochim Biophys Acta* **1618**: 153–162.

Suzuki M, Mizuno A (2004). A novel human Cl(−) channel family related to Drosophila flightless locus. *J Biol Chem* **279**: 22461–22468.

Thiagarajah JR, Verkman AS (2003). CFTR pharmacology and its role in intestinal fluid secretion. *Curr Opin Pharmacol* **3**: 594–599.

Uchida S, Sasaki S (2005). Function of chloride channels in the kidney. *Annu Rev Physiol* **67**: 759–778.

Verkman AS, Lukacs GL, Galietta LJ (2006). CFTR chloride channel drug discovery-inhibitors as antidiarrheals and activators for therapy of cystic fibrosis. *Curr Pharm Des* **12**: 2235–2247.

Zifarelli G, Pusch M (2007). CLC chloride channels and transporters: a biophysical and physiological perspective. *Rev Physiol Biochem Pharmacol* **158**: 23–76.

References

Accardi A, Miller C (2004). *Nature* **427**: 803–807.
Arniges M *et al.* (2004). *J Biol Chem* **279**: 54062–54068.
Arreola J *et al.* (2002). *J Physiol* **545**: 207–216.
Bahamonde MI *et al.* (2003). *J Biol Chem* **278**: 33284–33289.
Bell PD *et al.* (2003). *Proc Natl Acad Sci USA* **100**: 4322–4327.
Britton FC *et al.* (2002). *J Physiol* **539**: 107–117.
Diaz M *et al.* (2001). *J Physiol* **536**: 79–88.
Dutta AK *et al.* (2002). *J Physiol* **542**: 803–816.
Dutzler R *et al.* (2002). *Nature* **415**: 287–294.
Estévez R *et al.* (2001). *Nature* **414**: 558–561.
Gibson A *et al.* (2005). *J Biol Chem* **280**: 27205–27212.
Greenwood IA *et al.* (2002). *J Biol Chem* **277**: 22119–22122.
Hermoso M *et al.* (2002). *J Biol Chem* **277**: 40066–40074.
Ko SBH *et al.* (2004). *Nat Cell Biol* **6**: 343–350.
Lambert S, Oberwinkler J (2005). *J Physiol* **576**: 191–213.
Liantonio A *et al.* (2002). *Mol Pharmacol* **62**: 265–271.
Liantonio A *et al.* (2007). *Br J Pharmacol* **150**: 235–247.
Matchkov VV *et al.* (2004). *J Gen Physiol* **123**: 121–134.
Ogura T *et al.* (2002). *FASEB J* **16**: 863–865.
Okada SF *et al.* (2004). *J Gen Physiol* **124**: 513–526.
Picollo A, Pusch M (2005). *Nature* **436**: 420–423.
Piper AS, Large WA (2004). *J Physiol* **555**: 397–408.
Qu Z *et al.* (2003). *J Biol Chem* **278**: 49563–49572.
Qu Z *et al.* (2004). *J Gen Physiol* **123**: 327–340.
Sabirov RZ *et al.* (2001). *J Gen Physiol* **118**: 251–266.
Scheel O *et al.* (2005). *Nature* **436**: 424–427.
Scholl U *et al.* (2006). *Proc Natl Acad Sci USA* **103**: 11411–11416.
Stobrawa SM *et al.* (2001). *Neuron* **29**: 185–196.
Suzuki M, Mizuno A (2004). *J Biol Chem* **279**: 22461–22468.
Tsumura T *et al.* (1998). *J Physiol* **512**: 765–777.
Vergani P *et al.* (2005). *Biochem Soc Trans* **33**: 1003–1007.
Wang GX *et al.* (2003). *Am J Physiol Heart Circ Physiol* **285**: H1453–H1463.
Yamamoto-Mizuma S *et al.* (2004). *J Physiol* **557**: 439–356.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

Connexins and pannexins

Overview: Gap junctions are essential for many physiological processes including cardiac and smooth muscle contraction, regulation of neuronal excitability and epithelial electrolyte transport (see Evans and Martin, 2002; Bruzzone *et al.*, 2003; Connors and Long, 2004). Gap junction channels allow the passive diffusion of molecules of up to 1000 Daltons which can include nutrients, metabolites and second messengers (such as IP_3) as well as cations and anions. 21 connexin genes (Cx23, Cx25, Cx26, Cx30, Cx30.2, Cx30.3, Cx31, Cx31.1, Cx31.9, Cx32, Cx36, Cx37, Cx40, Cx40.1, Cx43, Cx45, Cx46, Cx47, Cx50, Cx59, Cx62) and 3 pannexin genes (Px1, Px2, Px3; which are structurally related to the invertebrate innexin genes) code for gap junction proteins in humans. Each connexin gap junction comprises 2 hemichannels or 'connexons' which are themselves formed from 6 connexin molecules. The various connexins have been observed to combine into both homomeric and heteromeric combinations, each of which may exhibit different functional properties. It is also suggested that individual hemichannels formed by a number of different connexins might be functional in at least some cells (see Herve *et al.*, 2007). Connexins have a common topology, with four α-helical transmembrane domains, two extracellular loops, a cytoplasmic loop, and N- and C-termini located on the cytoplasmic membrane face. In mice, the most abundant connexins in electrical synapses in the brain seem to be Cx36, Cx45 and Cx57 (Sohl *et al.*, 2005). Mutations in connexin genes are associated with the occurrence of a number of pathologies, such as peripheral neuropathies, cardiovascular diseases and hereditary deafness. The pannexin genes Px1 and Px2 are widely expressed in the mammalian brain (Vogt *et al.*, 2005). Like the connexins, at least some of the pannexins can form functional hemichannels (Bruzzone *et al.*, 2003; Pelegrin and Surprenant, 2007).

	Connexins	Pannexins
Nomenclature	Cx23, Cx25, Cx26, Cx30, Cx30.2, Cx30.3, Cx31, Cx31.1, Cx31.9, Cx32, Cx36, Cx37, Cx40, Cx40.1, Cx43, Cx45, Cx46, Cx47, Cx50, Cx59, Cx62	Px1, Px2, Px3
Ensembl ID	ENSG00000159248 (Cx36)[a]	ENSG00000110218 (Px1) ENSG00000073150 (Px2) ENSG00000154143 (Px3)
Inhibitors	Carbenoxolone Flufenamic acid Octanol Raising external calcium	Carbenoxolone Little block by flufenamic acid Unaffected by raising external calcium

Connexins are most commonly named according to their molecular weights, so, for example, Cx23 is the connexin protein of 23 kDa. This can cause confusion when comparing between species - for example the mouse connexin Cx57 is orthologous to the human connexin Cx62. No natural toxin or specific inhibitor of junctional channels has been identified yet however two compounds often used experimentally to block connexins are carbenoxolone and flufenamic acid (Salamah and Dhein, 2005). At least some pannexin hemichannels are more sensitive to carbenoxolone than connexins but much less sensitive to flufenamic acid (Bruzzone *et al.*, 2005). Recently it has been suggested that 2-aminoethoxydiphenyl borate (2-APB) may be a more effective blocker of some connexin channel subtypes (Cx26, Cx30, Cx36, Cx40, Cx45, Cx50) compared to others (Cx32, Cx43, Cx46, Bai *et al.*, 2006).

[a]Due to space constraints, the Ensembl ID for only connexin Cx36 is given. Ensembl information for the other connexins can be found from links therein.

Further Reading

Bennett MV, Zukin RS (2004). Electrical coupling and neuronal synchronization in the mammalian brain. *Neuron* **41**: 495–511.

Connors BW, Long MA (2004). Electrical synapses in the mammalian brain. *Annu Rev Neurosci* **27**: 393–418.

Cruciani V, Mikalsen SO (2006). The vertebrate connexin family. *Cell Mol Life Sci* **63**: 1125–1140.

Evans WH, De Vuyst E, Leybaert L (2006). The gap junction cellular internet: connexin hemichannels enter the signalling limelight. *Biochem J* **397**: 1–14.

Evans WH, Martin PEM (2002). Gap junctions: structure and function. *Mol Memb Biol* **19**: 121–136.

Harris AL (2007). Connexin channel permeability to cytoplasmic molecules. *Prog Biophys & Mol Biol* **94**: 120–143.

Herve JC (2007). Gap junction channels: from protein genes to diseases. *Prog Biophys & Mol Biol* **94**: 1–4.

Herve JC, Bourmeyster N, Sarrouilhe D, Duffy HS (2007). Gap junctional complexes: from partners to functions. *Prog Biophys & Mol Biol* **94**: 29–65.

Herve JC, Phelan P, Bruzzone R, White TW (2005). Connexins, innexins and pannexins: Bridging the communication gap. *Biochem Biophys Acta* **1719**: 3–5.

Herve JC, Sarrouilhe D (2005). Connexin-made channels as pharmacological targets. *Curr Pharm Des* **11**: 1941–1958.

Homuzdi SG, Filippov MA, Mitropoulou G, Monyer H, Bruzzone R (2004). Electrical synapses: a dynamic signaling system that shapes the activity of neuronal networks. *Biochem Biophys Acta* **1662**: 113–137.

Kumar NM, Gilula NB (1996). The gap junction communication channel. *Cell* **84**: 381–388.

Salameh A, Dhein S (2005). Pharmacology of gap junctions: New pharmacological targets for treatment of arrhythmia, seizure and cancer? *Biochem Biophys Acta* **1719**: 36–58.

Sohl G, Maxeiner S, Willecke K (2005). Expression and functions of neuronal gap junctions. *Nature Rev Neurosci* **6**: 191–200.

Spray DC, Dermietzel R (1996). *Neuroscience Intelligence Unit: Gap Junctions in the Nervous System*. Springer: New York.

Yen MR, Saier MH (2007). Gap junctional proteins of animals: The innexin/pannexin superfamily. *Prog Biophys Mol Biol* **94**: 5–14.

