Transient Receptor Potential channels (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database

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Abstract

The TRP superfamily of channels (nomenclature as agreed by NC-IUPHAR [145, 915]), 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 [630]). Established, or potential, physiological functions of the individual members of the TRP families are discussed in detail in the recommended reviews and in a number of books [344, 589, 979, 216]. The established, or potential, involvement of TRP channels in disease is reviewed in [384, 588] and [591], together with a special edition of Biochemica et Biophysica Acta on the subject [588]. Additional disease related reviews, for pain [542], stroke [967], sensation and inflammation [843], itch [109], and airway disease [261, 896], are available. The pharmacology of most TRP channels has been advanced in recent years. 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. See Rubaiy (2019) for a review of pharmacological tools for TRPC1/C4/C5 channels [692]. Most TRP channels are regulated by phosphoinositides such as PtIns(4,5)P2 although the effects reported are often complex, occasionally contradictory, and likely to be dependent upon experimental conditions, such as intracellular ATP levels (reviewed by [862, 592, 689]). 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 [46]). TRPA1 activation of sensory neurons contribute to nociception [356, 763, 516]. 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 [491, 47, 311, 493]. Alkenals with α, β-unsaturated bonds, such as propenal (acrolein), butenal (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 [21, 47]. Covalent modification leads to sustained activation of TRPA1. Chemicals including carvacrol, menthol, and local anesthetics reversibly activate TRPA1 by non-covalent binding [364, 438, 923, 922]. TRPA1 is not mechanosensitive under physiological conditions, but can be activated by cold temperatures [365, 175]. The electron cryo-EM structure of TRPA1 [639] 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 Ca\(^{2+}\) ions.

TRPC (canonical) family

Members of the TRPC subfamily (reviewed by [239, 673, 14, 4, 79, 382, 638, 55]) 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 [661, 814, 915]). A comprehensive listing of G-protein coupled receptors that activate TRPC channels is given in [4]. Heterooligomeric complexes of TRPC channels and their association with proteins to form signalling complexes are detailed in [14] and [383]. TRPC channels have frequently been proposed to act as store-operated channels (SOCs) (or components of mulimeric complexes that form SOCs), activated by depletion of intracellular calcium stores (reviewed by [640, 14, 665, 703, 954, 132, 626, 51, 133]). 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 [295, 294]. Activation of TRPC channels by lipids is discussed by [55]. Important progress has been recently made in TRPC pharmacology [692, 529, 372, 87]. TRPC channels regulate a variety of physiological functions and are implicated in many human diseases [248, 56, 759, 879].

TRPC1/C4/C5 subgroup

TRPC1 alone may not form a functional ion channel [191]. TRPC4/C5 may be distinguished from other TRP channels by their potentiation by micromolar concentrations of La\(^{3+}\). 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 [951, 625, 624, 952, 462, 988, 947].

TRPC3/C6/C7 subgroup

All members are activated by diacylglycerol independent of protein kinase C stimulation [295].

TRPM (melastatin) family

Members of the TRPM subfamily (reviewed by [30, 294, 640, 978]) 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 Go. 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 melanocytes. Isoforms of TRPM1 may present in melanocytes, melanoma, brain, and retina. In melanoma cells, TRPM1 is prevalent in highly dynamic intracellular vesicular structures [341, 609]. TRPM3 (reviewed by [615]) exists as multiple splice variants which differ significantly in their biophysical properties. TRPM3 is expressed in somatosensory neurons and may be important in development of heat hyperalgesia during inflammation (see review [803]). 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 [614, 802]. TRPM3 may contribute to the detection of noxious heat [870].

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, PIP_{2} must also be present (reviewed by [935]). Numerous splice variants of TRPM2 exist which differ in their activation mechanisms [200]. 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-disphosphoribose phosphate) [827]. TRPM2 is involved in warmth sensation [724], and contributes to neurological diseases [61]. Recent study shows that 2'-deoxy-ADPR is an endogenous TRPM2 superagonist [231].

