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THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: Voltage-gated ion channels

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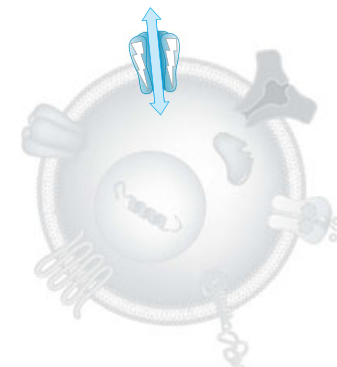
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Abstract

The Concise Guide to PHARMACOLOGY 2017/18 provides concise overviews of the key properties of nearly 1800 human drug targets with an emphasis on selective pharmacology (where available), plus links to an open access knowledgebase of drug targets and their ligands (www.guidetopharmacology.org), which provides more detailed views of target and ligand properties. Although the Concise Guide represents approximately 400 pages, the material presented is substantially reduced compared to information and links presented on the website. It provides a permanent, citable, point-in-time record that will survive database updates. The full contents of this section can be found at <http://onlinelibrary.wiley.com/doi/10.1111/bph.13884/full>. Voltage-gated ion channels are one of the eight major pharmacological targets into which the Guide is divided, with the others being: G protein-coupled receptors, ligand-gated ion channels, other ion channels, nuclear hormone receptors, catalytic receptors, enzymes and transporters. These are presented with nomenclature guidance and summary information on the best available pharmacological tools, alongside key references and suggestions for further reading. The landscape format of the Concise Guide is designed to facilitate comparison of related targets from material contemporary to mid-2017, and supersedes data presented in the 2015/16 and 2013/14 Concise Guides and previous Guides to Receptors and Channels. It is produced in close conjunction with the Nomenclature Committee of the Union of Basic and Clinical Pharmacology (NC-IUPHAR), therefore, providing official IUPHAR classification and nomenclature for human drug targets, where appropriate.

Conflict of interest

The authors state that there are no conflicts of interest to declare.

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Family structure

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Searchable database: <http://www.guidetopharmacology.org/index.jsp>

Full Contents of ConciseGuide: <http://onlinelibrary.wiley.com/doi/10.1111/bph.13884/full>

Voltage-gated ion channels S160

CatSper and Two-Pore channels

Voltage-gated ion channels → [CatSper and Two-Pore channels](#)

Overview: CatSper channels (CatSper1-4, **nomenclature as agreed by NC-IUPHAR [69]**) 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} [193]. In mammals, CatSper subunits are structurally most closely related to individual domains of voltage-activated calcium channels (Ca_v) [349]. CatSper1 [349], CatSper2 [341] and CatSper3 and 4 [173,

245, 338], in common with a putative 2TM auxiliary CatSper β protein [242] and two putative 1TM associated CatSper γ and CatSper δ proteins [64, 434], are restricted to the testis and localised to the principle piece of sperm tail.

Two-pore channels (TPCs) are structurally related to CatSper, Ca_v s and Na_v s. TPCs have a 2x6TM structure with twice the number of TMs of CatSper and half that of Ca_v s. There are three an-

imal TPCs (TPC1-TPC3). Humans have TPC1 and TPC2, but not TPC3. TPC1 and TPC2 are localized in endosomes and lysosomes [43]. TPC3 is also found on the plasma membrane and forms a voltage-activated, non-inactivating Na^+ channel [44]. All the three TPCs are Na^+ -selective under whole-cell or whole-organelle patch clamp recording [45, 46, 457]. The channels may also conduct Ca^{2+} [272].

| | CatSper1 | CatSper2 | CatSper3 | CatSper4 |
|----------------------------|---|--|--|--|
| Nomenclature | CatSper1 | CatSper2 | CatSper3 | CatSper4 |
| HGNC, UniProt | CATSPER1 , Q8NECS | CATSPER2 , Q96P56 | CATSPER3 , Q86XQ3 | CATSPER4 , Q7RTX7 |
| Activators | CatSper1 is constitutively active, weakly facilitated by membrane depolarisation, strongly augmented by intracellular alkalinisation. In human, but not mouse, spermatozoa progesterone ($\text{EC}_{50} \sim 8 \text{ nM}$) also potentiates the CatSper current (I_{CatSper}) [239, 390] | – | – | – |
| Channel blockers | ruthenium red ($\text{pIC}_{50} 5$) [193] – Mouse, HC-056456 ($\text{pIC}_{50} 4.7$) [50], Cd²⁺ ($\text{pIC}_{50} 3.7$) [193] – Mouse, Ni²⁺ ($\text{pIC}_{50} 3.5$) [193] – Mouse | – | – | – |
| Selective channel blockers | NNC55-0396 ($\text{pIC}_{50} 5.7$) [–80mV – 80mV] [239, 390], mibefradil ($\text{pIC}_{50} 4.4$ – 4.5) [390] | – | – | – |
| Functional Characteristics | Calcium selective ion channel ($\text{Ba}^{2+} > \text{Ca}^{2+} \gg \text{Mg}^{2+} \gg \text{Na}^+$); quasilinear monovalent cation current in the absence of extracellular divalent cations; alkalization shifts the voltage-dependence of activation towards negative potentials [$V_{1/2}$ @ pH 6.0 = +87 mV (mouse); $V_{1/2}$ @ pH 7.5 = +11 mV (mouse) or pH 7.4 = +85 mV (human)]; required for I_{CatSper} and male fertility (mouse and human) | Required for I_{CatSper} and male fertility (mouse and human) | Required for I_{CatSper} and male fertility (mouse) | Required for I_{CatSper} and male fertility (mouse) |

| | | |
|----------------------------|--|--|
| Nomenclature | TPC1 | TPC2 |
| HGNC, UniProt | <i>TPCN1</i> , Q9ULQ1 | <i>TPCN2</i> , Q8NHX9 |
| Activators | phosphatidyl (3,5) inositol bisphosphate (pEC ₅₀ 6.5) [45] | phosphatidyl (3,5) inositol bisphosphate (pEC ₅₀ 6.4) [439] |
| Channel blockers | verapamil (pIC ₅₀ 4.6) [45], Cd ²⁺ (pIC ₅₀ 3.7) [45] | verapamil (pIC ₅₀ 5) [439] |
| Functional Characteristics | Organelle voltage-gated Na ⁺ -selective channel (Na ⁺ ≫K ⁺ ≫Ca ²⁺); Required for the generation of action potential-like long depolarization in lysosomes. Voltage-dependence of activation is sensitive to luminal pH (determined from lysosomal recordings). $\psi_{1/2}$ @ pH4.6 = +91 mV; $\psi_{1/2}$ @ pH6.5 = +2.6 mV. Maximum activity requires PI(3,5)P2 and reduced [ATP] | Organelle voltage-independent Na ⁺ -selective channel (Na ⁺ ≫K ⁺ ≫Ca ²⁺). Sensitive to the levels of PI(3,5)P2. Activated by decreases in [ATP] or depletion of extracellular amino acids |

Comments: CatSper channel subunits expressed singly, or in combination, fail to functionally express in heterologous expression systems [341, 349]. 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 [193] and also mature human sperm [239, 390]. I_{CatSper} is also undetectable in the spermatozoa of *Catsper2*^(-/-), *Catsper3*^(-/-), *Catsper4*^(-/-), or CatSper δ ^(-/-) mice, and CatSper 1 associates with CatSper 2, 3, 4, β , γ , and δ [64, 242, 338]. Moreover, targeted disruption of *Catsper1*, 2, 3, 4, or δ genes results in an identical phenotype in which spermatozoa fail to exhibit the hyperactive movement (whiplike 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 Ca²⁺ entry into spermatozoa [51, 64, 338]. Thus, it is likely that the CatSper pore is formed by a heterotetramer of CatSper1-4 [338] in association with the auxiliary subunits (β ,

γ , δ) that are also essential for function [64]. CatSper channels are required for the increase in intracellular Ca²⁺ concentration in sperm evoked by egg *zona pellucida* glycoproteins [457]. Mouse and human sperm swim against the fluid flow and Ca²⁺ signaling through CatSper is required for the rheotaxis [268]. *In vivo*, CatSper1-null spermatozoa cannot ascend the female reproductive tracts efficiently [65, 151]. It has been shown that CatSper channels form four linear Ca²⁺ signaling domains along the flagella, which orchestrate capacitation-associated tyrosine phosphorylation [65]. The driving force for Ca²⁺ entry is principally determined by a mildly outwardly rectifying K⁺ channel (KSper) that, like CatSper, is activated by intracellular alkalinization [283]. Mouse KSper is encoded by *mSlo3*, a protein detected only in testis [262, 283, 478]. In human sperm, such alkalinization may result from the activation of H_v1, a proton channel [240]. Mutations in CatSper are associated with syndromic and non-syndromic male infertility [144]. In human ejaculated spermatozoa, progesterone (<50 nM) potentiates the CatSper current by

a non-genomic mechanism and acts synergistically with intracellular alkalinisation [239, 390]. Sperm cells from infertile patients with a deletion in CatSper2 gene lack I_{CatSper} and the progesterone response [375]. In addition, certain prostaglandins (*e.g.* PGF_{1 α} , PGE₁) also potentiate CatSper mediated currents [239, 390]. In human sperm, CatSper channels are also activated by various small molecules including endocrine disrupting chemicals (EDC) and proposed as a polymodal sensor [39, 39]. TPCs are the major Na⁺ conductance in lysosomes; knocking out TPC1 and TPC2 eliminates the Na⁺ conductance and renders the organelle's membrane potential insensitive to changes in [Na⁺] (31). The channels are regulated by luminal pH [45], PI(3,5)P2 [439], intracellular ATP and extracellular amino acids [46]. TPCs are also involved in the NAADP-activated Ca²⁺ release from lysosomal Ca²⁺ stores [43, 272]. Mice lacking TPCs are viable but have phenotypes including compromised lysosomal pH stability, reduced physical endurance [46], resistance to Ebola viral infection [358] and fatty liver [124]. No major human disease-associated TPC mutation has been reported.

Further reading on CatSper and Two-Pore channels

Clapham DE *et al.* (2005) International Union of Pharmacology. L. Nomenclature and structure-function relationships of CatSper and two-pore channels. *Pharmacol. Rev.* **57**: 451-4 [PMID:16382101]

Grimm C *et al.* (2017) Two-Pore Channels: Catalyzers of Endolysosomal Transport and Function. *Front Pharmacol* **8**: 45 [PMID:28223936]

Kintzer AF *et al.* (2017) On the Structure and Mechanism of Two-Pore Channels. *FEBS J* [PMID:28656706]

Cyclic nucleotide-regulated channels

Voltage-gated ion channels → Cyclic nucleotide-regulated channels

Overview: Cyclic nucleotide-gated (CNG) channels are responsible for signalling in the primary sensory cells of the vertebrate visual and olfactory systems. **A standardised nomenclature for CNG channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels [154].**

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 [107, 188], where light signals through rhodopsin and transducin to stimulate phosphodiesterase and reduce intracellular cyclic GMP level. This results in a closure of CNG channels and a reduced 'dark current'. Similar channels were found in

the cilia of olfactory neurons [282] and the pineal gland [95]. 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 | CNGB3 |
|----------------------------|---|--|--|---|
| HGNC, UniProt | CNGA1 , P29973 | CNGA2 , Q16280 | CNGA3 , Q16281 | CNGB3 , Q9NQW8 |
| Activators | cyclic GMP ($EC_{50} \sim 30 \mu\text{M}$) \gg cyclic AMP | cyclic GMP > cyclic AMP ($EC_{50} \sim 1 \mu\text{M}$) | cyclic GMP ($EC_{50} \sim 30 \mu\text{M}$) \gg cyclic AMP | – |
| Inhibitors | – | – | L-(cis)-diltiazem (high affinity binding requires presence of CNGB subunits) | – |
| Channel blockers | dequalinium (pIC_{50} 6.7) [0mV] [355], L-(cis)-diltiazem (high affinity binding requires presence of CNGB subunits) (pK_i 4) [-80mV – 80mV] [58] | dequalinium (pIC_{50} 5.6) [0mV] [354] | – | L-(cis)-diltiazem (Channel blocker when CNGB3 coexpressed with CNGA3) (pIC_{50} 5.5) [0mV] [116] – Mouse |
| Functional Characteristics | $\gamma = 25\text{--}30 \text{ pS}$ $P_{Ca}/P_{Na} = 3.1$ | $\gamma = 35 \text{ pS}$ $P_{Ca}/P_{Na} = 6.8$ | $\gamma = 40 \text{ pS}$ $P_{Ca}/P_{Na} = 10.9$ | – |

Comments: CNGA1, CNGA2 and CNGA3 express functional channels as homomers. Three additional subunits [CNGA4](#) ([Q8IV77](#)), [CNGB1](#) ([Q14028](#)) and [CNGB3](#) ([Q9NQW8](#)) do not, and are referred to as auxiliary subunits. The subunit composition of the native channels is believed to be as follows. Rod: CNGA1₃/CNGB1_a; Cone: CNGA3₂/CNGB3₂; Olfactory neurons: CNGA2₂/CNGA4/CNGB1_b [323, 445, 480, 481, 483].

