

# Transient Receptor Potential (TRP) Ion Channels

## Key References

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## Overview

The transient receptor potential family of ion channels consists of at least 28 mammalian members divided into six subfamilies: 7 TRPC (canonical), 6 TRPV (vanilloid), 8 TRPM (melastatin), 1 TRPA (ankyrin), 3 TRPP (polycystin) and 2 TRPML (mucolipin). Numerous invertebrate TRP channels have also been identified, including the prototypical "transient receptor potential" channels from *Drosophila* photoreceptors, TRP and TRP-like, and there is growing evidence for evolutionary conservation of their roles in cellular physiology and sensory biology. Structurally, TRP channels have six transmembrane domains and intracellular amino and carboxyl termini. Four subunits apparently comprise a functional channel. Other features shared by some, but not all, TRP channels include a TRP-domain found in the proximal portion of the sixth transmembrane domain of all TRPC and some TRPM channels, and a string of 3-14 ankyrin repeat domains found in the amino terminus of TRPC, TRPV and TRPA channels. Sequence homology among all family members is concentrated in ankyrin repeat, transmembrane, and TRP domains, and can be as little as ~20% overall. Functionally, TRP channels are versatile molecules that can be gated by G protein-coupled receptor (GPCR) signaling, lipids, ions, osmolarity, voltage, or even hot and cold temperatures. Upon activation, these channels mediate the influx of monovalent and/or divalent cations into excitable and nonexcitable cells.

There appears to be only one mammalian member of the TRPA subfamily, referred to as TRPA1. This channel contains 14 ankyrin repeat domains in its amino terminus. It is expressed in several locations, including a subset of primary sensory neurons and in hair cells of the inner ear. This channel can be activated by pungent compounds such as mustard oil (allyl isothiocyanate) or cinna-

maldehyde. It has also been reported to be activated by painful cold (<20 °C), although this claim has been disputed.

The TRPC subfamily can be further subdivided into several groups. TRPC1 is a widely distributed subtype that can form heteromultimers with other TRPC subfamily members. The TRPC2 gene is expressed in rodents, but is a pseudogene in humans. This channel is specifically expressed in the sensory cilia of vomeronasal organ pheromone sensing cells, and is essential for certain GPCR-mediated pheromone-driven behaviors in mice. TRPC4 and TRPC5 form homomultimeric channels, as well as heteromultimers that include TRPC1. They are activated by G<sub>q</sub>-coupled GPCR signaling pathways via an as yet unidentified mechanism. TRPC3, TRPC6, and TRPC7 can be activated directly by diacylglycerol. All TRPC channels pass non-selective cationic currents. It is believed that some TRPC channels participate in so-called "store-operated" calcium entry into cells following depletion of IP<sub>3</sub> receptor-dependent intracellular calcium stores.

The TRPM subfamily is characterized by exceptionally long amino and/or carboxyl terminal domains. TRPM1 is downregulated during metastatic progression of melanoma cells, although its functional properties are unknown. TRPM2 is a nonselective cation channel possessing a C-terminal NUDIX domain that allows this channel to be activated by ADP-ribose, NAD and reactive oxygen species. TRPM3 forms a nonselective cation channel with constitutive activity that can be augmented by hypo-osmolarity and may play a role in renal calcium homeostasis. TRPM4 and TRPM5 are voltage-dependent channels selective for monovalent cations that both exhibit extracellular calcium-dependent activation. Furthermore, TRPM4 can be regu-

lated by intracellular adenine nucleotides or by decavanadate ions. TRPM6 and TRPM7 appear to form heteromultimeric divalent cation-selective channels that are critical for magnesium homeostasis in humans. They also contain an intrinsic kinase domain within their carboxyl terminus that regulates responsiveness to intracellular magnesium. TRPM8, originally identified as being prostatic-specific, was subsequently found to be expressed in a subset of sensory neurons and to respond to modestly cold temperatures (<28°C) and the cold-mimetic chemicals, menthol and icilin. Icilin activation, however, requires intracellular calcium as a co-agonist.