References

Bai D *et al.* (2006). *J Pharmacol Exp Ther* **319**: 1452–1458.

Bruzzone R *et al.* (2003). *Proc Natl Acad Sci USA* **100**: 13644–13649.

Bruzzone R *et al*. (2005). *J Neurochem* **92**: 1033–1043.
Pelegrin P, Surprenant A (2007). *J Biol Chem* **282**: 2386–2394.
Vogt A *et al*. (2005). *Brain Res Mol Brain Res* **141**: 113–120.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

Cyclic nucleotide-gated

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*., 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 and Gold, 1987) and the pineal gland (Dryer and 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 and Zagotta, 2004).

Further Reading

Bradley J, Reisert J, Frings S (2005). Regulation of cyclic nucleotide-gated channels. *Curr Opin Neurobiol* **15**: 343–349.
Brown RL, Strassmaier T, Brady JD, Karpen JW (2006). The pharmacology of cyclic nucleotide-gated channels: emerging from the darkness. *Curr Pharm Des* **12**: 3597–3613.
Craven KB, Zagotta WN (2006). CNG and HCN channels: two peas, one pod. *Annu Rev Physiol* **68**: 375–401.
Hofmann F, Biel M, Kaup UB (2005). International Union of Pharmacology. LI. Nomenclature and structure-function relationships of cyclic nucleotide-regulated channels. *Pharmacol Rev* **57**: 455–462.
Kaupp UB, Seifert R (2002). Cyclic nucleotide-gated ion channels. *Physiol Rev* **82**: 769–824.
Matulef K, Zagotta WN (2003). Cyclic nucleotide-gated ion channels. *Annu Rev Cell Dev Biol* **19**: 23–44.
Yu FH, Catterall WA (2004). The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* **2004** (253): re15.

References

Dryer SE, Henderson D (1991). *Nature* **35**: 756–758.
Fesenko EE *et al*. (1985). *Nature* **313**: 310–313.
Kaupp UB *et al*. (1989). *Nature* **342**: 762–766.
Nakamura T, Gold GH (1987). *Nature* **325**: 442–444.
Peng CH *et al*. (2004). *Neuron* **42**: 401–410.
Weitz D *et al*. (2002). *Neuron* **36**: 881–889.
Zheng J *et al*. (2002). *Neuron* **36**: 891–896.
Zheng J, Zagotta WN (2004). *Neuron* **42**: 411–421.
Zhong H *et al*. (2002). *Nature* **420**: 193–198.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

Epithelial sodium (ENaC)

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

Nomenclature	Epithelial sodium channel (ENaC)
Ensembl ID	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. The action of aldosterone, which occurs in 'early' (1.5–3 h) and 'late' (6–24 h) phases (Garty and Palmer, 1997) is 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). ENaC is also constitutively activated by trypsin family serine peptidases (Planes and Caughey, 2007). Phosphatidylinositides such as $PtIns(4,5)P_2$ and $PtIns(3,4,5)P_3$) stabilise channel gating probably by binding to the β and γ ENaC subunits, respectively (Ma *et al*., 2007; Pochynyuk *et al*., 2007).

Data in the table refer to the 2αβγ heteromer. There are several human diseases resulting from mutations in ENaC subunits, or their regulation, most of which lead to over-expression or under-expression of the channel in epithelia. The best known of these is Liddle's syndrome, usually associated with gain of function mutations in the β and γ subunits that result in decreased down regulation of ENaC (Rotin, 2000; 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 and Hummler, 2000). Regulation of ENaC by phosphoinositides 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).

Further Reading

Alvarez de la Rosa D, Canessa CM, Fyfe GK, Zhang P (2000). Structure and regulation of amiloride-sensitive sodium channels. *Annu Rev Physiol* **62**: 573–594.

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

Garty H, Palmer LG (1997). Epithelial sodium channels: function, structure, and regulation. *Physiol Rev* **77**: 359–396.

Gormley K, Dong Y, Sagnella GA (2003). Regulation of the epithelial sodium channel by accessory proteins. *Biochem J* **371**: 1–14.

Hummler E, Vallon V (2005). Lessons from mouse mutants of epithelial sodium channel and its regulatory proteins. *J Am Soc Nephrol* **16**: 3160–3166.

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

Ma HP, Chou CF, Wei SP, Eaton DC (2007). Regulation of the epithelial sodium channel by phosphatidylinositides: experiments, implications, and speculations. *Pflügers Arch* **455**: 169–180.

Planes C, Caughey GH (2007). Regulation of the epithelial Na^+ channel by peptidases. *Curr Top Dev Biol* **78**: 23–46.

Pochynyuk O, Tong Q, Staruschenko A, Stockand JD (2007). Binding and direct activation of the epithelial Na^+ channel (ENaC) by phosphatidylinositides. *J Physiol* **580**: 365–372.

Rossier BC, Pradervand S, Schild L, Hummler E (2002). Epithelial sodium channel and the control of sodium balance: interaction between genetic and environmental factors. *Annu Rev Physiol*. **64**: 877–897.

Sagnella GA, Swift PA (2006). The renal epithelial sodium channel: genetic heterogeneity and implications for the treatment of high blood pressure. *Curr Pharm Des* **12**: 2221–2234.

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

References

Barker PM *et al*. (1990). *J Physiol* **424**: 473–485.

Canessa CM *et al*. (1993). *Nature* **361**: 467–470.

Canessa CM *et al*. (1994). *Nature* **367**: 463–466.

Debonneville C *et al*. (2001). *EMBO J* **20**: 7052–7059.

Firsov D *et al*. (1998). *EMBO J* **17**: 344–352.

Friedrich B *et al*. (2003). *Pflügers Arch* **445**: 693–696.

Guan Y *et al*. (2005). *Nature Med* **11**: 861–866.

Hummler E *et al*. (1996). *Nature Genet* **12**: 325–328.

Kellenberger S *et al*. (2003). *Mol Pharmacol* **64**: 848–856.

Morris RG, Schafer JA (2002). *J Gen Physiol* **120**: 71–85.
Rotin D (2000). *Curr Opin Nephrol Hypertens* **9**: 529–534.
Richard K *et al*. (2004). *FEBS Lett* **576**: 339–342.
Sayegh R *et al.* (1999). *J Biol Chem* **274**: 12431–12437.
Staub O *et al.* (1996). *EMBO J* **15**: 2371–2380.
Waldmann R *et al*. (1995). *J Biol Chem* **270**: 27411–27414.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

Hyperpolarisation-activated, cyclic nucleotide-gated (HCN)

Overview: The hyperpolarisation-activated, cyclic nucleotide-gated (HCN) channels are cation channels that are activated by hyperpolarisation at voltages negative to ~ −50 mV. 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. 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*., 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

Further Reading

Baruscotti M, Bucchi A, DiFrancesco D (2005). Physiology and pharmacology of the cardiac pacemaker ("funny") current. *Pharmacol Ther* **107**: 59–79.

Biel M, Ludwig A, Zong X, Hofmann F (1999). Hyperpolarisation-activated cation channels: a multi-gene family. *Rev Physiol Biochem Pharmacol* **136**: 165–181.

Biel M, Schneider A, Wahl C (2002). Cardiac HCN channels: structure, function and modulation. *Trends Cardiovasc Med* **12**: 206–213.

Bois P, Guinamard R, Chemaly AE, Faivre JF, Bescond J (2007). Molecular regulation and pharmacology of pacemaker channels. *Curr Pharm Des* **13**: 2338–2349.

Craven KB, Zagotta WN (2006). CNG and HCN channels: two peas, one pod. *Annu Rev Physiol* **68**: 375–401.

DiFrancesco D (1993). Pacemaker mechanisms in cardiac tissue. *Annu Rev Physiol* **55**: 455–472.

DiFrancesco D, Camm JA (2004). Heart rate lowering by specific and selective *I–f* current inhibition with ivabradine – a new therapeutic perspective in cardiovascular disease. *Drugs* **64**: 1757–1765.

Hofmann F, Biel M, Kaupp UB (2005). International Union of Pharmacology. LI. Nomenclature and structure-function relationships of cyclic nucleotide-regulated channels. *Pharmacol Rev* **57**: 455–462.

Kaupp UB, Seifert R (2001). Molecular diversity of pacemaker ion channels. *Annu Rev Physiol* **63**: 235–257.

Meldrum BS, Rogawski MA (2007). Molecular targets for antiepileptic drug development. *Neurotherapeutics* **4**: 18–61.

Pape HC (1996). Queer current and pacemaker: the hyperpolarisation-activated cation current in neurons. *Annu Rev Physiol* **58**: 299–327.

Yu FH, Catterall WA (2004). The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* **2004** (253): re15.

References

Altomare C *et al*. (2003). *J Physiol* **549**: 347–359.

Bosmith RE *et al*. (1993). *Br J Pharmacol* **110**: 343–349.

Bucchi A *et al*. (2002). *J Gen Physiol* **120**: 1–13.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

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.

Abbreviation: FKBP, FK506-binding protein

Further Reading

Berridge MJ, Lipp P, Bootman MD (2000). The versatility and universality of calcium signalling. *Nat Rev Mol Cell Biol* **1**: 11–21.

Bolton TB (2006). Calcium events in smooth muscles and their interstitial cells: physiological roles of sparks. *J Physiol* **570**: 5–11.

Bootman MD, Berridge MJ, Roderick HL (2002). Calcium signalling: more messengers, more channels, more complexity. *Curr Biol* **12**: R563–R565.

Bosanac I, Michikawa T, Mikoshiba K, Ikura M (2004). Structural insights into the regulatory mechanism of IP_3 receptor. *Biochim Biophys Acta* **1742**: 89–102.

Bultynck G, Sienaert I, Parys JB, Callewaert G, De Smedt H, Boens N *et al.* (2003). Pharmacology of inositol trisphosphate receptors. *Pflűgers Arch* **445**: 629–642.