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

The hyperpolarisation-activated, cyclic nucleotide-gated (HCN) channels are cation channels that are activated by hyperpolarisation at voltages negative to \sim -50 mV. The cyclic nucleotides **cyclic AMP** and **cyclic GMP** 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 [92, 308]. 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 [7]. **A standardised nomenclature for HCN channels has been proposed by the NC-IUPHAR subcommittee on voltage-gated ion channels [154].**

| | | | | |
|------------------|---|---|---|---|
| Nomenclature | HCN1 | HCN2 | HCN3 | HCN4 |
| HGNC, UniProt | <i>HCN1</i> , O60741 | <i>HCN2</i> , Q9UL51 | <i>HCN3</i> , Q9P1Z3 | <i>HCN4</i> , Q9Y3Q4 |
| Activators | cyclic AMP > cyclic GMP (both weak) | cyclic AMP > cyclic GMP | – | cyclic AMP > cyclic GMP |
| Channel blockers | ivabradine (pIC ₅₀ 5.7) [384], ZD7288 (pIC ₅₀ 4.7) [383], Cs ⁺ (pIC ₅₀ 3.7) [-40mV] [383] | ivabradine (pIC ₅₀ 5.6) [384] – Mouse, ZD7288 (pIC ₅₀ 4.4) [383], Cs ⁺ (pIC ₅₀ 3.7) [-40mV] [383] | ivabradine (pIC ₅₀ 5.7) [384], ZD7288 (pIC ₅₀ 4.5) [383], Cs ⁺ (pIC ₅₀ 3.8) [-40mV] [383] | ivabradine (pIC ₅₀ 5.7) [384], ZD7288 (pIC ₅₀ 4.7) [383], Cs ⁺ (pIC ₅₀ 3.8) [-40mV] [383] |

Comments: 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 [37] and ivabradine [42] have proven useful in identifying and studying functional HCN channels in native cells. Zatebradine and cilobradine are also useful blocking agents.

Further reading on Cyclic nucleotide-regulated channels

Herrmann S *et al.* (2015) HCN channels—modulators of cardiac and neuronal excitability. *Int J Mol Sci* **16**: 1429–47 [PMID:25580535]
 Hofmann F *et al.* (2005) International Union of Pharmacology. LI. Nomenclature and structure-function relationships of cyclic nucleotide-regulated channels. *Pharmacol Rev* **57**: 455–62 [PMID:16382102]

Podda MV *et al.* (2014) New perspectives in cyclic nucleotide-mediated functions in the CNS: the emerging role of cyclic nucleotide-gated (CNG) channels. *Pflugers Arch* **466**: 1241–57 [PMID:24142069]
 Tsantoulas C *et al.* (2016) HCN2 ion channels: basic science opens up possibilities for therapeutic intervention in neuropathic pain. *Biochem J* **473**: 2717–36 [PMID:27621481]

Potassium channels

Voltage-gated ion channels → Potassium channels

Overview: Activation of potassium channels regulates excitability and can control the shape of the action potential waveform. They are present in all cells within the body and can influence processes as diverse as cognition, muscle contraction and hormone secretion. Potassium channels are subdivided into families, based

on their structural and functional properties. The largest family consists of potassium channels that activated by membrane depolarization, with other families consisting of channels that are either activated by a rise of intracellular calcium ions or are constitutively active. A standardised nomenclature for potassium

channels has been proposed by the **NC-IUPHAR subcommittees** on potassium channels [120, 135, 211, 444], which has placed cloned channels into groups based on gene family and structure of channels that exhibit 6, 4 or 2 transmembrane domains (TM).

Calcium- and sodium-activated potassium channels

Voltage-gated ion channels → Potassium channels → Calcium- and sodium-activated potassium channels

Overview: The 6TM family of K channels comprises the voltage-gated K_v subfamilies, including the KCNQ subfamily, the EAG subfamily (which includes *herg* channels), the Ca^{2+} -activated Slo subfamily (actually with 6 or 7TM) and the Ca^{2+} - and Na^{+} -activated SK subfamily (**nomenclature as agreed by the NC-IUPHAR Subcommittee on Calcium- and sodium-activated potassium channels [181]**). As for the 2TM family, the pore-forming a subunits form tetramers and heteromeric channels may be formed within subfamilies (*e.g.* $K_v1.1$ with $K_v1.2$; KCNQ2 with KCNQ3).

| | | | | | |
|----------------------------|---|---|--|---|---|
| Nomenclature | $K_{Ca}1.1$ | $K_{Ca}2.1$ | $K_{Ca}2.2$ | $K_{Ca}2.3$ | $K_{Ca}3.1$ |
| HGNC, UniProt | <i>KCNMA1</i> , Q12791 | <i>KCNN1</i> , Q92952 | <i>KCNN2</i> , Q9H2S1 | <i>KCNN3</i> , Q9UGI6 | <i>KCNN4</i> , O15554 |
| Activators | NS004, NS1619 | EBIO Concentration range: 2×10^{-3} M [-80mV] [320, 442], NS309 Concentration range: 3×10^{-8} M- 1×10^{-7} M [-90mV] [388, 442] | NS309 (pEC ₅₀ 6.2) Concentration range: 3×10^{-8} M- 1×10^{-7} M [319, 388, 442], EBIO (pEC ₅₀ 3.3) [319, 442], EBIO (pEC ₅₀ 3) Concentration range: 2×10^{-3} M [48, 320] – Rat | EBIO (pEC ₅₀ 3.8) [442, 450], NS309 Concentration range: 3×10^{-8} M [388, 442] | NS309 (pEC ₅₀ 8) [-90mV] [388, 442], SKA-121 (pEC ₅₀ 7) [72], EBIO (pEC ₅₀ 4.1–4.5) [-100mV – -50mV] [320, 394, 442] |
| Inhibitors | paxilline (pK _i 8.7) [0mV] [360] – Mouse | UCL1684 (pIC ₅₀ 9.1) [387, 442], apamin (pIC ₅₀ 7.9–8.5) [367, 385, 387] | UCL1684 (pIC ₅₀ 9.6) [103, 442], apamin (pK _d 9.4) [180] | apamin (pIC ₅₀ 7.9–9.1) [407, 450], UCL1684 (pIC ₅₀ 8–9) [103, 442] | TRAM-34 (pK _d 7.6–8) [213, 456] |
| Channel blockers | charybdotoxin, iberiotoxin, tetraethylammonium | tetraethylammonium (pIC ₅₀ 2.7) [442] | tetraethylammonium (pIC ₅₀ 2.7) [442] | tetraethylammonium (pIC ₅₀ 2.7) [442] | charybdotoxin (pIC ₅₀ 7.6–8.7) [171, 176] |
| Functional Characteristics | Maxi K_{Ca} | SK K_{Ca} | SK K_{Ca} | SK K_{Ca} | IK K_{Ca} |
| Comments | – | The rat isoform does not form functional channels when expressed alone in cell lines. N- or C-terminal chimeric constructs permit functional channels that are insensitive to apamin [442]. Heteromeric channels are formed between $K_{Ca}2.1$ and 2.2 subunits that show intermediate sensitivity to apamin [68]. | – | – | – |

| | | | |
|----------------------------|--|--|--|
| Nomenclature | K_{Na}1.1 | K_{Na}1.2 | K_{Ca}5.1 |
| HGNC, UniProt | KCNT1 , Q5JUK3 | KCNT2 , Q6UVM3 | KCNU1 , A8MYU2 |
| Activators | bithionol (pEC ₅₀ 5–6) [470] – Rat, niclosamide (pEC ₅₀ 5.5) [32], loxapine (pEC ₅₀ 5.4) [32] | niflumic acid (pEC ₅₀ 8.7) [78, 115] | – |
| Gating inhibitors | bepridil (pIC ₅₀ 5–6) [470] – Rat | – | – |
| Channel blockers | quinidine (pIC ₅₀ 4) [29, 470] – Rat | Ba²⁺ (pIC ₅₀ 3) [29], quinidine Concentration range: 1×10 ⁻³ M [29] – Rat | quinidine Concentration range: 2×10 ⁻⁵ M [404, 454] – Mouse |
| Functional Characteristics | K _{Na} | K _{Na} | Sperm pH-regulated K ⁺ current, KSPER |

Inwardly rectifying potassium channels

[Voltage-gated ion channels](#) → [Potassium channels](#) → [Inwardly rectifying potassium channels](#)

Overview: 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) that are constitutively active, 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 (SUR1-3)). The pore-forming α subunits form tetramers, and heteromeric channels may be formed within subfamilies (*e.g.* K_{ir}3.2 with K_{ir}3.3).

| | |
|---------------------------------|---|
| Nomenclature | K_{ir}1.1 |
| HGNC, UniProt | KCNJ1 , P48048 |
| Ion Selectivity and Conductance | NH ₄ ⁺ [62pS] > K ⁺ [38. pS] > Tl ⁺ [21pS] > Rb ⁺ [15pS] (Rat) [62, 150] |
| Channel blockers | tertiapin-Q (pIC ₅₀ 8.9) [175], Ba²⁺ (pIC ₅₀ 2.3–4.2) Concentration range: 1×10 ⁻⁴ M [voltage dependent 0mV – -100mV] [150, 484] – Rat, Cs⁺ (pIC ₅₀ 2.9) [voltage dependent -120mV] [484] – Rat |
| Functional Characteristics | K _{ir} 1.1 is weakly inwardly rectifying, as compared to classical (strong) inward rectifiers. |

| (continued) | | | | |
|-----------------------------|--|--|---|--|
| Nomenclature | K _{ir} 2.1 | K _{ir} 2.2 | K _{ir} 2.3 | K _{ir} 2.4 |
| HGNC, UniProt | KCNJ2, P63252 | KCNJ12, Q14500 | KCNJ4, P48050 | KCNJ14, Q9UNX9 |
| Endogenous activators | PIP ₂ Concentration range: 1×10 ⁻⁵ M-5×10 ⁻⁵ M [-30mV] [158, 348, 379] – Mouse | – | – | – |
| Endogenous inhibitors | – | Intracellular Mg ²⁺ (pI _C ₅₀ 5) [469] | – | Intracellular Mg ²⁺ |
| Gating inhibitors | – | Ba ²⁺ Concentration range: 5×10 ⁻⁵ M [-150mV – -50mV] [397] – Mouse, Cs ⁺ Concentration range: 5×10 ⁻⁶ M-5×10 ⁻⁵ M [-150mV – -50mV] [397] – Mouse | – | – |
| Endogenous channel blockers | spermine (pK _d 9.1) [voltage dependent 40mV] [167, 471] – Mouse, spermidine (pK _d 8.1) [voltage dependent 40mV] [471] – Mouse, putrescine (pK _d 5.1) [voltage dependent 40mV] [167, 471] – Mouse, Intracellular Mg ²⁺ (pK _d 4.8) [voltage dependent 40mV] [471] – Mouse | – | Intracellular Mg ²⁺ (pK _d 5) [voltage dependent 50mV] [246], putrescine Concentration range: 5×10 ⁻⁵ M-1×10 ⁻³ M [-80mV – 80mV] [246], spermidine Concentration range: 2.5×10 ⁻⁵ M-1×10 ⁻³ M [-80mV – 80mV] [246], spermine Concentration range: 5×10 ⁻⁵ M-1×10 ⁻³ M [-80mV – 80mV] [246] | |
| Channel blockers | Ba ²⁺ (pK _d 3.9–5.6) Concentration range: 1×10 ⁻⁶ M-1×10 ⁻⁴ M [voltage dependent 0mV – -80mV] [6] – Mouse, Cs ⁺ (pK _d 1.3–4) Concentration range: 3×10 ⁻⁵ M-3×10 ⁻⁴ M [voltage dependent 0mV – -102mV] [3] – Mouse | – | Ba ²⁺ (pI _C ₅₀ 5) Concentration range: 3×10 ⁻⁶ M-5×10 ⁻⁴ M [-60mV] [260, 335, 405], Cs ⁺ (pK _i 1.3–4.5) Concentration range: 3×10 ⁻⁶ M-3×10 ⁻⁴ M [0mV – -130mV] [260] | Cs ⁺ (pK _d 3–4.1) [voltage dependent -100mV – -60mV] [159], Ba ²⁺ (pK _d 3.3) [voltage dependent 0mV] [159] |
| Functional Characteristics | IK ₁ in heart, 'strong' inward-rectifier current | IK ₁ in heart, 'strong' inward-rectifier current | IK ₁ in heart, 'strong' inward-rectifier current | IK ₁ in heart, 'strong' inward-rectifier current |
| Comments | K _{ir} 2.1 is also inhibited by intracellular polyamines | K _{ir} 2.2 is also inhibited by intracellular polyamines | K _{ir} 2.3 is also inhibited by intracellular polyamines | K _{ir} 2.4 is also inhibited by intracellular polyamines |

