Transient receptor potential (TRP) cation channels

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.*, 2004a; Moran *et al.*, 2004; Montell, 2005; Nilius and Voets, 2005; Pedersen *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 characterized, 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. The established, or potential, involvement of TRP channels in disease is reviewed in Kiselyov *et al.* (2007a) and Nilius *et al.* (2007) together with a special edition of *Biochemica et Biophysica Acta* on the subject edited by Nilius (2007).

TRPC family: Members of the TRPC subfamily (reviewed by Freichel *et al.*, 2005; Pedersen *et al.*, 2005; Putney, 2005; Ambudkar and Ong, 2007; Abramowitz and Birnbaumer, 2009; Beech *et al.*, 2009; Birnbaumer, 2009; Kiselyov and Patterson, 2009), 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, activated by depletion of intracellular calcium stores (reviewed by Pedersen *et al.*, 2005; Ambudkar and Ong, 2007; Potier and Trebak, 2008; Salido *et al.*, 2009; Yuan *et al.*, 2009), but this is highly controversial. 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; Trebak *et al.*, 2007).

Nomenclature	TRPC1	TRPC3	TRPC4
Other names	TRP1	TRP3	TRP4, CCE1
Ensembl ID	ENSG00000144935	ENSG00000138741	ENSG00000100991
Activators	$G_{q/11}$-coupled receptors, membrane stretch, 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), activated by $PI(4,5)_2$	$G_{q/11}$-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, GsMTx-4	Gd^{3+}, La^{3+}, Ni^{2+}, 2-APB, SKF96365, KB-R7943, BTP2	La^{3+} (at mM concentrations – augments in μM range), 2-APB, SKF96365
Functional characteristics	$\gamma = 16$ pS (estimated by fluctuation analysis), conducts mono- and divalent cations non-selectively; monovalent cation current suppressed by extracellular Ca^{2+}; non-rectifying, or mildly inwardly rectifying; non-inactivating	$\gamma = 66$ pS; conducts mono- and divalent 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	$\gamma = 30$–41 pS, conducts mono- and divalent cations non-selectively ($P_{Ca}/P_{Na} = 1.1$–7.7); dual (inward and outward) rectification, inhibited by $PI(4,5)_2$

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 (independent of G protein signalling), activated by NO-mediated cysteine S-nitrosylation (disputed), potentiated by extracellular protons	$G_{q/11}$-coupled receptors, membrane stretch, 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, chlorpromazine	La^{3+} ($IC_{50} \cong 6$ μM), Gd^{3+}, amiloride,,SKF96365, 2-APB, ACA, KB-R7943, ML-9 (independent of MLCK), extracellular protons, GsMTx-4	La^{3+}, SKF96365, amiloride, 2-APB

Functional characteristics	γ= 41–63 pS; conducts mono-and divalent 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, activated, or inhibited, by $PI(4,5)_2$	γ= 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, activated, or inhibited, by $PI(4,5)_2$	γ= 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, activated, or inhibited, by $PI(4,5)_2$

A comprehensive listing of G protein-coupled receptors that activate TRPC channels is given in Abramowitz and Birnbaumer (2009). In addition to the specific agents listed in the table several members of the TRPC family are modulated by lipid factors such as arachidonic acid and its metabolites, sphingosine-1-phosphate, cholesterol and gangliosides (reviewed by Beech *et al*., 2009). Hetero-oligomeric complexes of TRPC channels and their association with proteins to form signalling complexes are detailed in Ambudkar and Ong (2007) and Kiselyov *et al*. (2007b).