Choe CU, Ehrlich BE (2006). The inositol 1,4,5-triphosphate receptor (IP3R) and its regulators: sometimes good and sometimes bad team work. *Sci STKE* **2006**: re15.

Foskett JK, White C, Cheung KH, Mak DO (2007). Inositol trisphosphate receptor Ca^{2+} release channels. *Physiol Rev* **87**: 593–658.

Mikoshiba K (2007). The IP_3 receptor/Ca^{2+} channel and its cellular function. *Biochem Soc Symp* **74**: 9–22.

Nahorski SR (2006). Pharmacology of intracellular signalling pathways. *Br J Pharmacol* **147** (Suppl 1): S38–S45.

Patel S, Joseph SK, Thomas AP (1999). Molecular properties of inositol 1,4,5-trisphosphate receptors. *Cell Calcium* **25**: 247–264.

Patterson RL, Boehning D, Snyder SH (2004). Inositol 1,4,5-triphosphate receptors as signal integrators. *Annu Rev Biochem* **73**: 437–465.

Taylor CW, Traynor D (1995). Calcium and inositol trisphosphate receptors. *J Membr Biol* **145**: 109–118.

Verkhratsky A (2005). Physiology and pathophysiology of the calcium store in the endoplasmic reticulum of neurons. *Physiol Rev* **85**: 201–279.

Vermassen E, Parys JB, Mauger J-P (2004). Subcellular distribution of the inositol 1,4,5-triphosphate receptors: functional relevance and molecular determinants. *Biol Cell* **96**: 3–17.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

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 αsubunit often associated with auxiliary regulatory subunits. Since there are over 70 different genes encoding K channels αsubunits 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. Due to space constraints, the Ensembl ID for only one member of each subfamily is given. Ensembl information for the other subfamily members can be found from links therein. 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 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 αsubunits 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 ID	ENSG00000151704 ($K_{IR}1.1$)	ENSG00000123700 ($K_{IR}2.1$)	ENSG00000162989 ($K_{IR}3.1$)	ENSG00000177807 ($K_{IR}4.1$)
Activators	—	—	PIP_2, Gβγ	—
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 ID	ENSG00000153822 ($K_{IR}5.1$)	ENSG00000121361 ($K_{IR}6.1$)	ENSG00000115474 ($K_{IR}7.1$)
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 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 ID	ENSG0000 0135750 ($K_{2P}1.1$)	ENSG00000 082482 ($K_{2P}2.1$)	ENSG0000 0171301 ($K_{2P}3.1$)	ENSG0000 0164626 ($K_{2P}5.1$)	ENSG0000 0152315 ($K_{2P}13.1$)	ENSG0000 0186795 ($K_{2P}18.1$)
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

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 ID	ENSG00000111262 (K_V1.1)	ENSG00000158445 (K_V2.1)	ENSG00000129159 (K_V3.1)	ENSG00000102057 (K_V4.1)
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 β_1, K_V β_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_{Ca}1.1, K_{Ca}4.1–4.2, K_{Ca}5.1	K_{Ca}2.1–2.3 (SK1–SK3)
		K_V11.1–11.3 (erg1-3, herg 1–3)	Slo (BK), Slack, Slick	K_{Ca}3.1 (SK4, IK)
		K_V12.1–12.3 (elk1-3)		
Ensembl ID	ENSG00000053918 (K_V7.1)	ENSG00000143473 (K_V10.1)	ENSG00000156113 (K_{Ca}1.1)	ENSG00000105642 (K_{Ca}2.1)
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)	—	KCNMB1-4 (K_{Ca}1.1)

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′-trifluro-methylphenyl)-5-trifluro-methyl-2(3*H*)benzimidazolone; **PIP2**, phosphatidylinositol 4,5, bisphosphate; **TEA**, tetraethylammonium; **XE991**, 10,10-*bis*(4-pyridinylmethyl)-9(10*H*)-anthracene

Further Reading

Aguilar-Bryan L, Clement JP, Gonzalez G, Kunjilwar K, Babenko A, Bryan J (1998). Toward understanding the assembly and structure of K_{ATP} channels. *Physiol Rev* **78**: 227–245.

Ashcroft FM, Gribble FM (1998). Correlating structure and function in ATP-sensitive K^+ channels. *Trends Neurosci* **21**: 288–294.

Bauer CK, Schwartz JR (2001). Physiology of EAG channels. *J Membr Biol* **182**: 1–15.

Bean BP (2007). The action potential in mammalian central neurons. *Nat Rev Neurosci* **8**: 451–465.

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

Dalby-Brown W, Hansen HH, Korsgaard MP, Mirza N, Olesen SP (2006). K(v) channels: function, pharmacology and channel modulators. *Curr Top Med Chem* **6**: 999–1023.

Goldstein SAN, Bayliss DA, Kim D, Lesage F, Plant LD, Rajan S (2005). International union of pharmacology. LV. Nomenclature and molecular relationships of Two-P potassium channels. *Pharmacol Rev* **57**: 527–540.

Goldstein SAN, Bockenhauer D, O'Kelly I, Zilberberg N (2001). Potassium leak channels and the KCNK family of two-P domain subunits. *Nat Rev Neurosci* **2**: 175–184.

Gutman GA, Chandy KG, Grissmer S, Lazdunski M, McKinnon D, Pardo LA *et al.* (2005). International union of pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. *Pharmacol Rev* **57**: 473–508.

Hansen JB (2006). Towards selective Kir6.2/SUR1 potassium channel openers, medicinal chemistry and therapeutic perspectives. *Curr Med Chem* **13**: 26–376.

Honore E (2007). The neuronal background K2P channels: focus on TREK1. *Nature Rev Neurosci* **8**: 251–261.

Jenkinson DH (2006). Potassium channels—multiplicity and challenges. *Br J Pharmacol* **147** (Suppl 1): S63–S71.

Judge SI, Bever Jr CT (2006). Potassium channel blockers in multiple sclerosis: neuronal Kv channels and effects of symptomatic treatment. *Pharmacol Ther* **111**: 224–259.

Kaczorowski GJ, Garcia ML (1999). Pharmacology of voltage-gated and calcium-activated potassium channels. *Curr Opin Chem Biol* **3**: 448–458.

Kobayashi T, Ikeda K (2006). G protein-activated inwardly-rectifying potassium channels as potential therapeutic targets. *Curr Pharm Des* **12**: 4513–4523.
Kubo Y, Adelman JP, Clapham DE, Jan LY, Karschin A, Kurachi Y *et al*. (2005). International union of pharmacology. LIV. Nomenclature and molecular relationships of inwardly rectifying potassium channels. *Pharmacol Rev* **57**: 509–526.
Lawson K, McKay NG (2006). Modulation of potassium channels as a therapeutic approach. *Curr Pharm Des* **12**: 459–470.
Lesage F (2003). Pharmacology of neuronal background potassium channels. *Neuropharmacology* **44**: 1–7.
Lewis RJ, Garcia ML (2003). Therapeutic potential of venom peptides. *Nat Rev Drug Discov* **2**: 790–802.
Mannhold R (2006). Structure-activity relationships of K(AATP) channel openers. *Curr Top Med Chem* **6**: 1031–1047.
Mathie A, Veale EL (2007). Therapeutic potential of neuronal two pore domain potassium channel modulators. *Curr Opin Invest Drugs* **8**: 555–562.
Miller C (2003). A charged view of voltage-gated ion channels. *Nat Struct Biol* **10**: 422–424.
Nichols CG, Lopatin AN (1997). Inwardly rectifying potassium channels. *Annu Rev Physiol* **59**: 171–191.
O'Connell AD, Morton MJ, Hunter M (2002). Two-pore domain K^+ channels—molecular sensors. *Biochem Biophys Acta—Biomembrane* **1566**: 152–161.
Reimann F, Ashcroft FM (1999). Inwardly rectifying potassium channels. *Curr Opin Cell Biol* **11**: 503–508.
Robbins J (2001). KCNQ potassium channels: physiology, pathophysiology and pharmacology. *Pharmacol Ther* **90**: 1–19.
Salkoff L, Butler A, Ferreira G, Santi C, Wei A (2006). High-conductance potassium channels of the SLO family. *Nature Rev Neurosci* **7**: 921–931.
Sanguinetti MC (2000). Maximal function of minimal K^+ channel subunits. *Trends Pharmacol Sci* **21**: 199–201.
Seino S, Miki T (2003). Physiological and pathophysiological roles of ATP-sensitive K^+ channels. *Prog Biophys Mol Biol* **81**: 133–176.
Stanfield PR, Nakajima S, Nakajima Y (2002). Constitutively active and G-protein coupled inward rectifier K^+ channels: Kir2.0 and Kir3.0. *Rev Physiol Biochem Pharmacol* **145**: 47–179.
Stocker M (2004). Ca^{2+}-activated K^+ channels: molecular determinants and function of the SK family. *Nat Rev Neurosci* **5**: 758–770.
Trimmer JS, Rhodes KJ (2004). Localisation of voltage-gated ion channels in mammalian brain. *Annu Rev Physiol* **66**: 477–519.
Wang H, Tang Y, Wang L, Long CL, Zhang YL (2007). ATP-sensitive potassium channel openers and 2,3-dimethyl-2-butylamine derivatives. *Curr Med Chem* **14**: 133–155.
Wei AD, Gutman GA, Aldrich R, Chandy KG, Grissmer S, Wulff H (2005). International Union of Pharmacology. LII. Nomenclature and molecular relationships of calcium-activated channels. *Pharmacol Rev* **57**: 463–472.
Witchel HJ (2007). The hERG potassium channel as a therapeutic target. *Expert Opin Ther Targets* **11**: 321–336.
Yellen G (2002). The voltage-gated potassium channels and their relatives. *Nature* **419**: 35–42.
Yu FH, Catterall WA (2004). The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* **2004** (253): re15.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

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 and 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. A region of RyR likely to be involved in ion translocation and selection has been identified (Zhao *et al*., 1999; Gao *et al*., 2000).