| (continued) | | | | |
|----------------------------|---|--|--|---|
| Nomenclature | K _{ir} 3.1 | K _{ir} 3.2 | K _{ir} 3.3 | K _{ir} 3.4 |
| HGNC, UniProt | KCNJ3, P48549 | KCNJ6, P48051 | KCNJ9, Q92806 | KCNJ5, P48544 |
| Endogenous activators | PIP ₂ (pK _d 6.3) Concentration range: 5×10 ⁻⁵ M [physiological voltage] [158] | PIP ₂ (pK _d 6.3) Concentration range: 5×10 ⁻⁵ M [physiological voltage] [158] | PIP ₂ [145] | PIP ₂ [20, 145] |
| Gating inhibitors | – | pimozide (Data obtained using K _{ir} 3.1/3.2 heteromer) (pEC ₅₀ 5.5) [-70mV] [201] – Mouse | – | – |
| Channel blockers | tertiapin-Q (K _{ir} 3.1/3.4; expression in <i>Xenopus oocytes</i>) (pIC ₅₀ 7.9) [174], Ba ²⁺ (K _{ir} 3.1 expressed in <i>Xenopus oocytes</i>) (pIC ₅₀ 4.7) [80] – Rat | desipramine (Data obtained using K _{ir} 3.1/3.2 heteromer) (pIC ₅₀ 4.4) [-70mV] [202] – Mouse | – | tertiapin-Q (K _{ir} 3.1/3.4) (pIC ₅₀ 7.9) [174] |
| Functional Characteristics | G protein-activated inward-rectifier current | G protein-activated inward-rectifier current | G protein-activated inward-rectifier current | G protein-activated inward-rectifier current |
| Comments | K _{ir} 3.1 is also activated by G _{βγ} . K _{ir} 3.1 is not functional alone. The functional expression of K _{ir} 3.1 in <i>Xenopus oocytes</i> requires coassembly with the endogenous <i>Xenopus</i> K _{ir} 3.5 subunit. The major functional assembly in the heart is the K _{ir} 3.1/3.4 heteromultimer, while in the brain it is K _{ir} 3.1/3.2, K _{ir} 3.1/3.3 and K _{ir} 3.2/3.3. | K _{ir} 3.2 is also activated by G _{βγ} . K _{ir} 3.2 forms functional heteromers with K _{ir} 3.1/3.3. | K _{ir} 3.3 is also activated by G _{βγ} | K _{ir} 3.4 is also activated by G _{βγ} |

| | | | |
|----------------------------|---|---|--|
| Nomenclature | K _{ir} 4.1 | K _{ir} 4.2 | K _{ir} 5.1 |
| HGNC, UniProt | KCNJ10, P78508 | KCNJ15, Q99712 | KCNJ16, Q9NPI9 |
| Channel blockers | Ba ²⁺ Concentration range: 3×10 ⁻⁶ M-1×10 ⁻³ M [-160mV – 60mV] [205, 399, 403] – Rat, Cs ⁺ Concentration range: 3×10 ⁻³ M-3×10 ⁻⁴ M [-160mV – 50mV] [399] – Rat | Ba ²⁺ (K _{ir} 4.2 expressed in <i>Xenopus oocytes</i>) Concentration range: 1×10 ⁻⁵ M-1×10 ⁻⁴ M [-120mV – 100mV] [318] – Mouse, Cs ⁺ (K _{ir} 4.2 expressed in <i>Xenopus oocytes</i>) Concentration range: 1×10 ⁻⁵ M-1×10 ⁻⁴ M [-120mV – 100mV] [318] – Mouse | Ba ²⁺ (K _{ir} 5.1 expressed with PSD-95) Concentration range: 3×10 ⁻³ M [-120mV – 20mV] [402] – Rat |
| Functional Characteristics | Inward-rectifier current | Inward-rectifier current | Weakly inwardly rectifying |

| | | | |
|----------------------------|---|---|--|
| Nomenclature | K_{ir}6.1 | K_{ir}6.2 | K_{ir}7.1 |
| HGNC, UniProt | KCNJ8, Q15842 | KCNJ11, Q14654 | KCNJ13, O60928 |
| Associated subunits | SUR1, SUR2A, SUR2B | SUR1, SUR2A, SUR2B | – |
| Activators | cromakalim , diazoxide Concentration range: 2×10 ⁻⁴ M [-60mV] [466] – Mouse, minoxidil , nicorandil Concentration range: 3×10 ⁻⁴ M [-60mV – 60mV] [466] – Mouse | diazoxide (pEC ₅₀ 4.2) [physiological voltage] [162] – Mouse, cromakalim Concentration range: 3×10 ⁻⁵ M [-60mV] [163] – Mouse, minoxidil , nicorandil | – |
| Inhibitors | glibenclamide , tolbutamide | glibenclamide , tolbutamide | – |
| Channel blockers | – | – | Ba²⁺ (pK _i 3.2) [voltage dependent -100mV] [99, 210, 212, 311], Cs⁺ (pK _i 1.6) [voltage dependent -100mV] [99, 210, 311] |
| Functional Characteristics | ATP-sensitive, inward-rectifier current | ATP-sensitive, inward-rectifier current | Inward-rectifier current |

Two P domain potassium channels

Voltage-gated ion channels → Potassium channels → Two P domain potassium channels

Overview: The 4TM family of K channels mediate many of the background potassium currents observed in native cells. They are open across the physiological voltage-range and are regulated by a wide array of neurotransmitters and biochemical mediators. The pore-forming α -subunit contains two pore loop (P) domains and

two subunits assemble to form one ion conduction pathway lined by four P domains. It is important to note that single channels do not have two pores but that each subunit has two P domains in its primary sequence; hence the name two P domain, or K_{2P} channels (and not two-pore channels). Some of the K_{2P} subunits can

form heterodimers across subfamilies (*e.g.* K_{2P}3.1 with K_{2P}9.1). The nomenclature of 4TM K channels in the literature is still a mixture of IUPHAR and common names. The suggested division into subfamilies, below, is based on similarities in both structural and functional properties within subfamilies.

| | | | | |
|-----------------------|-----------------------------------|---|--|--|
| Nomenclature | K_{2P}1.1 | K_{2P}2.1 | K_{2P}3.1 | K_{2P}4.1 |
| HGNC, UniProt | KCNK1, O00180 | KCNK2, O95069 | KCNK3, O14649 | KCNK4, Q9N9G8 |
| Endogenous activators | – | arachidonic acid (studied at 1-10 μ M) (pEC ₅₀ 5) [314] | – | arachidonic acid (studied at 1-10 μ M) [108] |
| Activators | – | chloroform (studied at 1-5 mM) Concentration range: 8×10 ⁻³ M [313], halothane (studied at 1-5 mM) [313], isoflurane (studied at 1-5 mM) [313] | halothane (studied at 1-10 mM) | riluzole (studied at 1-100 μ M) [97] |
| Channel blockers | – | – | R-(+)-methanandamide (pIC ₅₀ ~6.2) [257], anandamide (pIC ₅₀ ~6.2) [257] | – |

| | | | | |
|----------------------------|--|---|---|--|
| (continued) | | | | |
| Nomenclature | K_{2p}1.1 | K_{2p}2.1 | K_{2p}3.1 | K_{2p}4.1 |
| Functional Characteristics | Background current | Background current | Background current | Background current |
| Comments | K _{2p} 1.1 is inhibited by acid pH _o external acidification with a pK _a ~ 6.7 [331]. K _{2p} 1 forms heterodimers with K _{2p} 3 and K _{2p} 9 [332]. | K _{2p} 2.1 is also activated by membrane stretch, heat and acid pH _i [256, 258]. K _{2p} 2 can heterodimerize with K _{2p} 4 [33] and K _{2p} 10 [228]. | Knock-out of the <i>kcnk3</i> gene leads to a prolonged QT interval in mice [83] and disrupted development of the adrenal cortex [143]. K _{2p} 3.1 is inhibited by acid pH _o with a pK _a of 6.4 [247]. K _{2p} 3 forms heterodimers with K _{2p} 1 [332] and K _{2p} 9 [77]. | K _{2p} 4 is activated by membrane stretch [255], and increased temperature (~12 to 20-fold between 17 and 40°C [183]) and can heterodimerize with K _{2p} 2 [33]. |

| | | | | |
|----------------------------|---|-----------------------------------|-----------------------------------|--|
| Nomenclature | K_{2p}5.1 | K_{2p}6.1 | K_{2p}7.1 | K_{2p}9.1 |
| HGNC, UniProt | KCNC5, O95279 | KCNC6, Q9Y257 | KCNC7, Q9Y2U2 | KCNC9, Q9NPC2 |
| Activators | – | – | – | halothane (studied at 1-5 mM) [401] |
| Inhibitors | – | – | – | <i>R</i> (+)-methanandamide (studied at 1-10 μM) [343], anandamide (studied at 1-10 μM) [343] |
| Functional Characteristics | Background current | Unknown | Unknown | Background current |
| Comments | K _{2p} 5.1 is activated by alkaline pH _o [351]. Knockout of the <i>kcnk5</i> gene in mice is associated with metabolic acidosis, hyponatremia and hypotension due to impaired bicarbonate handling in the kidney [441], as well as deafness [55]. The T108P mutation is associated with Balkan Endemic Nephropathy in humans [414]. | – | – | K _{2p} 9.1 is also inhibited by acid pH _o with a pK _a of ~6 [343]. Imprinting of the <i>KCNC9</i> gene is associated with Birk Barel syndrome [18]. K _{2p} 9 can form heterodimers with K _{2p} 1 [332] or K _{2p} 3 [77]. |

| | | | | | | | |
|-----------------------|---|------------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|--|
| Nomenclature | K_{2p}10.1 | K_{2p}12.1 | K_{2p}13.1 | K_{2p}15.1 | K_{2p}16.1 | K_{2p}17.1 | K_{2p}18.1 |
| HGNC, UniProt | KCNC10, P57789 | KCNC12, Q9HB15 | KCNC13, Q9HB14 | KCNC15, Q9H427 | KCNC16, Q96T55 | KCNC17, Q96T54 | KCNC18, Q7Z418 |
| Endogenous activators | arachidonic acid (studied at 1-10 μM) [225] | – | – | – | – | – | – |
| Activators | halothane (studied at 1-5 mM) [225] | – | – | – | – | – | – |
| Endogenous inhibitors | – | – | – | – | – | – | arachidonic acid (studied at 10-50 μM) [361] |

| (continued) | | | | | | | |
|----------------------------|---|--|---|------------------------------------|--|--|---|
| Nomenclature | K_{2p}10.1 | K_{2p}12.1 | K_{2p}13.1 | K_{2p}15.1 | K_{2p}16.1 | K_{2p}17.1 | K_{2p}18.1 |
| Inhibitors | norfluoxetine (pIC ₅₀ 5.1) [189] | – | halothane (studied at ~5 mM) [34] | – | – | – | – |
| Functional Characteristics | Background current | Does not function as a homodimer [342] but can form a functional heterodimer with K _{2p} 13 [34]. | Background current | Unknown | Background current | Background current | Background current |
| Comments | K _{2p} 10.1 is also activated by membrane stretch [225] and can heterodimerize with K _{2p} 2 [228]. | – | Forms a heterodimer with K _{2p} 12 [34]. | – | K _{2p} 16.1 current is increased by alkaline pH _o with a pK _a of 7.8 [184]. | K _{2p} 17.1 current is increased by alkaline pH _o with a pK _a of 8.8 [184]. | A frame-shift mutation (F139WfsX24) in the <i>KCNK18</i> gene, is associated with migraine with aura in humans [214]. |

Comments: The K_{2p}6, 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 [tetraethylammonium](#) and [fampridine](#), but are blocked to varying degrees by Ba²⁺ ions.

Voltage-gated potassium channels

Voltage-gated ion channels → [Potassium channels](#) → [Voltage-gated potassium channels](#)

Overview: The 6TM family of K channels comprises the voltage-gated K_V subfamilies, the EAG subfamily (which includes hERG channels), the Ca²⁺-activated Slo subfamily (actually with 7TM, termed BK) and the Ca²⁺-activated SK subfamily. These channels possess a pore-forming α subunit that comprise tetramers of identical subunits (homomeric) or of different subunits (heteromeric). Heteromeric channels can only be formed within subfamilies (e.g. K_V1.1 with K_V1.2; K_V7.2 with K_V7.3). The pharmacology largely reflects the subunit composition of the functional channel.

| | | | | |
|---------------------|---|---|--|--|
| Nomenclature | K_V1.1 | K_V1.2 | K_V1.3 | K_V1.4 |
| HGNC, UniProt | KCNA1 , Q09470 | KCNA2 , P16389 | KCNA3 , P22001 | KCNA4 , P22459 |
| Associated subunits | K _V 1.2, K _V 1.4, K _V β1 and K _V β2 [73] | K _V 1.1, K _V 1.4, K _V β1 and K _V β2 [73] | K _V 1.1, K _V 1.2, K _V 1.4, K _V 1.6, K _V β1 and K _V β2 [73] | K _V 1.1, K _V 1.2, K _V β1 and K _V β2 [73] |
| Channel blockers | α-dendrotoxin (pEC ₅₀ 7.7–9) [128, 160] – Rat, margatoxin (pIC ₅₀ 8.4) [19], tetraethylammonium (pK _d 3.5) [128] – Mouse | margatoxin (pIC ₅₀ 11.2) [19], α-dendrotoxin (pIC ₅₀ 7.8–9.4) [128, 160] – Rat, noxiustoxin (pK _d 8.7) [128] – Rat | margatoxin (pIC ₅₀ 10–10.3) [113, 117], noxiustoxin (pK _d 9) [128] – Mouse, maurotoxin (pIC ₅₀ 6.8) [352], tetraethylammonium (pK _d 2) [128] – Mouse | fampridine (pIC ₅₀ 1.9) [391] – Rat |

| | | | | |
|----------------------------|----------------------------------|----------------------------------|--|----------------------------------|
| (continued) | | | | |
| Nomenclature | K_v1.1 | K_v1.2 | K_v1.3 | K_v1.4 |
| Selective channel blockers | – | – | correolide (pIC ₅₀ 7.1) [106] | – |
| Functional Characteristics | K _V | K _V | K _V | K _A |
| Comments | – | – | Resistant to dendrotoxins | Resistant to dendrotoxins |