The TRPV subfamily is so-named because its founding member, TRPV1, is the receptor for capsaicin, the major pungent component of hot chili peppers and other compounds (e.g., resiniferatoxin) that possess a similar vanilloid chemical moiety. This channel is highly expressed in nociceptive sensory neurons that detect painful stimuli. TRPV1 can also be activated by protons, endocannabinoid compounds, or elevated temperature (>42°C). Accordingly, responses to all of these stimuli are diminished or absent in TRPV1 knockout mice. TRPV2, TRPV3, and TRPV4 can also be activated by heat, with temperature thresholds of ~52°C, ~34°C and ~27°C, respectively. Alternatively, TRPV4 can be activated by hypo-osmolarity or certain epoxyeicosatrienoic acids and TRPV2 can be activated by hypo-osmolarity or growth factor receptor stimulation. TRPV4 is necessary for normal maintenance of serum osmolarity in the mouse. TRPV5 and TRPV6 form homomultimeric and heteromultimeric calcium-selective channels that exhibit constitutive activity and participate in calcium uptake in the intestine and kidney.

## Transient Receptor Potential Channels (Ankyrin and Canonical Subfamilies)

NAME	TRPA1	TRPC1	TRPC2	TRPC3	TRPC4	TRPC5	TRPC6	TRPC7
<b>ALTERNATIVE NAMES</b>	ANKTM1	TRP1	Not known	mTRPC3	TRP4, CCE1, bCCE	TRP5, CCE2	Not known	TRP7
<b>STRUCTURAL INFORMATION</b>	1119 aa (human), 1125 aa (mouse)	793 aa (human), 809 aa (mouse)	human pseudogene, 1172 aa (mouse)	848 aa (human), 836 aa (mouse)	982 aa (human)	973 aa (human), 975 aa (mouse)	931 aa (human), 930 aa (mouse)	862 aa (human), 862 aa (mouse)
<b>ACTIVATORS</b>	Mustard oil, cinnamaldehyde <b>(W228613)</b> , Ca <sup>2+</sup> (intracellular), Cold (<20°C)?, THC <b>(T2386)</b>	GPCR-G <sub>q</sub> -PLC	GPCR-G <sub>q</sub> -PLC	DAG, direct interaction with IP <sub>3</sub> receptor	Weakly voltage dependent, GPCR-G <sub>q</sub> -PLC	Weakly voltage dependent, GPCR-G <sub>q</sub> -PLC	DAG	DAG
<b>INHIBITORS</b>	Ruthenium red <b>(R2751)</b> Gd <sup>3+</sup> (homomer),	2-APB (heteromer w/C1), <b>(D9754)</b> , La <sup>3+</sup> (heteromer w/C1), high external Ca <sup>2+</sup> , 2-APB <b>(D9754)</b>	Not known	2-APB <b>(D9754)</b> , PMA <b>(P8139)</b>	2-APB <b>(D9754)</b>	2-APB <b>(D9754)</b>	Not known	La <sup>3+</sup> , SKF96365 <b>(S7809)</b>
<b>MODULATORS</b>	Icilin <b>(I9532)</b>	Calmodulin <b>(P2277,</b> <b>P0270, P1431)</b>	Not known	Not known	La <sup>3+</sup> (augments currents)	La <sup>3+</sup> (augments currents)	Not known	Extracellular ATP, intracellular Ca <sup>2+</sup> , PKC
<b>SIGNAL TRANSDUCTION MECHANISM</b>	Non-selective cation channel	Non-selective cation channel	Non-selective cation channel	Non-selective cation channel	Non-selective cation channel	Non-selective cation channel	Non-selective cation channel	Non-selective cation channel
<b>RADIOLIGAND OF CHOICE</b>	Not known	Not known	Not known	Not known	Not known	Not known	Not known	Not known
<b>TISSUE EXPRESSION</b>	Sensory neurons, inner ear hair cells, vestibular organ	Heart, brain, testis, ovary	Vomer nasal organ, testis	Brain	Brain, endothelium, adrenal gland, retina, testis	Brain	Lung, brain	Eye, heart, lung
<b>PHYSIOLOGICAL EFFECTS</b>	Cold-evoked pain, chemically evoked pain	Cellular Ca <sup>2+</sup> homeostasis	Pheromone detection	Cellular Ca <sup>2+</sup> homeostasis	Cellular Ca <sup>2+</sup> homeostasis, vascular tone, permeability, neurotransmitter release	Cellular Ca <sup>2+</sup> homeostasis, neurite outgrowth	Cellular Ca <sup>2+</sup> homeostasis, cerebrovascular tone	Cellular Ca <sup>2+</sup> homeostasis,
<b>DISEASE RELEVANCE</b>	Chronic pain, cancer, deafness	Not known	Unlikely in humans	Not known	Hypertension	Not known	Not known	Not known