TRPM4/5 subgroup
TRPM4 and TRPM5 have the distinction within all TRP channels of being impermeable to Ca^{2+} [915]. A splice variant of TRPM4 (i.e. TRPM4b) and TRPM5 are molecular candidates for endogenous calcium-activated cation (CAN) channels [278]. TRPM4 is active in the late phase of repolarization of the cardiac ventricular action potential. TRPM4 deletion or knockout enhances beta adrenergic-mediated inotropy [507]. Mutations are associated with conduction defects [347, 507, 753]. TRPM4 has been shown to be an important regulator of Ca^{2+} entry in to mast cells [847] and dendritic cell migration [39]. TRPM5 in taste receptor cells of the tongue appears essential for the transduction of sweet, amino acid and bitter stimuli [460]. TRPM5 contributes to the slow afterdepolarization of layer 5 neurons in mouse prefrontal cortex [439]. Both TRPM4 and TRPM5 are required transduction of taste stimuli [206].

TRPM6/7 subgroup
TRPM6 and 7 combine channel and enzymatic activities (‘chanzymes’). These channels have the unusual property of permeation by divalent (Ca^{2+}, Mg^{2+}, Zn^{2+}) and monovalent cations, high single channel conductances, but overall extremely small inward conductance when expressed to the plasma membrane. They are inhibited by internal Mg^{2+} at ~0.6 mM, around the free level of Mg^{2+} in cells. Whether they contribute to Mg^{2+} 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. TRPM7 is responsible for oxidant- induced Zn^{2+} release from intracellular vesicles [3] and contributes to intestinal mineral absorption essential for postnatal survival [532].

TRPM8
Is a channel activated by cooling and pharmacological agents evoking a ‘cool’ sensation and participates in the thermosensation of cold temperatures [50, 147, 186] reviewed by [864, 481, 391, 556].

TRPML (mucolipin) family
The TRPML family [676, 964, 670, 926, 156] 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) cause the neurodegenerative disorder mucolipidosis type IV (MLIV) in man. TRPML1 is a cation selective ion channel that is important for sorting/transport of endosomes in the late endocytotic pathway and specifically, fission from late endosome-lysosome hybrid vesicles and lysosomal exocytosis [704]. TRPML2 and TRPML3 show increased channel activity in low extracellular sodium and are activated by similar small molecules [270]. A naturally occurring gain of function mutation in TRPML3 (i.e. A419P) results in the varitint waddler (Va) mouse phenotype (reviewed by [676, 593]).

TRPP (polycystin) family

The TRPP family (reviewed by [179, 177, 252, 905, 320]) or PKD2 family is comprised of PKD2 (PC2), PKD2L1 (PC2L1), PKD2L2 (PC2L2), which have been renamed TRPP1, TRPP2 and TRPP3, respectively [915]. It should also be noted that the nomenclature of PC2 was TRPP2 in old literature. However, PC2 has been uniformed to be called TRPP2 [293]. PKD2 family channels are clearly distinct from the PKD1 family, whose function is unknown. PKD1 and PKD2 form a hetero-oligomeric complex with a 1:3 ratio. [775]. Although still being sorted out, TRPP family members appear to be 6TM spanning nonselective cation channels.

TRPV (vanilloid) family

Members of the TRPV family (reviewed by [849]) 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 noxius heat (reviewed by [660, 756, 786]). Numerous splice variants 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 [722]. The pharmacology of TRPV1 channels is discussed in detail in [80] and [868]. TRPV2 is probably not a thermosensor in man [635], but has recently been implicated in innate immunity [69]. 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 [106, 454].

TRPV5/V6 subfamily

TRPV5 and TRPV6 are highly expressed in placenta, bone, and kidney. 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 [901, 168, 558, 227]).

Contents

This is a citation summary for Transient Receptor Potential channels in the Guide to Pharmacology database (GtoPdb). It exists purely as an adjunct to the database to facilitate the recognition of citations to and from the database by citation analyzers. Readers will almost certainly want to visit the relevant sections of the database which are given here under database links.

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Database links

Transient Receptor Potential channels
http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=78

Introduction to Transient Receptor Potential channels
http://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=78

Channels and Subunits

TRPA1
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=485

TRPC1
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=486

TRPC2
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=487

TRPC3
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=488

TRPC4
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=489

TRPC5
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=490

TRPC6
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=491

TRPC7
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=492

TRPM1
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=493

TRPM2
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=494

TRPM3
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=495

TRPM4
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=496

TRPM5
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=497

TRPM6
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=498

TRPM7
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=499

TRPM8
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=500

TRPML1
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=501

TRPML2
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=502

TRPML3
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=503

TRPP1
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=504

TRPP2
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=505
TRPP3
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=506
TRPV1
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=507
TRPV2
http://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=508
TRPV3
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TRPV4
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TRPV5
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