| | | | | |
|----------------------------|--|--|--|--|
| Nomenclature | K_v1.5 | K_v1.6 | K_v1.7 | K_v1.8 |
| HGNC, UniProt | KCNA5, P22460 | KCNA6, P17658 | KCNA7, Q96RP8 | KCNA10, Q16322 |
| Associated subunits | K _V β1 and K _V β2 | K _V β1 and K _V β2 | K _V β1 and K _V β2 | K _V β1 and K _V β2 |
| Channel blockers | fampridine (pIC ₅₀ 4.3) [105] | α-dendrotoxin (pIC ₅₀ 7.7) [129], tetraethylammonium (pIC ₅₀ 2.2) [129] | noxiustoxin (pIC ₅₀ 7.7) [182] – Mouse, fampridine (pIC ₅₀ 3.6) [182] – Mouse | fampridine (pIC ₅₀ 2.8) [217] |
| Functional Characteristics | K _V | K _V | K _V | K _V |
| Comments | Resistant to external TEA | – | – | – |

| | | | | | | |
|----------------------------|---|--|--|--|--|--|
| Nomenclature | K_v2.1 | K_v2.2 | K_v3.1 | K_v3.2 | K_v3.3 | K_v3.4 |
| HGNC, UniProt | KCNB1, Q14721 | KCNB2, Q92953 | KCNC1, P48547 | KCNC2, Q96PR1 | KCNC3, Q14003 | KCNC4, Q03721 |
| Associated subunits | K _V 5.1, K _V 6.1-6.4, K _V 8.1-8.2 and K _V 9.1-9.3 | K _V 5.1, K _V 6.1-6.4, K _V 8.1-8.2 and K _V 9.1-9.3 | – | – | – | MiRP2 is an associated subunit for K _V 3.4 |
| Channel blockers | tetraethylammonium (pIC ₅₀ 2) [142] – Rat | fampridine (pIC ₅₀ 2.8) [363], tetraethylammonium (pIC ₅₀ 2.6) [363] | fampridine (pIC ₅₀ 4.5) [128] – Mouse, tetraethylammonium (pIC ₅₀ 3.7) [128] – Mouse | fampridine (pIC ₅₀ 4.6) [233] – Rat, tetraethylammonium (pIC ₅₀ 4.2) [233] – Rat | tetraethylammonium (pIC ₅₀ 3.9) [419] – Rat | tetraethylammonium (pIC ₅₀ 3.5) [350, 365] – Rat |
| Selective channel blockers | – | – | – | – | – | sea anemone toxin BDS-I (pIC ₅₀ 7.3) [93] – Rat |
| Functional Characteristics | K _V | – | K _V | K _V | K _A | K _A |

| | | | |
|----------------------------|--|--|--|
| Nomenclature | K_v4.1 | K_v4.2 | K_v4.3 |
| HGNC, UniProt | KCND1, Q9NSA2 | KCND2, Q9NZV8 | KCND3, Q9UK17 |
| Associated subunits | KChIP 1–4, DP66, DPP10 | KChIP 1–4, DPP6, DPP10, K _v β1, NCS-1, Na _v β1 | KChIP 1–4, DPP6 and DPP10, MinK, MiRPs |
| Channel blockers | fampridine (pIC ₅₀ 2) [166] | – | – |
| Functional Characteristics | K _A | K _A | K _A |

| | | | | | |
|---------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Nomenclature | K_v5.1 | K_v6.1 | K_v6.2 | K_v6.3 | K_v6.4 |
| HGNC, UniProt | KCNF1, Q9H3M0 | KCNG1, Q9UIX4 | KCNG2, Q9UJ96 | KCNG3, Q8TAE7 | KCNG4, Q8TDN1 |

| | | | | | |
|----------------------------|---|--|---|--|---|
| Nomenclature | K_v7.1 | K_v7.2 | K_v7.3 | K_v7.4 | K_v7.5 |
| HGNC, UniProt | KCNQ1, P51787 | KCNQ2, O43526 | KCNQ3, O43525 | KCNQ4, P56696 | KCNQ5, Q9NR82 |
| Activators | – | retigabine (pEC ₅₀ 5.6) [406] | retigabine (pEC ₅₀ 6.2) [406] | retigabine (pEC ₅₀ 5.2) [406] | retigabine (pEC ₅₀ 5) [98] |
| Inhibitors | XE991 (pK _d 6.1) [436], linopirdine (pIC ₅₀ 4.4) [302] – Mouse | XE991 (pIC ₅₀ 6.2) [437], linopirdine (pIC ₅₀ 5.3) [437], | linopirdine (pIC ₅₀ 5.4) [437] – Rat | XE991 (pIC ₅₀ 5.3) [396], linopirdine (pIC ₅₀ 4.9) [396], | linopirdine (pK _d 4.8) [224], XE991 (pIC ₅₀ 4.2) [364] |
| Channel blockers | | tetraethylammonium (pIC ₅₀ 3.5–3.9) [136, 446] | – | tetraethylammonium (pIC ₅₀ 1.3) [13] | |
| Functional Characteristics | cardiac IK ₅ | M current as a heteromer between K _v 7.2 and K _v 7.3 | M current as heteromeric K _v 7.2/K _v 7.3 or K _v 7.3/K _v 7.5 | – | M current as heteromeric K _v 7.3/K _v 7.5 |

| | | | | | | | |
|---------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|
| Nomenclature | K_v8.1 | K_v8.2 | K_v9.1 | K_v9.2 | K_v9.3 | K_v10.1 | K_v10.2 |
| HGNC, UniProt | KCNV1, Q6PIU1 | KCNV2, Q8TDN2 | KCNS1, Q96KK3 | KCNS2, Q9ULS6 | KCNS3, Q9BQ31 | KCNH1, O95259 | KCNH5, Q8NCM2 |

| | | | | | | |
|----------------------------|---|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Nomenclature | K_v11.1 | K_v11.2 | K_v11.3 | K_v12.1 | K_v12.2 | K_v12.3 |
| HGNC, UniProt | KCNH2, Q12809 | KCNH6, Q9H252 | KCNH7, Q9NS40 | KCNH8, Q96L42 | KCNH3, Q9ULD8 | KCNH4, Q9UQ05 |
| Associated subunits | minK (KCNE1) and MiRP1 (KCNE2) | minK (KCNE1) | minK (KCNE1) | minK (KCNE1) | minK (KCNE1) and MiRP2 (KCNE3) | – |
| Channel blockers | astemizole (pIC ₅₀ 9) [486], terfenadine (pIC ₅₀ 7.3) [344], disopyramide (pIC ₅₀ 4) [190] | – | – | – | – | – |
| Inhibitor | E4031 (pIC ₅₀ 8.1) [485] | – | – | – | – | – |
| Selective channel blockers | dofetilide (pK _i 8.2) [372], ibutilide (pIC ₅₀ 7.6–8) [190 , 326] | – | – | – | – | – |
| Functional Characteristics | cardiac I _{KR} | – | – | – | – | – |
| Comments | RPR260243 is an activator of K _v 11.1 [185]. | – | – | – | – | – |

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Ryanodine receptors

Voltage-gated ion channels → **Ryanodine receptors**

Overview: The ryanodine receptors (RyRs) are found on intracellular Ca²⁺ storage/release organelles. The family of RyR genes encodes three highly related Ca²⁺ 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 Ca²⁺ signaling phenomena (neurotransmission, secretion, *etc.*). In addition to the three mammalian isoforms described below, various nonmammalian isoforms of the ryanodine receptor have been identified [392]. The function of the ryanodine receptor channels may also be influenced by closely associated proteins such as the tacrolimus (FK506)-binding protein, calmodulin [467], triadin, calsequestrin, junctin and sorcin, and by protein kinases and phosphatases.

| | RyR1 | RyR2 | RyR3 |
|----------------------------|--|---|--|
| Nomenclature | RyR1 | RyR2 | RyR3 |
| HGNC, UniProt | RYR1 , P21817 | RYR2 , Q92736 | RYR3 , Q15413 |
| Endogenous activators | cytosolic ATP (endogenous; mM range), cytosolic Ca²⁺ (endogenous; μ M range), luminal Ca²⁺ (endogenous) | cytosolic ATP (endogenous; mM range), cytosolic Ca²⁺ (endogenous; μ M range), luminal Ca²⁺ (endogenous) | cytosolic ATP (endogenous; mM range), cytosolic Ca²⁺ (endogenous; μ M range) |
| Activators | caffeine (pharmacological; mM range), ryanodine (pharmacological; nM - μ M range), suramin (pharmacological; μ M range) | caffeine (pharmacological; mM range), ryanodine (pharmacological; nM - μ M range), suramin (pharmacological; μ M range) | caffeine (pharmacological; mM range), ryanodine (pharmacological; nM - μ M range) |
| Endogenous antagonists | cytosolic Ca²⁺ Concentration range: $>1 \times 10^{-4}$ M, cytosolic Mg²⁺ (mM range) | cytosolic Ca²⁺ Concentration range: $>1 \times 10^{-3}$ M, cytosolic Mg²⁺ (mM range) | cytosolic Ca²⁺ Concentration range: $>1 \times 10^{-3}$ M, cytosolic Mg²⁺ (mM range) |
| Antagonists | dantrolene | – | dantrolene |
| Channel blockers | procaine , ruthenium red , ryanodine Concentration range: $>1 \times 10^{-4}$ M | procaine , ruthenium red , ryanodine Concentration range: $>1 \times 10^{-4}$ M | ruthenium red |
| Functional Characteristics | Ca ²⁺ : (P_{Ca}/P_{K} 6) single-channel conductance: 90 pS (50mM Ca ²⁺), 770 pS (200 mM K ⁺) | Ca ²⁺ : (P_{Ca}/P_{K} 6) single-channel conductance: 90 pS (50mM Ca ²⁺), 720 pS (210 mM K ⁺) | Ca ²⁺ : (P_{Ca}/P_{K} 6) single-channel conductance: 140 pS (50mM Ca ²⁺), 777 pS (250 mM K ⁺) |
| Comments | RyR1 is also activated by depolarisation <i>via</i> DHP receptor, calmodulin at low cytosolic Ca ²⁺ concentrations, CaM kinase and PKA; antagonised by calmodulin at high cytosolic Ca ²⁺ concentrations | RyR2 is also activated by CaM kinase and PKA; antagonised by calmodulin at high cytosolic Ca ²⁺ concentrations | RyR3 is also activated by calmodulin at low cytosolic Ca ²⁺ concentrations; antagonised by calmodulin at high cytosolic Ca ²⁺ concentrations |

Comments: The modulators of channel function included in this table are those most commonly used to identify ryanodine-sensitive Ca²⁺ 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 [112, 479].

Further reading on Ryanodine receptors

O'Brien F *et al.* (2015) The ryanodine receptor provides high throughput Ca²⁺-release but is precisely regulated by networks of associated proteins: a focus on proteins relevant to phosphorylation. *Biochem Soc Trans* **43**: 426-33 [PMID:26009186]
Samso M. (2017) A guide to the 3D structure of the ryanodine receptor type 1 by cryoEM. *Protein Sci* **26**: 52-68 [PMID:27671094]

Van Petegem F. (2015) Ryanodine receptors: allosteric ion channel giants. *J Mol Biol* **427**: 31-53 [PMID:25134758]

Zalk R *et al.* (2017) Ca²⁺ Release Channels Join the 'Resolution Revolution'. *Trends Biochem Sci* **42**: 543-555 [PMID:28499500]

Transient Receptor Potential channels

Voltage-gated ion channels → [Transient Receptor Potential channels](#)

Overview:

The TRP superfamily of channels (**nomenclature as agreed by NC-IUPHAR [70, 455]**), whose founder member is the *Drosophila* Trp channel, exists in mammals as six families; TRPC, TRPM, TRPV, TRPA, TRPP and TRPML based on amino acid homologies. TRP subunits contain six putative transmembrane domains and assemble as homo- or hetero-tetramers to form cation selective channels with diverse modes of activation and varied permeation properties (reviewed by [307]). Established, or potential, physiological functions of the individual members of the TRP families are discussed in detail in the recommended reviews and a compilation

edited by Islam [168]. The established, or potential, involvement of TRP channels in disease is reviewed in [196, 288] and [290], together with a special edition of *Biochimica et Biophysica Acta* on the subject [288]. The pharmacology of most TRP channels is poorly developed [455]. Broad spectrum agents are listed in the tables along with more selective, or recently recognised, ligands that are flagged by the inclusion of a primary reference. Most TRP channels are regulated by phosphoinositides such as $\text{PtdIns}(4,5)\text{P}_2$ and IP_3 although the effects reported are often complex, occasionally contradictory, and likely to be dependent upon experimental conditions, such as intracellular ATP levels (reviewed by [291,

353, 424]). Such regulation is generally not included in the tables. When thermosensitivity is mentioned, it refers specifically to a high Q₁₀ of gating, often in the range of 10-30, but does not necessarily imply that the channel's function is to act as a 'hot' or 'cold' sensor. In general, the search for TRP activators has led to many claims for temperature sensing, mechanosensation, and lipid sensing. All proteins are of course sensitive to energies of binding, mechanical force, and temperature, but the issue is whether the proposed input is within a physiologically relevant range resulting in a response.