Further Reading

Berridge M, Bootman MD, Roderick HL (2003). Calcium signalling: dynamics, homeostasis and remodelling. *Nat Rev Mol Cell Biol* **4**: 517–529.
Berridge MJ, Lipp P, Bootman MD (2000). The versatility and universality of calcium signalling. *Nat Rev Mol Cell Biol* **1**: 11–21.
Bolton TB (2006). Calcium events in smooth muscles and their interstitial cells: physiological roles of sparks. *J Physiol* **570**: 5–11.
Bouchard R, Pattarini E, Geiger JD (2003). Presence and functional significance of presynaptic ryanodine receptors. *Prog Neurobiol* **69**: 391–418.
Collin T, Marty A, Llano I (2005). Presynaptic calcium stores and synaptic transmission. *Curr Opin Neurobiol* **15**: 275–281.
Dulhunty AF, Beard NA, Pouliquin P, Casarotto MG (2007). Agonists and antagonists of the cardiac ryanodine receptor: potential therapeutic agents? *Pharmacol Ther* **113**: 247–263.
Eisner A, Diaz ME, O'Neill SC, Trafford AW (2004). Physiology and pathological modulation of ryanodine receptor function in cardiac muscle. *Cell Calcium* **35**: 583–589.
Fill M, Copello JA (2002). Ryanodine receptor calcium release channels. *Physiol. Rev* **82**: 893–922.
Meissner G (2004). Molecular regulation of cardiac ryanodine receptor ion channel. *Cell Calcium* **35**: 621–628.
Nahorski SR (2006). Pharmacology of intracellular signalling pathways. *Br J Pharmacol* **147** (Suppl 1): S38–S45.
Ross D, Sorrentino V (2002). Molecular genetics of ryanodine receptors Ca^{2+} release channels. *Cell Calcium* **32**: 307–319.
Shoshan-Barmatz V, Ashley RH (1998). The structure, function and cellular regulation of ryanodine-sensitive Ca^{2+}-release channels. *Int Rev Cytol* **183**: 185–270.
Sitsapesan R, Williams AJ (1998). *The Structure and Function of Ryanodine Receptors*. London: Imperial College Press.
Sutko JL, Airey JA (1996). Ryanodine Ca^{2+} release channels: does diversity in form equal diversity in function? *Physiol Rev* **76**: 1027–1071.
Sutko JL, Airey JA, Welch W, Ruest L (1997). The pharmacology of ryanodine and related compounds. *Pharmacol Rev* **49**: 53–98.
Taur Y, Frishman WH (2005). The cardiac ryanodine receptor (RyR2) and its role in heart disease. *Cardiol Rev* **13**: 142–146.
Verkhratsky A (2005). Physiology and pathophysiology of the calcium store in the endoplasmic reticulum of neurons. *Physiol Rev* **85**: 201–279.
Zucchi R, Ronca-Testoni S (1997). The sarcoplasmic reticulum Ca^{2+} channel/ryanodine receptor: modulation by endogenous effectors, drugs and disease states. *Pharmacol Rev* **49**: 1–51.

References

Gao L *et al*. (2000). *Biophys J* **79**: 828–840.
Yamaguchi N *et al*. (2003). *J Biol Chem* **278**: 23480–23486.
Zhao MC *et al*. (1999). *J Biol Chem* **274**: 25971–25974.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

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 αsubunit, which may be associated with either one or two βsubunits (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 β4 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*., 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).

Further Reading

Baker MD, Wood JN (2001). Involvement of Na^+ channels in pain pathways. *Trends Pharmacol Sci* **22**: 27–31.
Bean BP (2007). The action potential in mammalian central neurons. *Nat Rev Neurosci* **8**: 451–465.
Cantrell AR, Catterall WA (2001). Neuromodulation of Na^+ channels: an unexpected form of cellular plasticity. *Nat Rev Neurosci* **2**: 397–407.
Catterall WA (1995). Structure and function of voltage-gated ion channels. *Annu Rev Biochem* **64**: 493–531.
Catterall WA (2000). From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron* **26**: 13–25.
Catterall WA, Goldin AL, Waxman SG (2005). International Union of Pharmacology. XLVII. Nomenclature and structure function relationships of voltage-gated sodium channels. *Pharmacol Rev* **57**: 397–409.
Fozzard HA, Hanck DA (1996). Structure and function of voltage-dependent sodium channels – comparison of brain-II and cardiac isoforms. *Physiol Rev* **76**: 887–926.
Fozzard HA, Lee PJ, Lipkind GM (2005). Mechanism of local anesthetic drug action on voltage-gated sodium channels. *Curr Pharm Des* **11**: 2671–2686.
George AL (2005). Inherited disorders of voltage-gated sodium channels. *J Clin Invest* **115**: 1990–1999.
Goldin AL (2001). Resurgence of sodium channel research. *Annu Rev Physiol* **63**: 874–894.
Isom LL (2001). Sodium channel beta subunits: anything but auxiliary. *Neuroscientist* **7**: 42–54.
Kyle DJ, Ilyin VI (2007). Sodium channel blockers. *J Med Chem* **50**: 2583–2588.
Lai J, Porreca F, Hunter JC, Gold MS (2004). Voltage-gated sodium channels and hyperalgesia. *Ann Rev Pharmacol Toxicol* **44**: 371–397.
Lewis RJ, Garcia ML (2003). Therapeutic potential of venom peptides. *Nat Rev Drug Discov* **2**: 790–802.
Priest BT, Kaczorowski GJ (2007). Blocking sodium channels to treat neuropathic pain. *Expert Opin Ther Targets* **11**: 291–306.
Priestley T (2004). Voltage-gated sodium channels and pain. *Curr Drug Targets CNS Neurol Disord* **3**: 441–456.
Terlau H, Olivera BM (2004). Conus venoms: a rich source of novel ion channel-targeted peptides. *Physiol Rev* **84**: 41–68.
Trimmer JS, Rhodes KJ (2004). Localisation of voltage-gated ion channels in mammalian brain. *Annu Rev Physiol* **66**: 477–519.
Wood JN, Boorman J (2005). Voltage-gated sodium channel blockers; target validation and therapeutic potential. *Curr Top Med Chem* **5**: 529–537.
Yu FH, Catterall WA (2004). The VGL-chanome: a protein superfamily specialized for electrical signaling and ionic homeostasis. *Sci STKE* **2004** (253): re15.

Reference

Goldin AL *et al*. (2000). *Neuron* **28**: 365–368.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.

Transient receptor potential (TRP) cation

Overview: The TRP superfamily of cation channels (nomenclature agreed by NC-IUPHAR; Clapham *et al*., 2003), whose founder member is the *Drosophila* Trp channel, can be divided, in mammals, into six families; TRPC, TRPM, TRPV, TRPA, TRPP and TRPML based on amino acid homologies (see Clapham, 2003; Delmas *et al*., 2004; Moran *et al*., 2004, Montell, 2005, Nilius and Voets, 2005; Pedersen *et al*., 2005; Voets *et al*., 2005; Owsianik *et al*., 2006a; Minke, 2006; Ramsey *et al*., 2006; Venkatachalam and Montell, 2007). 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*., 2006b). 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. The established, or potential, involvement of TRP channels in disease is reviewed in Kiselyov *et al*. (2007a) and Nilius *et al*. (2005a, 2007).

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; Worley *et al*., 2007; 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 and Schaefer, 2003; Vazquez *et al*., 2004a; Trebak *et al*., 2007). 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), activated by NO-mediated cysteine S-nitrosylation	$G_{q/11}$-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, activated by NO-mediated cysteine S-nitrosylation, potentiated by extracellular protons
Blockers	Gd^{3+}, La^{3+}, 2-APB, SKF96365, Ca^{2+}-calmodulin inhibits	Gd^{3+}, La^{3+}, Ni^{2+}, 2-APB, SKF96365, KB-R7943, BTP2	La^{3+} (at mM concentrations–augments in μM range), 2-APB
Functional characteristics	γ = 16 pS (estimated by fluctuation analysis), conducts mono- and di-valent cations non-selectively; monovalent cation current suppressed by extracellular Ca^{2+}; non-rectifying, or mildly inwardly rectifying; non-inactivating; physically associates *via* Homer with IP_3 receptors, also associates with TRPC 3, 4 and 5, calmodulin, TRPP1, IP_3 receptors, caveolin-1, enkurin and plasma membrane Ca^{2+}-ATPase, STIM1, [see Rychkov and Barritt (2007) for additional interactions]	γ = 66 pS; conducts mono- and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 1.6$); monovalent cation current suppressed by extracellular Ca^{2+}; dual (inward and outward) rectification; relieved of inhibition by Ca^{2+}-calmodulin by IP_3 receptors, IP_3 receptor derived peptide (F2v) and calmidazolium; inhibited by PKG-mediated phosphorylation; associates with TRPC 1, 6 and 7; also associates with IP_3 receptors *via* Homer, ryanodine receptors, NXC1, FKBP12, syntaxin, VAMP2, caveolin-1 and calmodulin	γ = 30–41 pS, conducts mono- and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 1.1$–7.7); dual (inward and outward) rectification; physically associates *via* a PDZ binding domain on NHERF with phospholipase C isoforms; also associates with TRPC1 and 5, IP_3 receptors, calmodulin, STIM1, protein 4.1 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), lysophosphatidylcholine, activated by NO-mediated cysteine S-nitrosylation, potentiated by extracellular protons	$G_{q/11}$-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, hyperforin	$G_{q/11}$-coupled receptors. OAG (independent of PKC), thapsigargin (disputed)
Blockers	La^{3+} (at mM concentrations–augments in μM range), 2-APB, SKF96365, KB-R7943, BTP2, flufenamic acid, chloropromazine	La^{3+} ($IC_{50} \cong 6$ μM), Gd^{3+}, amiloride, SKF96365, 2-APB, ACA, KB-R7943, ML-9 (independent of MLCK), extracellular protons	La^{3+}, SKF96365, amiloride
Functional characteristics	$\gamma = 41$–63 pS; conducts mono-and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 1.8$–9.5); dual rectification (inward and outward) as a homomer, outwardly rectifying when expressed with TRPC1 or TRPC4; inhibited by xestospongin C; physically associates with STIM1 and *via* a PDZ binding domain on NHERF with phospholipase C isoforms, in neurons associates with synaptotagmin and stathmin 2	$\gamma = 28$–37 pS; conducts mono- and divalent cations with a preference for divalents ($P_{Ca}/P_{Na} = 4.5$–5.0); monovalent cation current suppressed by extracellular Ca^{2+} and Mg^{2+}, 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, FKPB12, calmodulin, Fyn and MxA	$\gamma = 25$–75 pS; 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+}, inhibited by intracellular Ca^{2+} *via* calmodulin, associates with TRPC 1, 3 and 6, FKBP12, MxA and calmodulin