### FOOTNOTES

## Transient Receptor Potential Channel (Melastatin Subfamily)

NAME	TRPM1	TRPM2	TRPM3	TRPM4	TRPM5	TRPM6	TRPM7	TRPM8
<b>ALTERNATIVE NAMES</b>	Melastatin	TRPC7, LTRPC7	KIAA1616, LTRPC3	FLJ20041, LTRPC4	Mtrl, LTRPC5	ChaK2	TRP-PLIK, LTRPC7, ChaK(1)	Trp-p8, CMR1
<b>STRUCTURAL INFORMATION</b>	1533 aa (human), 1749 aa (mouse)	1503 aa (human), 1507 aa (mouse), C term. NUDIX domain	1707 aa (human), 1337 aa (mouse)	1214 aa (human), 945 aa (mouse)	1165 aa (human), 1148 aa (mouse)	2022 aa (human), 2028 aa (mouse), C term. $\alpha$ -kinase domain	1865 aa (human), 1863 aa (mouse), C term. $\alpha$ -kinase domain	1104 aa (human), 1104 aa (mouse)
<b>ACTIVATORS</b>	Constitutively active?	$\beta$ -NAD ( <b>S783706</b> ), ADP-ribose ( <b>A0752</b> ), H <sub>2</sub> O <sub>2</sub> ( <b>H3410</b> )	Constitutive	Extracellular Ca <sup>2+</sup>	Extracellular Ca <sup>2+</sup>	Low intracellular, Mg <sup>2+</sup> and Mg <sup>2+</sup> ATP	Low intracellular, Mg <sup>2+</sup> and Mg <sup>2+</sup> ATP, constitutive?	Menthol ( <b>M2772</b> ), icilin ( <b>I9532</b> ) (coagonist w/Ca <sup>2+</sup> ), cold (<27°C), eucalyptol ( <b>C80601</b> )
<b>INHIBITORS</b>	La <sup>3+</sup>	Na <sup>+</sup>	Not known	La <sup>3+</sup> , Gd <sup>3+</sup> , adenine nucleotides	Not known	Not known	Mg <sup>2+</sup> , La <sup>3+</sup>	2-APB ( <b>D9754</b> ), low pH
<b>MODULATORS</b>		Intracellular Ca <sup>2+</sup> , TNF $\alpha$ ( <b>T7539</b> , <b>T6674</b> , <b>T5944</b> ), arachidonic acid	Hypotonicity (increase)	Decavanadate	PIP <sub>2</sub> ( <b>P9763</b> )	Not known	PIP <sub>2</sub> ? ( <b>P9763</b> )	Not known
<b>SIGNAL TRANSDUCTION MECHANISM</b>	Non-selective cation channel	Non-selective cation channel	Non-selective cation channel	Monovalent-selective cation channel	Monovalent-selective cation channel	Ca <sup>2+</sup> - and Mg <sup>2+</sup> -selective channel	Ca <sup>2+</sup> - and Mg <sup>2+</sup> -selective channel	Non-selective cation channel
<b>RADIOLIGAND OF CHOICE</b>	Not known	Not known	Not known	Not known	Not known	Not known	Not known	Not known
<b>TISSUE EXPRESSION</b>	Eye, melanocytes	Brain, pancreas, neutrophils	Kidney, brain	Prostate,colon, heart, kidney, neurons	Small intestine, liver, lung	Colon, kidney	Kidney, heart	Prostate, sensory neurons
<b>PHYSIOLOGICAL EFFECTS</b>	Tumor supressor, calcium homeostasis	Oxidative stress response, apoptosis	Renal calcium homeostasis	Cellular Ca <sup>2+</sup> homeostasis	Taste transduction	Cell Mg <sup>2+</sup> homeostasis, Mg <sup>2+</sup> absorbtion	Cell Mg <sup>2+</sup> homeostasis, Mg <sup>2+</sup> absorbtion	Cold sensation, cancer
<b>DISEASE RELEVANCE</b>	Melanoma	Not known	Not known	Not known	Not known	Hypomagnesemia	Hypomagnesemia	Cold pain, prostate cancer