TRPA (ankyrin) family

TRPA1 is the sole mammalian member of this group (reviewed by [114]). TRPA1 activation of sensory neurons contribute to nociception [177, 266, 386]. Pungent chemicals such as mustard oil (AITC), **allicin**, and **cinnamaldehyde** activate TRPA1 by modification of free thiol groups of cysteine side chains, especially those located in its amino terminus [22, 149, 251, 253]. Alkenals with α , β -unsaturated bonds, such as propenal (**acrolein**), butenol (**crotylaldehyde**), and **2-pentenal** can react with free thiols via Michael addition and can activate TRPA1. However, potency

appears to weaken as carbon chain length increases [11, 22]. Covalent modification leads to sustained activation of TRPA1. Chemicals including **carvacrol**, menthol, and local anesthetics reversibly activate TRPA1 by non-covalent binding [186, 222, 460, 461]. TRPA1 is not mechanosensitive under physiological conditions, but can be activated by cold temperatures [86, 187]. The electron cryo-EM structure of TRPA1 [315] indicates that it is a 6-TM homotetramer. Each subunit of the channel contains two short 'pore helices' pointing into the ion selectivity filter, which is big enough to allow permeation of partially hydrated Ca²⁺ ions. A coiled-

coil domain in the carboxy-terminal region forms the cytoplasmic stalk of the channel, and is surrounded by 16 ankyrin repeat domains, which are speculated to interdigitate with an overlying helix-turn-helix and putative β -sheet domain containing cysteine residues targeted by electrophilic TRPA1 agonists. The TRP domain, a helix at the base of S6, runs perpendicular to the pore helices suspended above the ankyrin repeats below, where it may contribute to regulation of the lower pore. The coiled-coil stalk mediates bundling of the four subunits through interactions between predicted α -helices at the base of the channel.

| | |
|----------------------------|--|
| Nomenclature | TRPA1 |
| HGNC, UniProt | TRPA1, O75762 |
| Chemical activators | Isothiocyanates (covalent) and 1,4-dihydropyridines (non-covalent) |
| Physical activators | Cooling (<17°C) (disputed) |
| Activators | acrolein (covalent) (pEC ₅₀ 5.3) [physiological voltage] [22], allicin (covalent) (pEC ₅₀ 5.1) [physiological voltage] [23], Δ⁹-tetrahydrocannabinol (non-covalent) (pEC ₅₀ 4.9) [-60mV] [177], nicotine (non-covalent) (pEC ₅₀ 4.8) [-75mV] [400], thymol (non-covalent) (pEC ₅₀ 4.7) Concentration range: 6.2×10 ⁻⁶ M–2.5×10 ⁻⁵ M [220], URB597 (non-covalent) (pEC ₅₀ 4.6) [287], (-)-menthol (Menthol is also active at the mouse TRPA1, but becomes inhibitory at > 100 μM) (pEC ₅₀ 4–4.5) [186, 458], cinnamaldehyde (covalent) (pEC ₅₀ 4.2) [physiological voltage] [14] – Mouse, icilin (non-covalent) Concentration range: 1×10 ⁻⁴ M [physiological voltage] [386] – Mouse |
| Selective activators | chlorobenzylidene malononitrile (covalent) (pEC ₅₀ 6.7) [41], formalin (covalent. This level of activity is also observed for rat TRPA1) (pEC ₅₀ 3.4) [253, 266] – Mouse |
| Channel blockers | AP18 (pIC ₅₀ 5.5) [328], ruthenium red (pIC ₅₀ 5.5) [-80mV] [280] – Mouse, HC030031 (pIC ₅₀ 5.2) [266] |
| Functional Characteristics | γ = 87–100 pS; conducts mono- and di-valent cations non-selectively (P _{Ca} /P _{Na} = 0.84); outward rectification; activated by elevated intracellular Ca ²⁺ |

TRPC (canonical) family

Members of the TRPC subfamily (reviewed by [2, 8, 27, 31, 111, 194, 312, 337]) fall into the subgroups outlined below. TRPC2 is a pseudogene in humans. It is generally accepted that all TRPC channels are activated downstream of G_{q/11}-coupled receptors, or receptor tyrosine kinases (reviewed by [333, 415, 455]). A comprehensive listing of G-protein coupled receptors that activate TRPC channels is given in [2]. Hetero-oligomeric complexes of TRPC channels and their association with proteins to form signalling complexes are detailed in [8] and [195]. TRPC channels have frequently been proposed to act as store-operated channels (SOCs)

(or components of multimeric complexes that form SOCs), activated by depletion of intracellular calcium stores (reviewed by [8, 61, 321, 334, 359, 475]). However, the weight of the evidence is that they are not directly gated by conventional store-operated mechanisms, as established for Stim-gated Orai channels. TRPC channels are not mechanically gated in physiologically relevant ranges of force. All members of the TRPC family are blocked by **2-APB** and **SKF96365** [139, 140]. Activation of TRPC channels by lipids is discussed by [27].

TRPC1/C4/C5 subgroup

TRPC4/C5 may be distinguished from other TRP channels by their

potentiation by micromolar concentrations of La³⁺. TRPC2 is a pseudogene in humans, but in other mammals appears to be an ion channel localized to microvilli of the vomeronasal organ. It is required for normal sexual behavior in response to pheromones in mice. It may also function in the main olfactory epithelia in mice [236, 304, 305, 472, 473, 474, 487].

TRPC3/C6/C7 subgroup

All members are activated by diacylglycerol independent of protein kinase C stimulation [140].

| | TRPC1 | TRPC2 | TRPC3 | TRPC4 |
|-----------------------|--------------------------------------|--|----------------------|---|
| Nomenclature | TRPC1 | TRPC2 | TRPC3 | TRPC4 |
| HGNC, UniProt | TRPC1, P48995 | TRPC2, – | TRPC3, Q13507 | TRPC4, Q9UBN4 |
| Chemical activators | NO-mediated cysteine S-nitrosylation | Diacylglycerol (SAG, OAG, DOG): strongly inhibited by Ca ²⁺ /CaM once activated by DAG [380] | diacylglycerols | NO-mediated cysteine S-nitrosylation, potentiation by extracellular protons |
| Physical activators | membrane stretch | – | – | – |
| Endogenous activators | – | Intracellular Ca ²⁺ | – | – |
| Activators | – | DOG Concentration range: 1×10 ⁻⁴ M [-80mV] [248] – Mouse, SAG Concentration range: 1×10 ⁻⁴ M [-80mV] [248] – Mouse | – | La³⁺ (μM range) |

| | | | | |
|----------------------------|---|---|---|---|
| (continued) | | | | |
| Nomenclature | TRPC1 | TRPC2 | TRPC3 | TRPC4 |
| Channel blockers | 2-APB [-70mV] [389], Gd³⁺ Concentration range: 2×10^{-5} M [-70mV] [487], La³⁺ Concentration range: 1×10^{-4} M [-70mV] [389] | 2-APB Concentration range: 5×10^{-5} M [-70mV – 80mV] [248] – Mouse, U73122 (may be indirect) Concentration range: 1×10^{-5} M – Mouse | Gd³⁺ (pEC ₅₀ 7) [-60mV] [137], BTP2 (pIC ₅₀ 6.5) [-80mV] [141], Pyr3 (pIC ₅₀ 6.2) [197], La³⁺ (pIC ₅₀ 5.4) [-60mV] [137], 2-APB (pIC ₅₀ 5) [physiological voltage] [234], Ni²⁺ , SKF96365 | ML204 (pIC ₅₀ 5.5) [269], La³⁺ (mM range), SKF96365 , niflumic acid Concentration range: 3×10^{-5} M [-60mV] [432] – Mouse |
| Functional Characteristics | It is not yet clear that TRPC1 forms a homomer. It does form heteromers with TRPC4 and TRPC5 | $\gamma = 42$ pS linear single channel conductance in 150 mM symmetrical Na ⁺ in vomeronasal sensory neurons. P _{Ca} /P _{Na} = 2.7; permeant to Na ⁺ , Cs ⁺ , Ca ²⁺ , but not NMDG [305, 473] | $\gamma = 66$ pS; conducts mono and di-valent cations non-selectively (P _{Ca} /P _{Na} = 1.6); monovalent cation current suppressed by extracellular Ca ²⁺ ; dual (inward and outward) rectification | $\gamma = 30$ –41 pS, conducts mono and di-valent cations non-selectively (P _{Ca} /P _{Na} = 1.1 – 7.7); dual (inward and outward) rectification |
| Nomenclature | TRPC5 | TRPC6 | TRPC7 | |
| HGNC, UniProt | TRPC5 , Q9UL62 | TRPC6 , Q9Y210 | TRPC7 , Q9HCX4 | |
| Chemical activators | NO-mediated cysteine S-nitrosylation (disputed), potentiation by extracellular protons | Diacylglycerols | diacylglycerols | |
| Physical activators | Membrane stretch | Membrane stretch | – | |
| Endogenous activators | intracellular Ca²⁺ (at negative potentials) (pEC ₅₀ 6.2), lysophosphatidylcholine | 20-HETE , arachidonic acid , lysophosphatidylcholine | – | |
| Activators | Gd³⁺ Concentration range: 1×10^{-4} M, La³⁺ (μ M range), Pb²⁺ Concentration range: 5×10^{-6} M, genistein (independent of tyrosine kinase inhibition) [452] | flufenamate , hyp 9 [226], hyperforin [227] | – | |
| Channel blockers | KB-R7943 (pIC ₅₀ 5.9) [207], ML204 (pIC ₅₀ ~5) [269], 2-APB (pIC ₅₀ 4.7) [-80mV] [464], La³⁺ Concentration range: 5×10^{-3} M [-60mV] [178] – Mouse | Gd³⁺ (pIC ₅₀ 5.7) [-60mV] [164] – Mouse, SKF96365 (pIC ₅₀ 5.4) [-60mV] [164] – Mouse, La³⁺ (pIC ₅₀ ~5.2), amiloride (pIC ₅₀ 3.9) [-60mV] [164] – Mouse, Cd²⁺ (pIC ₅₀ 3.6) [-60mV] [164] – Mouse, 2-APB , ACAA , GsMTx-4 , Extracellular H⁺ , KB-R7943 , ML9 | 2-APB , La³⁺ Concentration range: 1×10^{-4} M [-60mV] [303] – Mouse, SKF96365 Concentration range: 2.5×10^{-5} M [-60mV] [303] – Mouse, 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 | $\gamma = 28$ –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 | $\gamma = 25$ –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⁺ | |

TRPM (melastatin) family

Members of the TRPM subfamily (reviewed by [109, 139, 321, 482]) fall into the five subgroups outlined below.

TRPM1/M3 subgroup

In darkness, glutamate released by the photoreceptors and ON-bipolar cells binds to the metabotropic glutamate receptor 6, leading to activation of G_o . This results in the closure of TRPM1. When the photoreceptors are stimulated by light, glutamate release is reduced, and TRPM1 channels are more active, resulting in cell membrane depolarization. Human TRPM1 mutations are associated with congenital stationary night blindness (CSNB), whose patients lack rod function. TRPM1 is also found in melanocytes. Isoforms of TRPM1 may present in melanocytes, melanoma, brain, and retina. In melanoma cells, TRPM1 is prevalent in highly dynamic intracellular vesicular structures [165, 298]. TRPM3 (reviewed by [301]) exists as multiple splice variants four of which (mTRPM3 α 1, mTRPM3 α 2, hTRPM3 α and hTRPM3 $_{1325}$) have been characterised and found to differ significantly in their biophysical properties. TRPM3 is expressed in somatosensory neurons and may be important in development of heat hyperalgesia during inflammation. TRPM3 is frequently coexpressed with TRPA1 and TRPV1 in these neurons.

TRPM3 is expressed in pancreatic beta cells as well as brain, pituitary gland, eye, kidney, and adipose tissue [300, 408]. TRPM3 may contribute to the detection of noxious heat [428].

TRPM2

TRPM2 is activated under conditions of oxidative stress (respiratory burst of phagocytic cells) and ischemic conditions. However, the direct activators are ADPR(P) and calcium. As for many ion channels, PIP₂ must also be present (reviewed by [468]). Numerous splice variants of TRPM2 exist which differ in their activation mechanisms [96]. The C-terminal domain contains a TRP motif, a coiled-coil region, and an enzymatic NUDT9 homologous domain. TRPM2 appears not to be activated by NAD, NAAD, or NAADP, but is directly activated by ADPRP (adenosine-5'-O-diphosphoribose phosphate) [417].

TRPM4/5 subgroup

TRPM4 and TRPM5 have the distinction within all TRP channels of being impermeable to Ca²⁺ [455]. A splice variant of TRPM4 (*i.e.* TRPM4b) and TRPM5 are molecular candidates for endogenous calcium-activated cation (CAN) channels [130]. TRPM4 is active in the late phase of repolarization of the cardiac ventricular action potential. TRPM4 enhances beta adrenergic-mediated inotropy. Mutations are associated with conduction defects [170, 263, 381]. TRPM4 has been shown to be an important regulator

of Ca²⁺ entry in to mast cells [420] and dendritic cell migration [17]. TRPM5 in taste receptor cells of the tongue appears essential for the transduction of sweet, amino acid and bitter stimuli [235]. TRPM5 contributes to the slow afterdepolarization of layer 5 neurons in mouse prefrontal cortex [223].

TRPM6/7 subgroup

TRPM6 and 7 combine channel and enzymatic activities ('chanzymes'). These channels have the unusual property of permeation by divalent (Ca²⁺, Mg²⁺, Zn²⁺) and monovalent cations, high single channel conductances, but overall extremely small inward conductance when expressed to the plasma membrane. They are inhibited by internal Mg²⁺ at ~0.6 mM, around the free level of Mg²⁺ in cells. Whether they contribute to Mg²⁺ homeostasis is a contentious issue. When either gene is deleted in mice, the result is embryonic lethality. The C-terminal kinase region is cleaved under unknown stimuli, and the kinase phosphorylates nuclear histones.