The function and regulation of heterologously expressed TRPC1 has 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; Ambudkar *et al*., 2007; Worley *et al*., 2007). 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 and 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 and 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 indicate that it functions as a sensor of redox status in cells (reviewed by Eisfeld and Lückhoff, 2007). TRPM3 (reviewed by Oberwinkler and Philipp, 2007) exists as multiple splice variants four of which (mTRPM3α1, mTRPM3α2, hTRPM3a and $hTRPM3_{1325}$) have been characterised and found to differ significantly in their biophysical properties. A splice variant of TRPM4 (*i.e.*TRPM4b) and TRPM5 are molecular candidates for endogenous calcium-activated cation (CAN) channels (Nilius *et al*., 2003; Liman, 2007; Vennekens and Nilius, 2007). TRPM4 has recent been show to be an important regulator of Ca^{2+} entry in to mast cells. (Vennekens *et al*., 2007). TRPM5 in taste receptor cells of the tongue appears essential for the transduction of sweet, amino acid and bitter stimuli (Liman, 2007). TRPM6 and 7 combine channel and enzymatic activities ('chanzymes') and are involved in Mg^{2+} homeostasis (Schmitz *et al*., 2003; Voets *et al*., 2004a; reviewed by Bodding, 2007; Penner and Fleig, 2007). TRPM8 is a channel activated by cooling and pharmacological agents evoking a 'cool' sensation. $TRPM8^{(-/-)}$ mice display pronounced deficits in the thermosensation of cold temperatures (Bautista *et al*., 2007; Colburn *et al*., 2007; Dhaka *et al*., 2007).

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+} *via* calmodulin, activated by heat ~35 °C	Constitutively active, current augmented by strong depolarization, 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, ACA, activation by ADPR blocked by AMP (IC_{50} = 70 μM)	La^{3+}, Gd^{3+}, 2-APB, intracellar Mg^{2+}, extracellular Na^+ (TRPM3α2 only)
Functional characteristics	Permeable to Ca^{2+} and Ba^{2+}; down regulated by a short splice variant of TRPM1, interacts with the short transcript	γ = 52–60 pS at negative potentials, 76 pS at positive potentials; conducts mono- and di-valent cations non-selectively (P_{Ca}/P_{Na} = 0.6–0.7); non-rectifying; inactivation at negative potentials, activated by oxidative stress probably *via* PARP-1, PARP inhibitors reduce activation by oxidative stress, activation inhibited by suppression of APDR formation by glycohydrolase inhibitors	$TRPM3_{1235}$ γ = 83 pS (Na^+ current), 65 pS (Ca^{2+} current); conducts mono- and di-valent cations non-selectively (P_{Ca}/P_{Na} = 1.6); TRPM3α1; selective for monovalent cations (P_{Ca}/P_{Cs} ~ 0.1); TRPM3α2 conducts mono- and di-valent cations non-selectively (P_{Ca}/P_{Cs} = 1–10); outwardly rectifying (magnitude varies between spice variants).

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} 0.3–20 μM), activated by membrane depolarization ($V_{1/2}$ = −20 – + 60 mV dependent upon conditions) in the presence of elevated $[Ca^{2+}]_I$, heat (Q_{10} = 8.5 @ + 25 mV between 15–25 °C), positively modulated by $PtdIns(4,5)P_2$, enhanced by BTP2	$G_{q/11}$-coupled receptors, $Ins(1,4,5)P_3$, transiently activated by intracellular Ca^{2+} (EC_{50} 700–840 nM), activated by membrane depolarization ($V_{1/2}$ = 0 – + 120 mV dependent upon conditions), heat (Q_{10} = 10.3 @ −75 mV between 15 and 25 °C), stimulated by $PtdIns(4,5)P_2$	Constitutively active, activated by reduction of intracellular Mg^{2+}, potentiated by extracellular protons, 2APB
Blockers	Intracellular nucleotides (ATP^{4-}, ADP, AMP, AMP-PNP-IC_{50} range 1.3–19 μM) and adenosine (IC_{50} 630 μM); Intracellular spermine (IC_{50} = 35–61 μM) and flufenamic acid (IC_{50} = 2.8 μM), extracellular clotrimazole	Intracellular spermine (IC_{50} = 37 μM) and flufenamic acid (IC_{50} = 24 μM), 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} = 4.8–5.4 μM) and Mg^{2+} (IC_{50} = 1.1–3.4 μM)
Functional characteristics	γ = 23 pS (within the range 60 to + 60 mV); permeable to monovalent cations; impermeable to Ca^{2+}; strong outward rectification; slow activation at positive potentials, rapid deactivation at negative potentials, deactivation blocked by decavanadate; associates with calmodulin	γ = 15–25 pS; conducts monovalent cations selectively (P_{Ca}/P_{Na} = 0.05); strong outward rectification; slow activation at positive potentials, rapid inactivation at negative potentials; activated and subsequently desensitized by $[Ca^{2+}]_I$, desensitisation relieved by short chain synthetic $PtdIns(4,5)P_2$	γ = 40–87 pS; permeable to mono- and di-valent cations with a preference for divalents ($Mg^{2+} > Ca^{2+}$; P_{Ca}/P_{Na} = 6.9), conductance sequence $Zn^{2+} > Ba^{2+} > Mg^{2+} = Ca^{2+} = Mn^{2+} > Sr^{2+} > Cd^{2+} > Ni^{2+}$; 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, potentiated by extracellular protons	Depolarization ($V_{1/2} \cong +50$ mV at 15 °C), cooling (< 22–26 °C), PtdIns(4,5)P_2; WS-12, 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+}, Mg^{2+}, 2-APB	BCTC, capsazepine, 2-APB, La^{3+}, ACA, anandamide, NADA, insensitive to ruthenium red
Functional characteristics	$\gamma = 40$–105 pS at negative and positive potentials respectively; conducts mono- and di-valent cations with a preference for monovalents ($P_{Ca}/P_{Na} = 0.34$); conductance sequence $Ni^{2+} > Zn^{2+} > Ba^{2+} = Mg^{2+} > Ca^{2+} = Mn^{2+} > Sr^{2+} > Cd^{2+}$, 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, snapin, Gq-PLCβ and TK(EGF)-PLCγ; kinase domain phosphorylates annexin1; activated by membrane stretch; activated by intracellular alkalinization; sensitive to osmotic gradients	$\gamma = 40$–83 pS at positive potentials; conducts mono- and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 1.0$–3.3); pronounced outward rectification; demonstrates densensitization to chemical agonists and adaptation to a cold stimulus in the presence of Ca^{2+}; modulated by lysophospholipids and PUFAs

TRPM1 is decreased in melanoma cells with an inverse correlation with melanoma progression (Nilius *et al*., 2005a, 2007). 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 co-expressed with the latter, which is important for apoptosis and cell death. TRPM4 exists as multiple splice variants: 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). The $V_{1/2}$ for activation of TRPM4 and TRPM5 demonstrates a pronounced negative shift with increasing temperature. TRPM6 is important for Mg^{2+} homeostasis, mediating absorption and reabsorption of Mg^{2+} by the kidney intestine, respectively (Voets *et al*., 2004a) Loss-of-function mutations of TRPM6 result in hypomagnesaemia with secondary hypocalcaemia (HSH) (Nilius *et al*., 2005a, 2007). 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). TRPM7 present in synaptic vesicles influences neurotransmitter release from sympathetic neurones (Krapivinsky *et al*., 2006). Activation of TRPM8 by depolarization is strongly temperature-dependent *via* a channel-closing rate that decreases with decreasing temperature. The potential for half maximal depolarisation ($V_{1/2}$) is shifted in the hyperpolarizing direction both by decreasing temperature and by exogenous agonists, such as menthol (Voets *et al*., 2004b) whereas antagonists produce depolarizing shifts in $V_{1/2}$ (Mälkiä *et al*., 2007). The $V_{1/2}$ for the native channel is far more positive than that of heterologously expressed TRPM8 (Mälkiä *et al*., 2007). It should be noted that menthol and structurally related compounds can elicit release of Ca^{2+} from the endoplasmic reticulum independent of activation of TRPM8 (Mahieu *et al*., 2007). Intracellular pH modulates activation of TRPM8 by cold and icilin, but not menthol (Anderson *et al*., 2004). TRPM8 is up-regulated in a variety of primary tumours (*e.g*. prostate, breast, colon, lung, skin).