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. TRPM1 may exist as five splice variants and is involved in normal melanocyte pigmentation (Oancea *et al*., 2009). TRPM2 functions as a sensor of redox status in cells (reviewed by Eisfeld and Lückhoff, 2007). TRPM3 (reviewed by Oberwinkler and Phillipp, 2007) exists as multiple splice variants four of which (mTRPM3α1, mTRPM3α2, hTRPM3a and $hTRPM3_{1325}$) have been characterized 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 channels (Nilius *et al*., 2003; Liman, 2007; Vennekens and Nilius, 2007). TRPM4 has been shown to be an important regulator of Ca^{2+} entry in to mast cells (Vennekens *et al*., 2007) and dendritic cell migration (Barbet *et al*., 2008). 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	Intracellular ADP ribose (ADPR) and cyclic ADPR (cADPR); agents producing reactive oxygen (e.g. H_2O_2) and nitrogen (e.g. GEA3162) species; intracellular Ca^{2+} via calmodulin, potentiated by arachidonic acid, activated by heat ~35°C	Small constitutive activity, activated by pregnenolone sulphate and nifedipine, 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, miconazole, econazole, flufenamic acid, ACA, 2-APB, activation by ADPR and cADPR blocked by AMP (IC_{50} = 10–70 μM) and 8-bromo-cADPR respectively	La^{3+}, Gd^{3+}, 2-APB, intracellar Mg^{2+}, extracellular Na^+ (TRPM3α2 only)
Functional characteristics	Conducts mono- and divalent cations non-selectively, outwardly rectifying	γ= 52–60 pS at negative potentials, 76 pS at positive potentials; conducts mono- and divalent 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 divalent cations non-selectively (P_{Ca}/P_{Na} = 1.6) TRPM3α1: selective for monovalent cations (P_{Ca}/P_{Cs} ~ 0.1) TRPM3α2: conducts mono- and divalent 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 ($V_{½}$ = –20–+60 mV dependent upon conditions) in the presence of elevated $[Ca^{2+}]_i$, heat (Q_{10} = 8.5 at +25 mV between 15 and 25°C), positively modulated by $PI(4,5)P_2$, 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 ($V_{½}$ = 0–+120 mV dependent upon conditions), heat (Q_{10} = 10.3 at –75 mV between 15 and 25°C), stimulated by $PI(4,5)P_2$	Constitutively active, activated by reduction of intracellular Mg^{2+}, potentiated by extracellular protons and 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 and 9-phenanthrol	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–+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	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 $[Ca^{2+}]_i$, desensitization relieved by short chain synthetic $PtdIns(4,5)P_2$	γ = 40–87 pS; permeable to mono- and divalent 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) and ATP

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 $PI(4,5)P_2$, potentiated by extracellular protons	Depolarization ($V_{½} \cong$ +50 mV at 15°C), cooling (<22–26°C), $PI(4,5)P_2$; WS-12, (-)-menthol, icilin (requires intracellular Ca^{2+} as a cofactor for full agonist activity, blocks activation by menthol); agonist activities are temperature-dependent and potentiated by cooling
Blockers	Spermine (permeant blocker), carvacrol, La^{3+}, Mg^{2+}, 2-APB	Clotrimazole, BCTC, capsazepine, 2-APB, La^{3+}, ACA, anandamide, NADA, linoleic acid, cannabinoids (e.g. cannabidiol, THC); insensitive to ruthenium red
Functional characteristics	γ = 40–105 pS at negative and positive potentials respectively; conducts mono- and divalent cations with a preference for monovalents (P_{Ca}/P_{Na} = 0.34); 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^{2+}, Zn^{2+}, Mn^{2+} and Mg.ATP (disputed); inhibited by G_i-coupled receptors activated by membrane stretch and intracellular alkalinization; sensitive to osmotic gradients, activated, or inhibited, by $PI(4,5)_2$	γ = 40–83 pS at positive potentials; conducts mono- and divalent 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

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 $V_{½}$ for activation of TRPM4 and TRPM5 demonstrates a pronounced negative shift with increasing temperature. Activation of TRPM8 by depolarization is strongly temperature-dependent via a channel-closing rate that decreases with decreasing temperature. The $V_{½}$ 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 $V_{½}$ (Mälkiä *et al.*, 2007). The $V_{½}$ 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 (Andersson *et al.*, 2004).

TRPV family: Members of the TRPV family (reviewed by Vennekens *et al.*, 2008; Vriens *et al.*, 2009), 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; Starowicz *et al.*, 2007; Szallasi

et al., 2007; Vriens *et al*., 2009). 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 Wissenbach and Niemeyer, 2007; de Groot *et al*., 2008).