TRPM8

Is a channel activated by cooling and pharmacological agents evoking a 'cool' sensation and participates in the thermosensation of cold temperatures [24, 71, 90] reviewed by [200, 244, 277, 425].

| | | | |
|-----------------------------|--|--|---|
| Nomenclature | TRPM1 | TRPM2 | TRPM3 |
| HGNC, UniProt | TRPM1, Q7Z4N2 | TRPM2, O94759 | TRPM3, Q9HCF6 |
| Physical activators | – | Heat ~ 35°C | heat (Q ₁₀ = 7.2 between 15 - 25°C; Vriens <i>et al.</i> , 2011), hypotonic cell swelling [428] |
| Endogenous activators | pregnenolone sulphate [216] | intracellular cADPR (pEC ₅₀ 5) [-80mV – -60mV] [26, 204, 410], intracellular ADP ribose (pEC ₅₀ 3.9–4.4) [-80mV] [325], intracellular Ca ²⁺ (perhaps <i>via</i> calmodulin), H ₂ O ₂ Concentration range: 5×10 ⁻⁷ M–5×10 ⁻⁵ M [physiological voltage] [110, 138, 209, 376, 443], membrane PIP ₂ [416], arachidonic acid Concentration range: 1×10 ⁻⁵ M–3×10 ⁻⁵ M [physiological voltage] [138] | sphingosine (pEC ₅₀ 4.9) [physiological voltage] [127], epipregnanolone sulphate [259], pregnenolone sulphate [429], sphinganine Concentration range: 2×10 ⁻⁵ M [physiological voltage] [127] |
| Activators | – | GEA 3162 | nifedipine |
| Gating inhibitors | – | – | 2-APB Concentration range: 1×10 ⁻⁴ M [physiological voltage] [464] |
| Endogenous channel blockers | Zn ²⁺ (pIC ₅₀ 6) | Zn ²⁺ (pIC ₅₀ 6), extracellular H ⁺ | Mg ²⁺ Concentration range: 9×10 ⁻³ M [-80mV – 80mV] [299] – Mouse, extracellular Na ⁺ (TRPM3 α 2 only) |

| (continued) | | | |
|----------------------------|---|---|--|
| Nomenclature | TRPM1 | TRPM2 | TRPM3 |
| Channel blockers | – | 2-APB (pIC ₅₀ 6.1) [-60mV] [411], ACAA (pIC ₅₀ 5.8) [physiological voltage] [208], clotrimazole Concentration range: 3×10 ⁻⁶ M–3×10 ⁻⁵ M [-60mV – -15mV] [147], econazole Concentration range: 3×10 ⁻⁶ M–3×10 ⁻⁵ M [-60mV – -15mV] [147], flufenamic acid Concentration range: 5×10 ⁻⁵ M–1×10 ⁻³ M [-60mV – -50mV] [146, 411], miconazole Concentration range: 1×10 ⁻⁵ M [-60mV] [411] | Gd³⁺ Concentration range: 1×10 ⁻⁴ M [-80mV – 80mV] [126, 219], La³⁺ Concentration range: 1×10 ⁻⁴ M [physiological voltage] [126, 219] |
| Functional Characteristics | Conducts mono- and di-valent cations non-selectively, dual rectification (inward and outward) | 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 <i>via</i> 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 |
| HGNC, UniProt | TRPM4, Q8TD43 | TRPM5, Q9NZQ8 | TRPM6, Q9BX84 |
| EC number | – | – | 2.7.11.1 |
| Other channel blockers | Intracellular nucleotides including ATP , ADP , adenosine 5'-monophosphate and AMP-PNP with an IC ₅₀ range of 1.3–1.9 μM | – | – |
| Other chemical activators | – | – | constitutively active, activated by reduction of intracellular Mg ²⁺ |
| Physical activators | Membrane depolarization (V _{1/2} = -20 mV to +60 mV dependent upon conditions) in the presence of elevated [Ca ²⁺] _i , heat (Q ₁₀ = 8.5 @ +25 mV between 15 and 25°C) | membrane depolarization (V _{1/2} = 0 to +120 mV dependent upon conditions), heat (Q ₁₀ = 10.3 @ -75 mV between 15 and 25°C) | – |
| Endogenous activators | intracellular Ca²⁺ (pEC ₅₀ 3.9–6.3) [-100mV – 100mV] [289, 293, 294, 398] | intracellular Ca²⁺ (pEC ₅₀ 4.5–6.2) [-80mV – 80mV] [155, 241, 418] – Mouse | extracellular H⁺ (μM range), intracellular Mg²⁺ |
| Activators | BTP2 (pEC ₅₀ 8.1) [-80mV] [398], decavanadate (pEC ₅₀ 5.7) [-100mV] [293] | – | 2-APB (Potentiation) (pEC ₅₀ 3.4–3.7) [-120mV – 100mV] [230] |
| Gating inhibitors | flufenamic acid (pIC ₅₀ 5.6) [100mV] [418] – Mouse, clotrimazole Concentration range: 1×10 ⁻⁶ M–1×10 ⁻⁵ M [100mV] [297] | – | – |
| Endogenous channel blockers | – | – | Mg²⁺ (inward current mediated by monovalent cations is blocked) (pIC ₅₀ 5.5–6), Ca²⁺ (inward current mediated by monovalent cations is blocked) (pIC ₅₀ 5.3–5.3) |

| | | | |
|----------------------------|--|--|---|
| (continued) | | | |
| Nomenclature | TRPM4 | TRPM5 | TRPM6 |
| Channel blockers | 9-phenanthrol (pIC ₅₀ 4.6–4.8) [122], spermine (pIC ₅₀ 4.2) [100mV] [295], adenosine (pIC ₅₀ 3.2) | flufenamic acid (pIC ₅₀ 4.6), intracellular spermine (pIC ₅₀ 4.4), Extracellular H⁺ (pIC ₅₀ 3.2) | ruthenium red (pIC ₅₀ 7) [voltage dependent -120mV] |
| Functional Characteristics | $\gamma = 23$ 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 | $\gamma = 15$ –25 pS; conducts monovalent cations selectively ($P_{Ca}/P_{Na} = 0.05$); strong outward rectification; slow activation at positive potentials, rapid inactivation at negative potentials; activated and subsequently desensitized by [Ca ²⁺] _i | $\gamma = 40$ –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) and ATP |
| Comments | – | TRPM5 is not blocked by ATP | – |

| | | |
|----------------------------|---|---|
| Nomenclature | TRPM7 | TRPM8 |
| HGNC, UniProt | TRPM7, Q96QT4 | TRPM8, Q7Z2W7 |
| EC number | 2.7.11.1 | – |
| Physical activators | – | depolarization ($V_{\frac{1}{2}} \sim +50$ mV at 15°C), cooling (< 22–26°C) |
| Endogenous activators | intracellular ATP , Extracellular H⁺ , cyclic AMP (elevated cAMP levels) | – |
| Activators | 2-APB Concentration range: >1×10 ⁻³ M [279] – Mouse | icilin (pEC ₅₀ 6.7–6.9) [physiological voltage] [9, 28] – Mouse, (-)-menthol (inhibited by intracellular Ca ²⁺) (pEC ₅₀ 4.6) [-120mV – 160mV] [423] |
| Selective activators | – | WS-12 (pEC ₅₀ 4.9) [physiological voltage] [249, 369] – Rat |
| Channel blockers | spermine (Reversible, voltage dependent inhibition in RBL2H3 rats) (pK _i 5.6) [-110mV – 80mV] [206] – Rat, 2-APB (Reversible inhibition) (pIC ₅₀ 3.8) [-100mV – 100mV] [230] – Mouse, carvacrol (Reversible inhibition) (pIC ₅₀ 3.5) [-100mV – 100mV] [310] – Mouse, Mg²⁺ (Reversible inhibition) (pIC ₅₀ 2.5) [80mV] [279] – Mouse, La³⁺ Concentration range: 2×10 ⁻³ M [-100mV – 100mV] [356] – Mouse | BCTC (pIC ₅₀ 6.1) [physiological voltage] [28] – Mouse, 2-APB (pIC ₅₀ 4.9–5.1) [100mV – -100mV] [157, 284] – Mouse, capsazepine (pIC ₅₀ 4.7) [physiological voltage] [28] – Mouse |
| 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 ²⁺ , Zn ²⁺ , Mn ²⁺ and Mg.ATP (disputed); activated by and intracellular alkalization; 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 desensitization to chemical agonists and adaptation to a cold stimulus in the presence of Ca ²⁺ ; modulated by lysophospholipids and PUFAs |
| Comments | 2-APB acts as a channel blocker in the μ M range. | cannabidiol and Δ^9 -tetrahydrocannabinol are examples of cannabinoid activators. TRPM8 is insensitive to ruthenium red . icilin requires intracellular Ca ²⁺ for full agonist activity. |

TRPML (mucolipin) family

The TRPML family [75, 336, 339, 463, 476] 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 one cause of the neurodegenerative disorder mucopolipidosis 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 and TRPML3 show increased channel activity in low extracellular sodium and are activated by similar small molecules [125]. 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 (Va) mouse phenotype (reviewed by [292, 339]).

| | TRPML1 | TRPML2 | TRPML3 |
|----------------------------|---|---|--|
| Nomenclature | TRPML1 | TRPML2 | TRPML3 |
| HGNC, UniProt | <i>MCOLN1</i> , <i>Q9GZU1</i> | <i>MCOLN2</i> , <i>Q8IZK6</i> | <i>MCOLN3</i> , <i>Q8TDD5</i> |
| 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 acidification) Wild type TRPML3: Activated by Na ⁺ -free extracellular (extracytosolic) solution and membrane depolarization, current inhibited by extracellular acidification (equivalent to intralysosomal acidification) |
| Channel blockers | | | Cd ³⁺ (pIC ₅₀ 4.7) [-80mV] [281] – Mouse |
| 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⁺ \gg Cu ²⁺) protons; monovalent cation flux suppressed by divalent cations (<i>e.g.</i> 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 |

TRPP (polycystin) family

The TRPP family (reviewed by [87, 89, 118, 153, 451]) or PKD2 family is comprised of PKD2, PKD2L1 and PKD2L2, which have been renamed TRPP1, TRPP2 and TRPP3, respectively [455]. They are clearly distinct from the PKD1 family, whose function is unknown. Although still being sorted out, TRPP family members appear to be 6TM spanning nonselective cation channels.

| | TRPP1 | TRPP2 | TRPP3 |
|----------------------------|---|---|---|
| Nomenclature | TRPP1 | TRPP2 | TRPP3 |
| HGNC, UniProt | PKD2 , Q13563 | PKD2L1 , Q9P0L9 | PKD2L2 , Q9NZM6 |
| Activators | – | Calmidazolium (in primary cilia): 10 μ M | – |
| Channel blockers | – | phenamil (pIC ₅₀ 6.9), benzamil (pIC ₅₀ 6), ethylisopropylamiloride (pIC ₅₀ 5), amiloride (pIC ₅₀ 3.8), Gd³⁺ Concentration range: 1×10 ⁻⁴ M [-50mV] [59], La³⁺ Concentration range: 1×10 ⁻⁴ M [-50mV] [59], flufenamate | – |
| Functional Characteristics | The channel properties of TRPP1 (PKD2) have not been determined | Currents have been measured directly from primary cilia and also when expressed on plasma membranes. Primary cilia appear to contain heteromeric TRPP2 + PKD1-L1, underlying a gently outwardly rectifying nonselective conductance (P _{Ca} /P _{Na} ⁻ 6: PKD1-L1 is a 12 TM protein of unknown topology). Primary cilia heteromeric channels have an inward single channel conductance of 80 pS and an outward single channel conductance of 95 pS. Presumed homomeric TRPP2 channels are gently outwardly rectifying. Single channel conductance is 120 pS inward, 200 pS outward [82]. | – |

TRPV (vanilloid) family

Members of the TRPV family (reviewed by [421]) can broadly be divided into the non-selective cation channels, TRPV1-4 and the more calcium selective channels TRPV5 and TRPV6.

TRPV1-V4 subfamily

TRPV1 is involved in the development of thermal hyperalgesia following inflammation and may contribute to the detection of noxious heat (reviewed by [330, 382, 395]). Numerous splice vari-

ants of TRPV1 have been described, some of which modulate the activity of TRPV1, or act in a dominant negative manner when co-expressed with TRPV1 [366]. The pharmacology of TRPV1 channels is discussed in detail in [132] and [427]. TRPV2 is probably not a thermosensor in man [309], but has recently been implicated in innate immunity [238]. TRPV3 and TRPV4 are both thermosensitive. There are claims that TRPV4 is also mechanosensitive, but this has not been established to be within a physiological range in

a native environment [47, 232].