TRPV family: Members of the TRPV family (reviewed by Gunthorpe *et al*., 2002), on the basis of structure and function, comprise four groups: TRPV1/2, TRPV3, TRPV4 and TRPV5/6. TRPV1–4 are thermosensitive, non-selective cation channels that can additionally be activated by numerous chemicals (reviewed by Benham *et al*., 2003, Nilius *et al*., 2004; Pedersen *et al*., 2005). Members of the TRPV family function as tetrameric complexes. Numerous splice variants of TRPV1 have been described, some of which act in a dominant negative manner when co-expressed with TRPV1 (see Pringle *et al*., 2007; Szallasi *et al*., 2007). 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	
Ensembl ID	ENSG00000043316	ENSG00000154039	ENSG00000167723
Activators	Depolarization ($V_{1/2} \cong 0$ mV at 35 °C), noxious heat (> 43 °C at pH 7.4), extracellular protons ($pEC_{50} = 5.4$ at 37 °C), capsaicin, resiniferatoxin, vannilotoxins, phenylaceytlrivanil, olvanil, anandamide, camphor, allicin, some eicosanoids (*e.g.*12-(S)-HPETE, 15-(S)-HPETE, 5-(S)-HETE, leukotriene B_4), NADA, 2-APB, DPBA, activated by NO-mediated cysteine S-nitrosylation	Noxious heat (> 53 °C), probenecid, 2-APB, DPBA	Depolarization ($V_{1/2} \sim \approx +80$ mV, reduced to more negative values following heat stimuli), heat (23–39 °C, temperature threshold influenced by 'thermal history' of the cell), 6-tert-butyl-*m*-cresol, carvacrol, eugenol, thymol, camphor, menthol, 2-APB, DPBA, activated by NO-mediated cysteine S-nitrosylation
Blockers (IC_{50})	Ruthenium red (0.09–0.22 μM), 5′-iodoresiniferatoxin (3.9 nM), 6-iodo-nordihydrocapsaicin (10 nM), BCTC 6–35 nM), capsazepine (40–280 nM)., A-425619 (5 nM), A-778317 (5 nM), AMG517 (0.9 nM), AMG 628 (3.7 nM), JNJ17203212 (65 nM), JYL1421 (9.2 nM), SB366791 (18 nM), SB452533, SB-705498 (3–6 nM)	Ruthenium red (0.6 μM), SKF96365, TRIM, La^{3+}	Ruthenium red (< 1 μM), DPTHF (6–10 μM)
Probes (K_D)	[^{3}H]-A778317 (3.4 nM), [^{3}H]-resiniferatoxin, [^{125}I]-resiniferatoxin	-	-
Functional characteristics	$\gamma = 35$ pS at–60 mV; 77 pS at +60 mV, conducts mono- and di-valent cations with a selectivity for divalents ($P_{Ca}/P_{Na} = 9.6$); conducts the charged local anaesthetic QX-314; 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 (disputed) and Ca^{2+}/calmodulin; cooling reduces vanilloid-evoked currents; may be tonically active at body temperature; associates with TRPV3, calmodulin, PLCγTrkA, PP2B, calcineurin/cyclosporin, synaptotagmin and synapsin	Conducts mono- and di-valent cations ($P_{Ca}/P_{Na} = 0.9$–2.9); dual (inward and outward) rectification; current increases upon repetitive activation by heat; translocates to cell surface in response to IGF-1 to induce a constitutively active conductance, translocates to the cell surface in response to membrane stretch; associates with PKA, AKAP (ACBD3), RGA (recombinase gene activator) and dystrophin-glycoprotein complex	$\gamma = 197$ pS at = +40 to +80 mV, 48 pS at negative potentials; conducts mono- and di-valent cations; outward rectification; potentiated by arachidonic acid

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; sensitized by PKC, activated by NO-mediated cysteine S-nitrosylation	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 μM), Cd^{2+}, Mg^{2+}, La^{3+}
Functional characteristics	γ = ~60 pS at –60 mV, ~90–100 pS at +60 mV; conducts mono- and di-valent cations with a preference for divalents (P_{Ca}/P_{Na} = 6–10); dual (inward and outward) rectification; potentiated by intracellular Ca^{2+} *via* Ca^{2+}/calmodulin; inhibited by elevated intracellular Ca^{2+} *via* an unknown mechanism (IC_{50} = 0.4 μM); potentiated by Src family tyrosine kinase; associates with MAP7 and calmodulin, functionally associates with RyR2	γ = 65–78 pS for monovalent ions at negative potentials, conducts mono- and di-valents with high selectivity for divalents (P_{Ca}/P_{Na} > 107); voltage- and time- dependent inward rectification; inhibited by intracellular Ca^{2+} promoting fast inactivation and slow downregulation; feedback inhibition by Ca^{2+} reduced by calcium binding protein 80-K-H; inhibited by extracellular acidosis; upregulated by 1,25-dihydrovitamin D3; associates with TRPV6, S100A10–annexin II, calmodulin, calbindin D_{28} and Rab11; activated by klotho *via* deglycosylation	γ = 58–79 pS for monovalent ions at negative potentials, conducts mono- and di-valents with high selectivity for divalents (P_{Ca}/P_{Na} > 130); voltage- and time-dependent inward rectification; inhibited by intracellular Ca^{2+} promoting fast and slow inactivation; gated by voltage-dependent channel blockade by intracellular Mg^{2+}; slow inactivation due to Ca^{2+}-dependent calmodulin binding; phosphorylation by PKC inhibits Ca^{2+}-calmodulin binding and slow inactivation; upregulated by 1,25-dihydroxyvitamin D3; associates with TRPV5

Activation of TRPV1 by depolarisation is strongly temperature-dependent *via* a channel opening rate that increases with increasing temperature. The potential for half maximal depolarisation ($V_{1/2}$) is shifted in the hyperpolarizing direction both by increasing temperature and by exogenous agonists (Voets *et al*., 2004b). 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 Starowicz *et al*., 2007). Adenosine has been proposed to be an endogenous antagonist of TRPV1 (Puntambekar *et al*., 2004). TRPV2 likely plays a role in skeletal muscle and cardiac muscle degeneration and the pain pathway (Nilius *et al*., 2005b, 2007). The rodent, but not human, orthologues of TRPV2 are reported to be activated by heat, or 2-APB. TRPV3 can co-assemble with TRPV1 to form a functional hetero-oligomer (Smith *et al*., 2002). The sensitivity of TRPV4 to heat, but not 4α-PDD, is lost upon patch excision. TRPV4 is activated by anandamide and arachidonic acid following P450 epoxygenase-dependent metabolism to 5′,6′-epoxyeicosatrienoic acid (reviewed by Nilius *et al*., 2004). Activation of TRPV4 by cell swelling, but not heat, or phorbol esters, is mediated *via* the formation of 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 hyperpolarized potentials when Ca^{2+} is present extracellularly. Single channel events cannot be resolved (probably due to greatly reduced conductance) in the presence of extracellular divalent cations. Measurements of P_{Ca}/P_{Na} for TRPV5 and TRPV6 are dependent upon ionic conditions due to anomalous mole fraction behaviour. Blockade of TRPV5 and TRPV6 by extracellular Mg^{2+} is voltage-dependent. Intracellular Mg^{2+} also exerts a voltage dependent block that is alleviated by hyperpolarization and contributes to the time-dependent activation and deactivation of TRPV6 mediated monovalent cation currents. TRPV5 and TRPV6 differ in their kinetics of Ca^{2+}-dependent inactivation and recovery from inactivation. TRPV5 and TRPV6 function as homo- and hetero-tetramers. TRPV6 is up-regulated in prostate cancer. TRPV5 and TRPV6 are essential for the re-absorption and absorption of Ca^{2+} in the kidney and intestine, respectively.

TRPA family: The TRPA family currently comprises one mammalian member, TRPA1 (reviewed by Garcia-Anoveros and Nagata, 2007), which in some (Story *et al*., 2003; Bandell *et al*., 2004; Sawada *et al*., 2007), but not other (Jordt *et al*., 2004; Nagata *et al*., 2005), studies is activated by noxious cold. A recent study suggests that activation of TRPA1 is secondary to a cold-induced elevation of $[Ca^{2+}]_i$ (Zurborg *et al*., 2007). Additionally, TRPA1 has been proposed to be a component of a mechanosensitive transduction channel of vertebrate hair cells (Corey *et al*., 2004; Nagata *et al*., 2005), but $TRPA1^{(-/-)}$ mice demonstrate no impairment in hearing, or vestibular function (Bautista *et al*. 2006; Kwan *et al*., 2006). TRPA1 acts as a nociceptor ion channel (Nagata *et al*., 2005; 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 °C) (disputed), (-)-menthol (1–100 μM), thymol (1–100 μM), isothiocyanates, THC, cinnamaldehyde, allicin, carvacrol, formalin, 4-hydroxy-2-nonenal, methyl-p-hydroxybenzoate, URB597, 15-deoxy-Δ(12,14)-prostaglandin J2, (insensitive to capsaicin)
Blockers	Ruthenium red (IC_{50} <1–3 μM), menthol (1 mM), Gd^{3+}, gentamicin, HC-030031
Functional characteristics	γ = 87–100 pS; conducts mono- and di-valent cations non-selectively ($P_{Ca}/P_{Na} = 0.84$); outward rectification; inactivates in response to prolonged cooling; sensitises in response to repeated applications of cinnamaldehyde; activated by OAG and arachidonic acid downstream of receptor-mediated PLC stimulation; sensitized by PAR2 activation probably due to relief of inhibition by $PtdIns(4,5)P_2$; activated by elevated intracellular Ca^{2+}.

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; Macpherson *et al*., 2007). Activation of TRPA1 by pungent chemicals has been claimed to require intracellular polyphosphates (Kim and Cavanaugh, 2007).

TRPML family: The TRPML family (see Qian and Noben-Trauth, 2005; Cantiello *et al*., 2005; Zeevi *et al*., 2007) consists of three mammalian members (TRPML1-3). TRPML channels are probably restricted to intracellular vesicles and mutations in the gene (*MCOLN1*) encoding TRPML1 (mucolipin-1) are the cause of 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), Gd^{3+}, La^{3+}, Ni^{2+}
Functional characteristics	γ = 46 pS (main state in the presence of a K^+ gradient), multiple conductance states may correspond to complexes with variable channel numbers; conducts mono- and di-valent cations; channel opening decreased at negative potentials; channel opening blocked by 'intravesicular' acidification; loop between TM1 and TM2 is a lipase

Data in the table are for *in vitro* transcribed/translated TRPML1 incorporated into liposomes 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*., 2005; Qian and Noben-Trauth, 2005).