Nomenclature	TRPV1	TRPV2	TRPV3
Other names	VR1, vanilloid/capsaicin receptor, OTRPC1	VRL-1, OTRPC2, GRC	–
Ensembl ID	ENSG00000043316	ENSG00000154039	ENSG00000167723
Activators	Depolarization ($V_{½} \cong 0$ mV at 35°C), noxious heat (>43°C at pH 7.4), extracellular protons ($pEC_{50} = 5.4$ at 37°C), capsaicin, resiniferatoxin, vanillotoxins, 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, rodent, not human), probenecid, 2-APB (rodent, not human), DPBA, cannabidiol, THC	Depolarization ($V_{½} \sim +80$ 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, incensole acetate, 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), AMG628 (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, amiloride, 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 divalent 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/up-regulated by PKC stimulation; extracellular acidification facilitates activation by PKC; desensitization inhibited by PKA; activated, or inhibited, by $PI(4,5)_2$, inhibited by Ca^{2+}/calmodulin; cooling reduces vanilloid-evoked currents; may be tonically active at body temperature	Conducts mono- and divalent cations ($P_{Ca}/P_{Na} = 0.9–2.9$); dual (inward and outward) rectification; current increases upon repetitive activation by heat; translocates to cell surface in response to IGF-1 to induce a constitutively active conductance, translocates to the cell surface in response to membrane stretch	$\gamma = 197$ pS at = +40–+80 mV, 48 pS at negative potentials; conducts mono- and divalent 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 divalent cations with a preference for divalents (P_{Ca}/P_{Na} = 6–10); dual (inward and outward) rectification; potentiated by intracellular Ca^{2+} via Ca^{2+}/calmodulin; inhibited by elevated intracellular Ca^{2+} via an unknown mechanism (IC_{50} = 0.4 μM); potentiated by Src family tyrosine kinase	γ = 59–78 pS for monovalent ions at negative potentials, conducts mono- and divalents with high selectivity for divalents (P_{Ca}/P_{Na} > 107); voltage- and time-dependent inward rectification; inhibited by intracellular Ca^{2+} promoting fast inactivation and slow down-regulation; feedback inhibition by Ca^{2+} reduced by calcium binding protein 80-K-H; inhibited by extracellular and intracellular acidosis; up-regulated by 1,25-dihydrovitamin D3	γ = 58–79 pS for monovalent ions at negative potentials, conducts mono- and divalents with high selectivity for divalents (P_{Ca}/P_{Na} > 130); voltage- and time-dependent inward rectification; inhibited by intracellular Ca^{2+} promoting fast and slow inactivation; gated by voltage-dependent channel blockade by intracellular Mg^{2+}; slow inactivation due to Ca^{2+}-dependent calmodulin binding; phosphorylation by PKC inhibits Ca^{2+}-calmodulin binding and slow inactivation; up-regulated by 1,25-dihydroxyvitamin D3

Activation of TRPV1 by depolarization is strongly temperature-dependent via a channel opening rate that increases with increasing temperature. The $V_{½}$ 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; Vriens *et al.*, 2009). Adenosine has been proposed to be an endogenous antagonist of TRPV1 (Puntambekar *et al.*, 2004). 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.

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; Karashima *et al.*, 2009), but not other (Jordt *et al.*, 2004; Nagata *et al.*, 2005), studies is activated by noxious cold. One study suggests that activation of TRPA1 is secondary to a cold-induced elevation of $[Ca^{2+}]_i$ (Zurborg *et al.*, 2007), but this has recently been refuted (Karashima *et al.*, 2009). 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 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, cyclopentone prostaglandins, 1,4-dihydropyridines, isoflurane, desflurane, propofol, etomidate
Blockers	Ruthenium red (IC_{50} < 1–3 μM), menthol (1 mM, mouse, not human), Gd^{3+}, gentamicin, HC-030031
Functional characteristics	γ = 87–100 pS; conducts mono- and divalent cations non-selectively (P_{Ca}/P_{Na} = 0.84); outward rectification; inactivates in response to prolonged cooling; sensitizes in response to repeated applications of cinnamaldehyde; activated by OAG and arachidonic acid downstream of receptor-mediated PLC stimulation; sensitized by PAR2 activation possibly due to relief of inhibition by $PI(4,5)P_2$; activated by elevated intracellular Ca^{2+}.

Icilin activates TRPM8 in addition to TRPA1 (Jordt *et al.*, 2004). Activation of TRPA1 by isothiocyanates and other reactive agents 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). TRPA1 is potently activated by intracellular zinc (EC_{50} = 8 nM) (Andersson *et al.*, 2009; Hu *et al.*, 2009).

TRPML family: The TRPML family (see Qian and Noben-Trauth, 2005; Zeevi *et al.*, 2007; Puertollano and Kiselyov, 2009) 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) remains to be functionally characterized in detail. TRPML3 is important for

hair cell maturation, stereocilia maturation and intracellular vesicle transport. A naturally occurring gain of function mutation in TRPML3 (i.e. A419P) results in the varitint waddler (V*a*) mouse phenotype (reviewed by Qian and Noben-Trauth, 2005; Nilius *et al*., 2007).