TRPV5/V6 subfamily

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 [81, 104, 278, 449]).

| | TRPV1 | TRPV2 |
|---------------------------|--|---|
| Nomenclature | TRPV1 | TRPV2 |
| HGNC, UniProt | TRPV1 , Q8NER1 | TRPV2 , Q9YSS1 |
| Other chemical activators | NO-mediated cysteine S-nitrosylation | – |
| Physical activators | depolarization (V _{1/2} ~0 mV at 35°C), noxious heat (> 43°C at pH 7.4) | noxious heat (> 35°C; rodent, not human) [285] |
| Endogenous activators | extracellular H ⁺ (at 37°C) (pEC ₅₀ 5.4), 12S-HPETE (pEC ₅₀ 5.1) [-60mV] [161] – Rat, 15S-HPETE (pEC ₅₀ 5.1) [-60mV] [161] – Rat, LTB₄ (pEC ₅₀ 4.9) [-60mV] [161] – Rat, 5S-HETE | – |
| Activators | resiniferatoxin (pEC ₅₀ 8.4) [physiological voltage] [374], capsaicin (pEC ₅₀ 7.5) [-100mV – 160mV] [423], camphor , diphenylboronic anhydride , phenylacetylirivanil [12] | 2-APB (pEC ₅₀ 5) [285, 340] – Rat, Δ^9-tetrahydrocannabinol (pEC ₅₀ 4.8) [340] – Rat, cannabidiol (pEC ₅₀ 4.5) [340], probenecid (pEC ₅₀ 4.5) [15] – Rat, 2-APB (pEC ₅₀ 3.8–3.9) [physiological voltage] [157, 179] – Mouse, diphenylboronic anhydride Concentration range: 1×10 ⁻⁴ M [-80mV] [66, 179] – Mouse |
| Selective activators | olvanil (pEC ₅₀ 7.7) [physiological voltage] [374], DkTx (pEC ₅₀ 6.6) [physiological voltage] [36] – Rat | – |

| | | |
|----------------------------|--|--|
| (continued) | | |
| Nomenclature | TRPV1 | TRPV2 |
| Channel blockers | 5'-iodoresiniferatoxin (pIC ₅₀ 8.4), 6-iodo-nordihydrocapsaicin (pIC ₅₀ 8), BCTC (pIC ₅₀ 7.5) [57], capsazepine (pIC ₅₀ 7.4) [-60mV] [265], ruthenium red (pIC ₅₀ 6.7–7) | ruthenium red (pIC ₅₀ 6.2), TRIM Concentration range: 5×10 ⁻⁴ M [179] – Mouse |
| Selective channel blockers | AMG517 (pIC ₅₀ 9) [35], AMG628 (pIC ₅₀ 8.4) [435] – Rat, A425619 (pIC ₅₀ 8.3) [100], A778317 (pIC ₅₀ 8.3) [30], SB366791 (pIC ₅₀ 8.2) [134], JYL1421 (pIC ₅₀ 8) [440] – Rat, JNJ17203212 (pIC ₅₀ 7.8) [physiological voltage] [393], SB452533 (pK _B 7.7), SB705498 (pIC ₅₀ 7.1) [133] | – |
| Labelled ligands | [³H]A778317 (Channel blocker) (pK _d 8.5) [30], [¹²⁵I]resiniferatoxin (Channel blocker) (pIC ₅₀ 8.4) [-50mV] [430] – Rat, [³H]resiniferatoxin (Activator) | – |
| Functional Characteristics | γ = 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); 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 Ca ²⁺ / calmodulin; cooling reduces vanilloid-evoked currents; may be tonically active at body temperature | 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 |
| | | |
| Nomenclature | TRPV3 | TRPV4 |
| HGNC, UniProt | TRPV3, Q8NET8 | TRPV4, Q9HBA0 |
| Other chemical activators | NO-mediated cysteine S-nitrosylation | Epoxyeicosatrienoic acids and NO-mediated cysteine S-nitrosylation |
| Physical activators | depolarization (V _{1/2} ~ +80 mV, reduced to more negative values following heat stimuli), heat (23°C - 39°C, temperature threshold reduces with repeated heat challenge) | Constitutively active, heat (> 24°C - 32°C), mechanical stimuli |
| Activators | incensole acetate (pEC ₅₀ 4.8) [273] – Mouse, 2-APB (pEC ₅₀ 4.6) [-80mV – 80mV] [67] – Mouse, diphenylboronic anhydride (pEC ₅₀ 4.1–4.2) [voltage dependent -80mV – 80mV] [66] – Mouse, (-)-menthol (pEC ₅₀ 1.7) [-80mV – 80mV] [252] – Mouse, camphor Concentration range: 1×10 ⁻³ M–2×10 ⁻³ M [-60mV] [271] – Mouse, carvacrol Concentration range: 5×10 ⁻⁴ M [-80mV – 80mV] [461] – Mouse, eugenol Concentration range: 3×10 ⁻³ M [-80mV – 80mV] [461] – Mouse, thymol Concentration range: 5×10 ⁻⁴ M [-80mV – 80mV] [461] – Mouse | phorbol 12-myristate 13-acetate (pEC ₅₀ 7.9) [physiological voltage] [459] |
| Selective activators | 6-tert-butyl-m-cresol (pEC ₅₀ 3.4) [426] – Mouse | GSK1016790A (pEC ₅₀ 8.7) [physiological voltage] [409], 4α-PDH (pEC ₅₀ 7.1) [physiological voltage] [198] – Mouse, RN1747 (pEC ₅₀ 6.1) [physiological voltage] [422], bisandrographolide (pEC ₅₀ 6) [-60mV] [377] – Mouse, 4α-PDD Concentration range: 3×10 ⁻⁷ M [physiological voltage] [459] |
| Channel blockers | diphenyltetrahydrofuran (pIC ₅₀ 5–5.2) [-80mV – 80mV] [66] – Mouse, ruthenium red Concentration range: 1×10 ⁻⁶ M [-60mV] [322] – Mouse | Gd³⁺ , La³⁺ , ruthenium red Concentration range: 1×10 ⁻⁶ M [physiological voltage] [172], ruthenium red Concentration range: 2×10 ⁻⁷ M [physiological voltage] [131] – Rat |
| Selective channel blockers | – | HCO67047 (pIC ₅₀ 7.3) [-40mV] [102], RN1734 (pIC ₅₀ 5.6) [physiological voltage] [422] |

| | | |
|----------------------------|---|--|
| (continued) | | |
| Nomenclature | TRPV3 | TRPV4 |
| Functional Characteristics | $\gamma = 197$ pS at +40 to +80 mV, 48 pS at negative potentials; conducts mono- and di-valent cations; outward rectification; potentiated by arachidonic acid | $\gamma = \sim 60$ pS at –60 mV, ~ 90 –100 pS at +60 mV; conducts mono- and di-valent cations with a preference for divalents ($P_{Ca}/P_{Na} = 6$ –10); dual (inward and outward) rectification; potentiated by intracellular Ca^{2+} via Ca^{2+} /calmodulin; inhibited by elevated intracellular Ca^{2+} via an unknown mechanism ($IC_{50} = 0.4$ μ M) |
| | | |
| Nomenclature | TRPV5 | TRPV6 |
| HGNC, UniProt | TRPV5, Q9NQAS | TRPV6, Q9H1D0 |
| Other channel blockers | $Pb^{2+} = Cu^{2+} = Gd^{3+} > Cd^{2+} > Zn^{2+} > La^{3+} > Co^{2+} > Fe^{2+}$ | – |
| Activators | constitutively active (with strong buffering of intracellular Ca^{2+}) | 2-APB constitutively active (with strong buffering of intracellular Ca^{2+}) |
| Channel blockers | ruthenium red (pIC_{50} 6.9), Mg²⁺ | ruthenium red (pIC_{50} 5) [–80mV] [152] – Mouse, Cd²⁺ , La³⁺ , Mg²⁺ |
| Functional Characteristics | $\gamma = 59$ –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 and intracellular acidosis; upregulated by 1,25-dihydrovitamin D3 | $\gamma = 58$ –79 pS for monovalent ions at negative potentials, conducts mono- and di-valents with high selectivity for divalents ($P_{Ca}/P_{Na} > 130$); voltage- and time-dependent inward rectification; inhibited by intracellular Ca^{2+} promoting fast and slow inactivation; gated by voltage-dependent channel blockade by intracellular Mg^{2+} ; slow inactivation due to Ca^{2+} -dependent calmodulin binding; phosphorylation by PKC inhibits Ca^{2+} -calmodulin binding and slow inactivation; upregulated by 1,25-dihydroxyvitamin D3 |

Comments:**TRPA (ankyrin) family**

Agents activating TRPA1 in a covalent manner are thiol reactive electrophiles that bind to cysteine and lysine residues within the cytoplasmic domain of the channel [149, 250]. TRPA1 is activated by a wide range of endogenous and exogenous compounds and only a few representative examples are mentioned in the table; an exhaustive listing can be found in [16]. In addition, TRPA1 is potentially activated by intracellular zinc ($EC_{50} = 8$ nM) [10, 156].

TRPM (melastatin) family

Ca^{2+} activates all splice variants of TRPM2, but other activators listed are effective only at the full length isoform [96]. Inhibition of TRPM2 by **clotrimazole**, **miconazole**, **econazole**, **flufenamic acid** is largely irreversible. 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 [418]. The $V_{1/2}$ 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 $V_{1/2}$ is shifted in the hyperpolarizing direction both by decreasing temperature and by exogenous agonists, such as (-)-**menthol** [423] whereas antagonists produce depolarizing shifts in $V_{1/2}$ [276]. The $V_{1/2}$ for the native channel is far more positive than that of heterologously expressed TRPM8 [276]. 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 [254]. Intracellular pH modulates activation of TRPM8 by cold and **icilin**, but not

(-)-**menthol** [9].

TRPML (mucolipin) family

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 characterisation by patch-clamp recording [94, 123, 191, 281, 462]. Data for wild type TRPML3 are also tabulated [191, 192, 281, 462]. It should be noted that alternative methodologies, particularly in the case of TRPML1, have resulted in channels with differing biophysical characteristics (reviewed by [336]).

TRPP (polycystin) family

Data in the table are extracted from [79, 89] and [370]. Broadly similar single channel conductance, mono- and di-valent cation selectivity and sensitivity to blockers are observed for TRPP2 co-

expressed with TRPP1 [88]. Ca²⁺, Ba²⁺ and Sr²⁺ permeate TRPP3, but reduce inward currents carried by Na⁺. Mg²⁺ is largely impermeant and exerts a voltage dependent inhibition that increases with hyperpolarization.

TRPV (vanilloid) family

Activation of TRPV1 by depolarisation is strongly temperature-dependent via a channel opening rate that increases with increasing temperature. The V_{1/2} is shifted in the hyperpolarizing direction both by increasing temperature and by exogenous agonists [423]. The sensitivity of TRPV4 to heat, but not 4 α -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 [296]). Activation of TRPV4 by cell swelling, but not heat, or phorbol esters, is mediated via the formation of epoxyeicosatrienoic acids. Phorbol esters bind directly to TRPV4. TRPV5 preferentially conducts Ca²⁺ under physiological conditions, but in the absence of extracellular Ca²⁺, conducts monovalent cations. Single channel conductances listed for TRPV5 and TRPV6 were determined in divalent cation-free extracellular solution. Ca²⁺-induced inactivation occurs at hyperpolarized potentials when Ca²⁺ is present extracellularly. Single channel events cannot be resolved (proba-

bly 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 Mg²⁺ is voltage-dependent. Intracellular Mg²⁺ 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 Ca²⁺-dependent inactivation and recovery from inactivation. TRPV5 and TRPV6 function as homo- and hetero-tetramers.

Further reading on Transient Receptor Potential channels

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Voltage-gated calcium channels

[Voltage-gated ion channels](#) → [Voltage-gated calcium channels](#)

Overview: Calcium (Ca²⁺) channels are voltage-gated ion channels present in the membrane of most excitable cells. The nomenclature for Ca²⁺ channels was proposed by [101] and **approved by the NC-IUPHAR Subcommittee on Ca²⁺ channels** [54]. Ca²⁺ channels form hetero-oligomeric complexes. The α 1 subunit is pore-forming and provides the binding site(s) for practically all agonists and antagonists. The 10 cloned α 1-subunits

can be grouped into three families: (1) the high-voltage activated dihydropyridine-sensitive (L-type, Cav1.x) channels; (2) the high-voltage activated dihydropyridine-insensitive (Cav2.x) channels and (3) the low-voltage-activated (T-type, Cav3.x) channels. Each α 1 subunit has four homologous repeats (I–IV), each repeat having six transmembrane domains and a pore-forming region between transmembrane domains S5 and S6. Gating is thought to be associated with the membrane-spanning S4

segment, which contains highly conserved positive charges. Many of the α 1-subunit genes give rise to alternatively spliced products. At least for high-voltage activated channels, it is likely that native channels comprise co-assemblies of α 1, β and α 2- δ subunits. The γ subunits have not been proven to associate with channels other than the α 1s skeletal muscle Cav1.1 channel. The α 2- δ 1 and α 2- δ 2 subunits bind [gabapentin](#) and [pregabalin](#).