TRPP family: The TRPP family (reviewed by Delmas *et al*., 2004a, Delmas, 2005; Giamarchi *et al*., 2006; Witzgall, 2007) 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), PDKREJ, PKD1L1, PKD1L2 and PKD1L3. The PKD2-like members comprise PKD2, PKD2L1 and PKD2L2, which have 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 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, enhanced by intracellular Ca^{2+}
Blockers (IC_{50})	La^{3+}, Gd^{3+}, amiloride	Phenamil (0.14 μM), benzamil (1.1 μM), EIPA (10.5 μM), amiloride (143 μM), La^{3+}, Gd^{3+}, flufenamate
Functional characteristics	γ = 123–177 pS (with K^+ as charge carrier); $P_{Na}/P_K = 0.14–1.1$; conducts both mono- and di-valent cations; probably associates with TRPV4; also associates with cortactin and cadherin *via* TRPP1; 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	γ = 137 pS (outward conductance) 399 pS (inward conductance), conducts mono- and di-valent cations with a preference for divalents ($P_{Ca}/P_{Na} = 4.3$); slight inward rectification; activated and subsequently inactivated by intracellular Ca^{2+}; inhibited by extracellular acidosis; possibly interacts with TRPA1

Data in the table are extracted from Delmas *et al*. (2004a) and Dai *et al*. (2007). 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. Ca^{2+}, Ba^{2+} and Sr^{2+} permeate TRPP3, but reduce inward currents carried by Na^{+}. Mg^{2+} is largely impermeant and exerts a voltage dependent inhibition that increases with hyperpolarization. TRPP3 plays a role in retinal development.

Abbreviations: **2-APB**, 2-amino ethoxyphenylborate; 4α-PDD, 4α-phorbol 12, 13-didecanoate; **5-(*S*)-HETE**, 5-(*S*)-hydroxyeicosatetraenoic acid; **12-(*S*)-HPETE and 15-(*S*)-HPETE**, 12- and 15-(*S*)-hydroperoxyeicosatetraenoic acids; **20-HETE**, 20-hydroxyeicosatetraenoic acid; **A-425619**, 1-isoquinolin-5-yl-3-(4-trifluoromethyl-benzyl)urea; **A-778317**, 1-((*R*)-5-*tert*-butyl-indan-1-yl)-3-isoquinolin-5-yl-urea; **ACA**, *N*-(p-amylcinnamoyl)anthranilic acid; **AMG 517**, *N*-{4-[6-(4-trifluoromethyl-phenyl)-pyrimidin-4-yloxy]-benzothiazol-2-yl}-acetamide; **AMG628**, (R)-N-(4-(6-(4-(1-(4-fluorophenyl)ethyl)piperazin-1-yl)pyrimidin-4-yloxy)benzo[d]thiazol-2-yl)acetamide; **BCTC**, *N*-(4-tertiarybutylphenyl)-4-(3-chloropyridin-2-yl)tetrahydropyrazine-1(2*H*)-carbox-amide; **BTP2**, 4-methy-4′-[3,5-bis(trifluoromethyl)-1*H*-pyrazol-1-yl]-1,2,3-thiadiazole-5-carboxanilide; **DPBA**, diphenylboronic anhydride; **DPTHF**, diphenyltetrahydrofuran; **GEA3162**, 1,2,3,4-oxatriazolium-5-amino-3-(3,4-dichlorophenyl)-chloride; **JYL1421**, *N*-(4-*tert*-butylbenzyl)-*N*′-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea; **JNJ17203212**, 4-(3-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide; **KB-R7943**, 2-[2-[4-(4-nitrobenzyloxy)phenyl]ethyl]isothiourea methanesulfonate; **OAG**, 1-oleoyl-2-acetyl-*sn*-glycerol; **ML-9**, 1-(5-chloronaphtalene-1-sulphonyl)homopiperazine; **NADA**, *N*-arachidonyl dopamine; **PMA**, phorbol 12 myristate 13-acetate; **RHC80267**, 1,6-di[O-(carbamoyl)cyclohexanone oxime]hexane; **SB366791**, *N*-(3-methoxyphenyl)-4-chlorocinnamide; **SB705498**, *N*-(2-bromophenyl)-N′-[((*R*)-1-(5-trifluoromethyl-2-pyridyl)pyrrolidin-3-yl)]urea; **SDZ249665**, 1-[4-(2-amino-ethoxy)-3-methoxy-benzyl]-3-(4-*tert*-butyl-benzyl)-urea; **SKF96265**, 1-(β-(3-(4-methoxyphenyl)propoxy)-4-methoxyphenethyl)-1H-imidazole hydrochloride; **THC**, Δ^9-tetrahydrocannabinol; **TRIM**, 1-(2-(trifluoromethyl)phenyl) imidazole; **URB597**, 3′-carbamoylbiphenyl-3-yl cyclohexylcarbamate; **WS-12**, 2-isopropyl-5-methyl-cyclohexanecarboxylic acid (4-methoxy-phenyl)-amide

Further reading

Aarts MM, Tymianski M (2005). TRPM7 and ischemic brain injury. *Neuroscientist* **11**: 116–123.

Ambudkar IS, Ong HL, Liu X, Bandyopadhyay B, Cheng KT (2007). TRPC1: the link between functionally distinct store-operated calcium channels. *Cell Calcium* **42**: 213–223.

Beech DJ (2005). TRPC1: store-operated channel and more. *Pflügers Arch* **451**: 53–60.

Beech DJ, Muraki K, Flemming R (2004). Non-selective cationic channels of smooth muscle and the mammalian homologues of *Drosophila TRP*. *J Physiol* **559**: 685–706.

Benham CD, Gunthorpe MJ, Davis JB (2003). TRPV channels as temperature sensors. *Cell Calcium* **33**: 479–487.

Bodding M (2007). TRPM6: A Janus-like protein. *Handb Exp Pharmacol* **179**: 299–311.

Cantiello HF, Montalbetti N, Goldman WH, Raychowdhury MK, González-Perrett S, Timpanaro GA *et al.* (2005). Cation channel activity of mucolipin-1: the effect of calcium. *Pflügers Arch* **451**: 304–312.

Caterina MJ, Julius D (2001). The vanilloid receptor: a molecular gateway to the pain pathway. *Annu Rev Neurosci* **24**: 487–517.

Clapham DE (2003). TRP channels as cellular sensors. *Nature* **426**: 517–524.

Clapham DE, Montell C, Schultz G, Julius D (2003). International Union of Pharmacology. XLIII. Compendium of Voltage-gated ion channels. Transient receptor potential channels. *Pharmacol Rev* **55**: 591–596.

Delmas P (2005). Polycystins: polymodal receptor/ion-channel cellular sensors. *Pflügers Arch* **451**: 264–276.

Delmas P, Padilla F, Osorio N, Coste B, Raoux M, Crest M (2004a). Polycystins, calcium signaling, and human diseases. *Biochem Biophys Res Commun* **322**: 1374–1383.

Den Dekker E, Hoenderop JG, Nilius B, Bindels RJ (2003). The epithelial calcium channels, TRPV5 & TRPV6: from identification towards regulation. *Cell Calcium* **33**: 497–507.

Dhaka A, Viswanath V, Patapoutian A (2006). Trp ion channels and temperature sensation. *Annu Rev Neurosci* **29**: 135–161.

Eisfeld A, Lückhoff J (2007). TRPM2. *Handb Exp Pharmacol* **179**: 237–252.

Fleig A, Penner R (2004). The TRPM ion channel subfamily: molecular, biophysical and functional features. *Trends Pharmacol Sci* **25**: 633–639.

Freichel M, Vennekens R, Olausson J, Stolz S, Philipp SE, Weißgerber P *et al.* (2005). Functional role of TRPC proteins in native systems: implications from knockout and knock-down studies. *J Physiol* **567**: 59–66.

Garcia-Anoveros J, Nagata K (2007). TRPA1. *Handb Exp Pharmacol* **179**: 347–362.

Giamarchi A, Padilla F, Coste B, Raoux M, Crest M, Honore E *et al.* (2006). The versatile nature of the calcium-permeable cation channel TRPP2. *EMBO Rep* **7**: 787–793.

Gunthorpe MJ, Benham CD, Randall A, Davis JD (2002). The diversity in the vanilloid (TRPV) receptor family of ion channels. *Trends Pharmacol Sci* **23**: 183–191.

Harteneck C (2005). Function and Pharmacology of TRPM cations channels. *Naunyn-Schmiedeberg's Arch Pharmacol* **371**: 307–314.

Jordt SE, McKemy DD, Julius D (2003). Lessons from peppers and peppermint: the molecular logic of thermosensation. *Curr Opin Neurobiol* **13**: 487–492.

Kiselyov K, Shin DM, Kim JY, Yuan JP, Muallem S (2007b). TRPC channels: interacting proteins. *Handb Exp Pharmacol* **179**: 559–574.

Kiselyov K, Soyombo A, Muallem S (2007a). TRPpathies. *J Physiol* **578**: 641–653.

Liman ER (2007). TRPM5 and taste transduction. *Handb Exp Pharmacol* **179**: 287–298.

Macpherson LJ, Hwang SW, Miyamoto T, Dubin AE, Patapoutian A, Story GM (2006). More than cool: promiscuous relationships of menthol and other sensory compounds. *Mol Cell Neurosci* **32**: 335–343.

McKemy DD (2005). How cold is it? TRPA 8 and TRPA1 in the molecular logic of cold sensation. *Mol Pain* **1**: 16.