Nomenclature	TRPML1	TRPML2	TRPML3
Other names	MCLN1, mucolipin-1 (ML1)	MCLN2	
Ensembl ID	ENSG00000090674	ENSG00000153898	ENSG00000055732
Activators	$TRPML1^{Va}$: constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification)	$TRPML2^{Va}$: constitutively active, current potentiated by extracellular acidification (equivalent to intralysosomal acidification)	$TRPML3^{va}$: constitutively active, current inhibited by extracellular acidification (equivalent to intralysosomal acidicification) Wild-type TRPML3: activated by Na^+-free extracellular (extracytosolic) solution and membrane depolarization, current inhibited by extracellular acidification (equivalent to intralysosomal acidicification)
Blockers	–	–	Gd^{3+}
Functional characteristics	$TRPML1^{Va}$: $\gamma = 40$ pS and 76–86 pS at very negative holding potentials with Fe^{2+} and monovalent cations as charge carriers respectively; conducts $Na^+ \cong K^+ > Cs^+$ and divalent cations ($Ba^{2+} > Mn^{2+} > Fe^{2+} > Ca^{2+} > Mg^{2+} > Ni^{2+} > Co^{2+} > Cd^{2+} > Zn^{2+} >> Cu^{2+}$) but not Fe^{3+}, impermeable to protons; monovalent cation flux suppressed by divalent cations (e.g. Ca^{2+}, Fe^{2+}); inwardly rectifying	$TRPML1^{Va}$: conducts Na^+; monovalent cation flux suppressed by divalent cations; inwardly rectifying	$TRPML3^{Va}$: $\gamma = 49$ pS at very negative holding potentials with monovalent cations as charge carrier; conducts $Na^+ > K^+ > Cs^+$ with maintained current in the presence of Na^+, conducts Ca^{2+} and Mg^{2+}, but not Fe^{2+}, impermeable to protons; inwardly rectifying Wild-type TRPML3: $\gamma = 59$ pS at negative holding potentials with monovalent cations as charge carrier; conducts $Na^+ > K^+ > Cs^+$ and Ca^{2+} ($P_{Ca}/P_K \cong 350$), slowly inactivates in the continued presence of Na^+ within the extracellular (extracytosolic) solution; outwardly rectifying

Data in the table are for TRPML proteins mutated (i.e. $TRPML1^{Va}$, $TRPML2^{Va}$ and $TRPML3^{Va}$) at loci equivalent to TRPML3 A419P to allow plasma membrane expression when expressed in HEK-293 cells and subsequent characterization by patch-clamp recording (Grimm *et al*., 2007; Kim *et al*., 2007; Xu *et al*., 2007; Dong *et al*., 2008; Nagata *et al*., 2008). Data for wild-type TRPML3 are also tabulated (Kim *et al*., 2007; 2008; Xu *et al*., 2007; Nagata *et al*., 2008). It should be noted that alternative methodologies, particularly in the case of TRPML1, have resulted in channels with differing biophysical characteristics (reviewed by Puertollano and Kiselyov, 2009).

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 *et al*., 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 membrane depolarization; changes in cell volume affect voltage-dependent gating (increased channel opening probability with cell swelling)
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	$\gamma = 123$–177 pS (with K^+ as charge carrier); $P_{Na}/P_K = 0.14$–1.1; conducts both mono- and divalent cations; probably associates with TRPV4; also associates with cortactin and cadherin via TRPP1; channel activity increased by association with α-actinin	$\gamma = 105$–137 pS (outward conductance) 184–399 pS (inward conductance), conducts mono- and divalent cations with a preference for divalents ($P_{Ca}/P_{Na} = 4.0$–4.3); steady state currents rectify outwardly, whereas instantaneous currents show strong inward rectification; activated and subsequently inactivated by intracellular Ca^{2+} (human, but not mouse); inhibited by extracellular acidification and potentiated by extracellular alkalization

Data in the table are extracted from Delmas *et al*. (2004a), Dai *et al*. (2007) and Shimizu *et al*. (2009). Broadly similar single-channel conductance, mono- and divalent cation selectivity and sensitivity to blockers are observed for TRPP2 co-expressed with TRPP1 (Delmas *et al*., 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; **AMG517**, *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; **JNJ17203212**, 4-(3-trifluoromethyl-pyridin-2-yl)-piperazine-1-carboxylic acid (5-trifluoromethyl-pyridin-2-yl)-amide; **JYL1421**; *N*-(4-*tert*-butylbenzyl)-*N*′-[3-fluoro-4-(methylsulfonylamino)benzyl]thiourea; **KB-R7943**, 2-[2-[4-(4-nitrobenzyloxy)phenyl]ethyl]isothiourea methanesulfonate; **ML-9**, 1-(5-chloronaphtalene-1-sulphonyl)homopiperazine; **NADA**, *N*-arachidonyl dopamine; **OAG**, 1-oleoyl-2-acetyl-*sn*-glycerol; **PMA**, phorbol 12 myristate 13-acetate; **RHC80267**, 1,6-di[O-(carbamoyl)cyclohexanone oxime]hexane; **SB366791**, *N*-(3-methoxyphenyl)-4-chlorocinnamide; **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

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