| | | | | |
|---------------------------------------|---|--|---|---|
| Nomenclature | Ca_v1.1 | Ca_v1.2 | Ca_v1.3 | Ca_v1.4 |
| HGNC, UniProt | CACNA1S, Q13698 | CACNA1C, Q13936 | CACNA1D, Q01668 | CACNA1F, O60840 |
| Activators | FPL64176 (pEC ₅₀ ~7.8), (-)-(S)-BayK8644 (pEC ₅₀ ~7.8) | (-)-(S)-BayK8644 (pEC ₅₀ ~7.8), FPL64176 Concentration range: 1×10 ⁻⁶ M-5×10 ⁻⁶ M [243] – Rat | FPL64176 (pEC ₅₀ ~7.8), (-)-(S)-BayK8644 (pEC ₅₀ ~7.8) | (-)-(S)-BayK8644 (pEC ₅₀ ~7.8) |
| Gating inhibitors | nifedipine (pIC ₅₀ 6.3) Concentration range: 1×10 ⁻⁷ M-1×10 ⁻⁴ M [voltage dependent -90mV] [215] – Rat, nimodipine (pIC ₅₀ ~6) [-70mV], nitrendipine (pIC ₅₀ 6) [-80mV] [25] – Rat | nifedipine (pIC ₅₀ 7.7) [-80mV] [329] – Rat, nimodipine (pIC ₅₀ 6.8) [-80mV] [465] – Rat, nitrendipine (pIC ₅₀ 6) [-80mV] [465] – Rat | nitrendipine (pIC ₅₀ 8.4) [373], nifedipine (pIC ₅₀ 7.7) [373], nimodipine (pIC ₅₀ 5.7–6.6) [-80mV – -40mV] [357, 465] – Rat | nifedipine (pIC ₅₀ 6) [-100mV] [267], nimodipine (pIC ₅₀ ~6) [-70mV], nitrendipine (pIC ₅₀ ~6) [-70mV] |
| Selective gating inhibitors | – | – | – | – |
| Channel blockers | diltiazem , verapamil | diltiazem , verapamil | verapamil | diltiazem (pIC ₅₀ 4) [-80mV] [21] – Mouse, verapamil Concentration range: 1×10 ⁻⁴ M [-80mV] [21] – Mouse |
| Sub/family-selective channel blockers | calciseptine | calciseptine | – | – |
| Functional Characteristics | L-type calcium current: High voltage-activated, slow voltage dependent inactivation | L-type calcium current: High voltage-activated, slow voltage-dependent inactivation, rapid calcium-dependent inactivation | L-type calcium current: Voltage-activated, slow voltage-dependent inactivation, more rapid calcium-dependent inactivation | L-type calcium current: Moderate voltage-activated, slow voltage-dependent inactivation |
| Comments | – | – | Ca _v 1.3 activates more negative potentials than Ca _v 1.2 and is incompletely inhibited by dihydropyridine antagonists. | Ca _v 1.4 is less sensitive to dihydropyridine antagonists than other Cav1 channels |

| | | | |
|---------------------------------------|--|--|--|
| Nomenclature | Ca_v2.1 | Ca_v2.2 | Ca_v2.3 |
| HGNC, UniProt | CACNA1A, O00555 | CACNA1B, Q00975 | CACNA1E, Q15878 |
| Selective gating inhibitors | ω-agatoxin IVA (P current component: K _d = ~2nM, Q component K _d = > 100nM) (pIC ₅₀ 7–8.7) [-100mV – -90mV] [38, 270] – Rat, ω-agatoxin IVB (pK _d 8.5) [-80mV] [4] – Rat | – | SNX482 (pIC ₅₀ 7.5–8) [physiological voltage] [286] |
| Channel blockers | – | – | Ni²⁺ (pIC ₅₀ 4.6) [-90mV] [448] |
| Sub/family-selective channel blockers | ω-conotoxin MVIIC (pIC ₅₀ 8.2–9.2) Concentration range: 2×10 ⁻⁶ M-5×10 ⁻⁶ M [physiological voltage] [229] – Rat | ω-conotoxin GVIA (pIC ₅₀ 10.4) [-80mV] [229] – Rat, ω-conotoxin MVIIC (pIC ₅₀ 6.1–8.5) [-80mV] [148, 229, 264] – Rat | – |

| | | | |
|----------------------------|---|--|--|
| (continued) | | | |
| Nomenclature | Ca_v2.1 | Ca_v2.2 | Ca_v2.3 |
| Functional Characteristics | P/Q-type calcium current: Moderate voltage-activated, moderate voltage-dependent inactivation | N-type calcium current: High voltage-activated, moderate voltage-dependent inactivation | R-type calcium current: Moderate voltage-activated, fast voltage-dependent inactivation |
| | | | |
| Nomenclature | Ca_v3.1 | Ca_v3.2 | Ca_v3.3 |
| HGNC, UniProt | CACNA1G, O43497 | CACNA1H, O95180 | CACNA1I, Q9P0X4 |
| Gating inhibitors | kurtoxin (pIC ₅₀ 7.3–7.8) [-90mV] [63, 371] – Rat | kurtoxin (pIC ₅₀ 7.3–7.6) [-90mV] [63, 371] – Rat | – |
| Channel blockers | mibefradil (pIC ₅₀ 6–6.6) [-110mV – -100mV] [261], Ni²⁺ (pIC ₅₀ 3.6–3.8) [voltage dependent -90mV] [218] – Rat | mibefradil (pIC ₅₀ 5.9–7.2) [-110mV – -80mV] [261], Ni²⁺ (pIC ₅₀ 4.9–5.2) [voltage dependent -90mV] [218] | mibefradil (pIC ₅₀ 5.8) [-110mV] [261], Ni²⁺ (pIC ₅₀ 3.7–4.1) [voltage dependent -90mV] [218] – Rat |
| Functional Characteristics | T-type calcium current: Low voltage-activated, fast voltage-dependent inactivation | T-type calcium current: Low voltage-activated, fast voltage-dependent inactivation | T-type calcium current: Low voltage-activated, moderate voltage-dependent inactivation |

Comments: 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. Both of these physiologically defined current types are conducted by alternative forms of Cav2.1. Ziconotide (a synthetic peptide equivalent to *ω-conotoxin MVIIA*) has been approved for the treatment of chronic pain [447].

Further reading on Voltage-gated calcium channels

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Voltage-gated proton channel

Voltage-gated ion channels → Voltage-gated proton channel

Overview: The voltage-gated proton channel (provisionally denoted H_v1) is a putative 4TM proton-selective channel gated by membrane depolarization and which is sensitive to the transmembrane pH gradient [49, 84, 85, 346, 362]. The structure of H_v1 is homologous to the voltage sensing domain (VSD) of the superfamily of voltage-gated ion channels (*i.e.* segments S1 to S4)

and contains no discernable pore region [346, 362]. Proton flux through H_v1 is instead most likely mediated by a water wire completed in a crevice of the protein when the voltage-sensing S4 helix moves in response to a change in transmembrane potential [345, 453]. H_v1 expresses largely as a dimer mediated by intracellular C-terminal coiled-coil interactions [231] but individual promoters

nonetheless support gated H⁺ flux via separate conduction pathways [203, 221, 327, 412]. Within dimeric structures, the two protomers do not function independently, but display co-operative interactions during gating resulting in increased voltage sensitivity, but slower activation, of the dimeric, *versus* monomeric, complexes [121, 413].

| | |
|----------------------------|--|
| Nomenclature | H _v 1 |
| HGNC, UniProt | HVCN1, Q96D96 |
| Channel blockers | Zn ²⁺ (pIC ₅₀ ~5.7–6.3), Cd ²⁺ (pIC ₅₀ ~5) |
| Functional Characteristics | Activated by membrane depolarization mediating macroscopic currents with time-, voltage- and pH-dependence; outwardly rectifying; voltage dependent kinetics with relatively slow current activation sensitive to extracellular pH and temperature, relatively fast deactivation; voltage threshold for current activation determined by pH gradient ($\Delta\text{pH} = \text{pH}_o - \text{pH}_i$) across the membrane |

Comments: The voltage threshold (V_{thr}) for activation of H_v1 is not fixed but is set by the pH gradient across the membrane such that V_{thr} is positive to the Nernst potential for H⁺, which ensures that only outwardly directed flux of H⁺ occurs under physiological conditions [49, 84, 85]. Phosphorylation of H_v1 within the N-terminal domain by PKC enhances the gating of the chan-

nel [274]. Tabulated IC₅₀ values for Zn²⁺ and Cd²⁺ are for heterologously expressed human and mouse H_v1 [346, 362]. Zn²⁺ is not a conventional pore blocker, but is coordinated by two, or more, external protonation sites involving histamine residues [346]. Zn²⁺ binding may occur at the dimer interface between pairs of histamine residues from both monomers where it may

interfere with channel opening [275]. Mouse knockout studies demonstrate that H_v1 participates in charge compensation in granulocytes during the respiratory burst of NADPH oxidase-dependent reactive oxygen species production that assists in the clearance of bacterial pathogens [347]. Additional physiological functions of H_v1 are reviewed by [49].

Further reading on Voltage-gated proton channel

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Voltage-gated sodium channels

Voltage-gated ion channels → Voltage-gated sodium channels

Overview: Sodium channels are voltage-gated sodium-selective ion channels present in the membrane of most excitable cells. Sodium channels comprise of one pore-forming α subunit, which may be associated with either one or two β subunits [169]. 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. The

crystal structure of the bacterial NavAb channel has revealed a number of novel structural features compared to earlier potassium channel structures including a short selectivity filter with ion selectivity determined by interactions with glutamate side chains [316]. Interestingly, the pore region is penetrated by fatty acyl chains that extend into the central cavity which may allow the entry of small, hydrophobic pore-blocking drugs [316]. Auxiliary β 1, β 2, β 3 and β 4 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) [119] and approved by the NC-IUPHAR Subcommittee on sodium channels (Catterall *et al.*, 2005, [52]).

| | | | | |
|---------------------------------------|--|--|---|---|
| Nomenclature | Nav1.1 | Nav1.2 | Nav1.3 | Nav1.4 |
| HGNC, UniProt | SCN1A, P35498 | SCN2A, Q99250 | SCN3A, Q9NY46 | SCN4A, P35499 |
| Sub/family-selective activators | batrachotoxin, veratridine | batrachotoxin (pK_d 9.1) [physiological voltage] [237] – Rat, veratridine (pK_d 5.2) [physiological voltage] [53] – Rat | batrachotoxin, veratridine | batrachotoxin Concentration range: 5×10^{-6} M [-100mV] [438] – Rat, veratridine Concentration range: 2×10^{-4} M [-100mV] [438] – Rat |
| Channel blockers | tetrodotoxin (pK_d 8) [-100mV] [378] – Rat | – | – | – |
| Sub/family-selective channel blockers | Hm1a [306] – Rat, saxitoxin | saxitoxin ($pI_{C_{50}}$ 8.8) [-120mV] [40] – Rat, tetrodotoxin ($pI_{C_{50}}$ 8) [-120mV] [40] – Rat, lacosamide ($pI_{C_{50}}$ 4.5) [-80mV] [1] – Rat | tetrodotoxin ($pI_{C_{50}}$ 8.4) [60], saxitoxin | saxitoxin ($pI_{C_{50}}$ 8.4) [-100mV] [324] – Rat, tetrodotoxin ($pI_{C_{50}}$ 7.6) [-120mV] [56], μ -conotoxin GIIIA ($pI_{C_{50}}$ 5.9) [-100mV] [56] |
| Functional Characteristics | Activation $V_{0.5} = -20$ mV. Fast inactivation ($\tau = 0.7$ ms for peak sodium current). | Activation $V_{0.5} = -24$ mV. Fast inactivation ($\tau = 0.8$ ms for peak sodium current). | Activation $V_{0.5} = -24$ mV. Fast inactivation (0.8 ms) | Activation $V_{0.5} = -30$ mV. Fast inactivation (0.6 ms) |

| | | | | | |
|---------------------------------|--|----------------------------|----------------------------|----------------|----------------|
| Nomenclature | Nav1.5 | Nav1.6 | Nav1.7 | Nav1.8 | Nav1.9 |
| HGNC, UniProt | SCN5A, Q14524 | SCN8A, Q9UQD0 | SCN9A, Q15858 | SCN10A, Q9Y5Y9 | SCN11A, Q9UI33 |
| Sub/family-selective activators | batrachotoxin (pK_d 7.6) [physiological voltage] [368] – Rat, veratridine (pEC_{50} 6.3) [-30mV] [433] – Rat | batrachotoxin, veratridine | batrachotoxin, veratridine | – | – |

| (continued) | | | | | |
|---------------------------------------|---|---|--|---|---|
| Nomenclature | Nav1.5 | Nav1.6 | Nav1.7 | Nav1.8 | Nav1.9 |
| Sub/family-selective channel blockers | tetrodotoxin (pK _d 5.8) [-80mV] [74, 477] – Rat | tetrodotoxin (pIC ₅₀ 9) [-130mV] [91] – Rat, saxitoxin | tetrodotoxin (pIC ₅₀ 7.6) [-100mV] [199], saxitoxin (pIC ₅₀ 6.2) [431] | tetrodotoxin (pIC ₅₀ 4.2) [-60mV] [5] – Rat | tetrodotoxin (pIC ₅₀ 4.4) [-120mV] [76] – Rat |
| Selective channel blockers | – | – | – | PF-01247324 (pIC ₅₀ 6.7) [voltage dependent] [317] | – |
| Functional Characteristics | Activation V _{0.5} = -26 mV. Fast inactivation (τ = 1 ms for peak sodium current). | Activation V _{0.5} = -29 mV. Fast inactivation (1 ms) | Activation V _{0.5} = -27 mV. Fast inactivation (0.5 ms) | Activation V _{0.5} = -16 mV. Inactivation (6 ms) | Activation V _{0.5} = -32 mV. Slow inactivation (16 ms) |

Comments: Sodium channels are also blocked by local anaesthetic agents, antiarrhythmic drugs and antiepileptic drugs. In general, these drugs are not highly selective among channel subtypes. There are two clear functional fingerprints for distinguishing different subtypes. These are sensitivity to tetrodotoxin (Nav1.5, Nav1.8 and Nav1.9 are much less sensitive to block) and rate of fast inactivation (Nav1.8 and particularly Nav1.9 inactivate more slowly). All sodium channels also have a slow inactivation process that is engaged during long depolarizations (> 100 msec) or repetitive trains of stimuli. All sodium channel subtypes are blocked by intracellular QX-314.

Further reading on Voltage-gated sodium channels

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