Minke B (2006). TRP channels and Ca^{2+} signaling. *Cell Calcium* **40**: 261–275.

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

Montell C (2005). The TRP superfamily of cation channels. *Science STKE* **272**: re3.

Moran MM, Xu H, Clapham DE (2004). TRP ion channels in the nervous system. *Curr Opin Neurobiol* **14**: 362–369.

Nijenhuis T, Hoenderop JG, Nilius B, Bindels RJ (2003). (Patho)physiological implications of the novel epithelial Ca^{2+} channels TRPV5 and TRPV6. *Pflügers Arch* **446**: 401–409.

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

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

Nilius B, Droogmans G, Wondergem R (2003). Transient receptor potential channels in endothelium: solving the calcium entry puzzle? *Endothelium* **10**: 5–15.

Nilius B, Vriens J, Prenen J, Droogmans G, Voets T (2004). TRPV4 calcium channel: a paradigm for gating diversity. *Am J Physiol* **286**: C195–C205.

Nilius B, Owsianik G, Voets T, Peters JA (2007). Transient receptor potential (TRP) cation channels in disease. *Physiol Rev* **87**: 165–217.

Nilius B, Talavera K, Owsianik G, Prenen J, Droogmans G, Voets T (2005b). Gating of TRP channels: a voltage connection? *J Physiol* **567**: 35–44.
Nilius B, Voets T (2005). A TR(I)P through a world of multifunctional cation channels. *Pflügers Arch* **451**: 1–10.
Nilius B, Voets T, Peters J (2005a). TRP Channels in disease. *Sci STKE* **295**: re8.
Owsianik G, D'hoedt D, Voets T, Nilius B (2006a). Structure-function relationship of the TRP channel superfamily. *Rev Physiol Biochem Pharmacol* **156**: 61–90.
Owsianik G, Talavera G, Voets, Nilius B (2006b). Permeation and selectivity of TRP channels. *Annu Rev Physiol* **68**: 685–717.
Patapoutian A, Peier AP, Story G, Viswanath V (2003). ThermoTRPs and beyond: Mechanisms of temperature sensation. *Nat Rev Neurosci* **4**: 529–539.
Pedersen SF, Owsianik G, Nilius B (2005). TRP Channels: an overview. *Cell Calcium* **38**: 233–252.
Penner R, Fleig A (2007). The Mg^{2+} and Mg^{2+}-nucleotide-regulated channel-kinase TRPM7. *Handb Exp Pharmacol* **179**: 313–328.
Plant TD, Schaefer M (2003). TRPC4 and TRPC5: receptor-operated Ca^{2+}-permeable non-selective cation channels. *Cell Calcium* **33**: 441–450.
Pringle SC, Matta JA, Ahern GP (2007). Capsaicin receptor: TRPV1 a promiscuous TRP channel. *Handb Exp Pharmacol* **179**: 153–169.
Putney J (Ed.) (2004). *Mammalian TRP Channels as Molecular Targets—Novartis Foundation Symposium No. 258* pp1 286 Wiley: Europe.
Putney JW (2005). Physiological mechanisms of TRPC activation. *Pflügers Arch* **451**: 29–34.
Qian F, Noben-Trauth K (2005). Cellular and molecular function of mucolipins (TRPML) and polycystin 2 (TRPP2). *Pflügers Arch* **451**: 277–285.
Ramsey IS, Delling M, Clapham DE (2006). An introduction to TRP channels. *Annu Rev Physiol* **68**: 619–647.
Rychkov G, Barritt GJ (2007). TRPC1 Ca^{2+}-permeable channels in animal cells. *Handb Exp Pharmacol* **179**: 23–52.
Starowicz K, Nigam S, Di Marzo V (2007). Biochemistry and pharmacology of endovanilloids. *Pharmacol Ther* **114**: 13–33.
Szallasi A, Cortright DN, Blum CA, Eid SR (2007). The vanilloid receptor TRPV1: 10 years from channel cloning to antagonist proof-of-concept. *Nat Rev Drug Discov* **6**: 357–372.
Trebak M, Lemonnier L, Smyth JT, Vazquez G, Putney Jr JW (2007). Phospholipase C-coupled receptors and activation of TRPC channels. *Handb Exp Pharmacol* **179**: 593–614.
Vazquez G, Wedel BJ, Aziz O, Trebak M, Putney JW (2004). The mammalian TRPC cation channels. *Biochim Biophys Acta* **1742**: 21–36.
Venkatachalam K, Montell C (2007). TRP channels. *Annu Rev Biochem* **76**: 387–417.
Vennekens R, Droogmans G, Nilius B (2001). Function properties of the epithelial Ca^{2+} channel, ECaC. *Gen Physiol Biophys* **20**: 239–253.
Vennekens R, Nilius B (2007). Insights into TRPM4 function, regulation and physiological role. *Handb Exp Pharmacol* **179**: 269–285.
Voets T, Nilius B (2003). TRPs make sense. *J Membrane Biol* **192**: 1–8.
Voets T, Nilius B (2007). Modulation of TRPs by PIPs. *J Physiol* **582**: 939–944.
Voets T, Owsainik G, Nilius B (2007). TRPM8. *Handb Exp Pharmacol* **179**: 329–344.
Voets T, Talavera K, Owsianik G, Nilius B (2005). Sensing with TRP channels. *Nature Chem Biol* **2**: 85–92.
Witzgall R (2007). TRPP2 channel regulation. *Handb Exp Pharmacol* **179**: 363–375.
Worley PF, Zeng W, Huang GN, Yuan JP, Kim JY, Lee MG *et al.* (2007). TRPC channels as STIM1-regulated store-operated channels. *Cell Calcium* **42**: 205–211.
Zeevi DA, Frumkin A, Bach G (2007). TRPML and lysosomal function. *Biochim Biophys Acta* **1772**: 851–858.
Zitt C, Halaszovich CR, Luckhoff A (2002). The TRP family of cation channels: probing and advancing the concepts on receptor-activated calcium entry. *Prog Neurobiol* **66**: 243–264.
Zu MX, Tang J (2004). TRPC channel interactions with calmodulin and IP_3 receptors. *Novartis Found Symp* **258**: 44–58.

References

Anderson DA *et al.* (2004). *J Neurosci* **24**: 5364–5369.
Babich V *et al.* (2004). *J Biol Chem* **279**: 25582–25589.
Bandell M *et al.* (2004). *Neuron* **41**: 849–857.
Bautista DM *et al.* (2006). *Cell* **124**: 1269–1282.
Bautista DM *et al.* (2007). *Nature* **448**: 204–208.
Colburn RW *et al.* (2007). *Neuron* **54**: 379–386.
Corey DP *et al.* (2004). *Nature* **432**: 723–730.
Dai XQ *et al.* (2007). *Mol Pharmacol* **72**: 1576–1585.
Delmas P *et al.* (2004b). *FASEB J* **18**: 740–742.
Dhaka A *et al.* (2007). *Neuron* **54**: 371–378.
Freichel M *et al.* (2001). *Nature Cell Biol* **3**: 121–127.
Hanaoka K *et al.* (2000). *Nature* **408**: 990–994.
Inoue R *et al.* (2001). *Circ Res* **88**: 325–332.
Jordt SE *et al.* (2004). *Nature* **427**: 260–265.
Kim D, Cavanaugh EJ (2007). *J Neurosci* **27**: 6500–6509.
Kim SJ *et al.* (2003). *Nature* **426**: 285–291.
Krapivinsky G *et al.* (2006). *Neuron* **52**: 485–496.
Kwan KY *et al.* (2006). *Neuron* **50**: 277–289.
Macpherson LJ *et al.* (2007). *Nature* **445**: 541–545.
Mahieu F *et al.* (2007). *J Biol Chem* **282**: 3325–3336.
Mälkiä A *et al.* (2007). *J Physiol* **581**: 155–174.
Matsushita M *et al.* (2005). *J Biol Chem* **280**: 20793–20803.
Nadler MJS *et al.* (2001). *Nature* **411**: 590–595.
Nagata K *et al.* (2005). *J Neurosci* **25**: 4052–4061.
Nilius B *et al.* (2003). *J Biol Chem* **278**: 30813–30820.
Puntambekar P *et al.* (2004). *J Neurosci* **24**: 3663–3671.
Runnels LW *et al.* (2001). *Science* **291**: 1043–1047.
Sawada Y *et al.* (2007). *Brain Res* **1160**: 39–46.
Schmitz C *et al.* (2003). *Cell* **114**: 191–200.
Smith GD *et al.* (2002). *Nature* **418**: 186–190.
Story GM *et al.* (2003). *Cell* **112**: 819–829.
Strübing C *et al.* (2001). *Neuron* **29**: 645–655.
Takezawa R *et al.* (2004). *Proc Natl Acad Sci USA* **101**: 6009–6014.
Tang J *et al.* (2001). *J Biol Chem* **276**: 21303–21310.

Tiruppathi C *et al.* (2002). *Circ Res* **91**: 70–76.
Ullrich ND *et al.* (2005). *Cell Calcium* **37**: 267–278.
Vazquez G *et al.* (2004b). *J Biol Chem* **279**: 40521–40528.
Vennekens R *et al.* (2007). *Nat Immunol* **8**: 312–320.
Ventakatchalam K *et al.* (2001). *J Biol Chem* **276**: 33980–33985.
Voets T *et al.* (2004a). *J Biol Chem* **279**: 19–25.
Voets T *et al.* (2004b). *Nature* **430**: 748–754.
Yuan JP *et al.* (2003). *Cell* **114**: 777–789.
Zurborg S *et al.* (2007). *Nat Neurosci* **10**: 277–279.

Citation Information

We recommend that any citations to information in the Guide are presented in the following format:

Alexander SPH, Mathie A, Peters JA (2008). Guide to Receptors and Channels (GRAC), 3rd edn. *Br J Pharmacol* **153** (Suppl. 2): S1–S209.