### Abbreviations

**2APB:** 2-Aminoethoxydiphenyl borate

**DAG:** Diacylglycerol

**IP<sub>3</sub>R:**Inositol triphosphate receptor

**NAD:** Nicotinamide adenine dinucleotide

**NUDIX:** Nucleoside diphosphate pyrophosphatase

**PMA:** Phorbol myristoyl acetate

**PIP<sub>2</sub>:** Phosphatidyl inositol biphosphate

**PLC:** Phospholipase C

**THC:**  $\Delta$ 9-Tetrahydrocannabinol

### FOOTNOTES

## Transient Receptor Potential Channels (Vanilloid Subfamily)

NAME	TRPV1	TRPV2	TRPV3	TRPV4	TRPV5	TRPV6
<b>ALTERNATIVE NAMES</b>	Vanilloid receptor (VR1), Capsaicin receptor	VRL-1, GRC, OTRPC1	VRL-3, OTRPC2	VRL-2, Trp12, VR-OAC, OTRPC4	ECaC1, CaT2, OTRPC3	ECaC2, CaT1, CaT1, CaT-like
<b>STRUCTURAL INFORMATION</b>	839 aa (human), 839 aa (mouse)	764 aa (human), 756 aa (mouse)	790 aa (human), 791 aa (mouse)	871 aa (human), 871 aa (mouse)	729 aa (human), 723 aa (mouse)	725 aa (human), 727 aa (mouse)
<b>SUBTYPE-SELECTIVE AGONISTS</b>	Capsaicin ( <b>M2028</b> ), resiniferatoxin ( <b>R8756</b> ), olvanil ( <b>O0257</b> ), nuvanil, N-arachidonyl dopamine ( <b>A8848</b> )	Not known	Not known	4 $\alpha$ -PDD	Not known	Not known
<b>ACTIVATORS WITH OTHER KNOWN TARGETS</b>	Anandamide ( <b>A0580</b> ), protons, 2-APB ( <b>D9754</b> ), heat (>42°C)	Hypoosmolarity, heat (>52°C), 2-APB ( <b>D9754</b> )	Heat (>34°C), 2-APB ( <b>D9754</b> )	Hypoosmolarity, heat (>27°C), 5',6'-eicosatrienoic acid	Not known	Not known
<b>RECEPTOR-SELECTIVE ANTAGONISTS</b>	SB366791 ( <b>S0441</b> ), 5'-iodoresiniferatoxin ( <b>I9281</b> )	Not known	Not known	Not known	Not known	Not known
<b>ANTAGONISTS WITH OTHER KNOWN ACTIVITIES</b>	Capsazepine ( <b>C191</b> ), BCTC, ruthenium red ( <b>R2751</b> )	Ruthenium red ( <b>R2751</b> )	Ruthenium red ( <b>R2751</b> )	Ruthenium red ( <b>R2751</b> )	Ruthenium red ( <b>R2751</b> ), 2-APB	Ruthenium red ( <b>R2751</b> )
<b>MODULATORS</b>	Protons, sulfhydryl reagents, nerve growth factor (indirect), GPCR-G <sub>q</sub> activation (indirect)	EGF (indirect)	Not known	Not known	Vitamin D (expression level)	Vitamin D (expression level) 2-APB ( <b>D9754</b> )
<b>SIGNAL TRANSDUCTION MECHANISM</b>	Non-selective cation channel	Non-selective cation channel	Non-selective cation channel	Non-selective cation channel	Ca <sup>2+</sup> -preferring cation channel	Ca <sup>2+</sup> -preferring cation channel
<b>RADIOLIGAND OF CHOICE</b>	[ <sup>3</sup> H]-Resiniferatoxin	Not known	Not known	Not known	Not known	Not known
<b>TISSUE EXPRESSION</b>	Sensory neurons, brain, urinary bladder epithelium, skin keratinocytes, mast cells, hepatocytes	Sensory neurons, brain, lung, skeletal, cardiac muscle, intestines, mast cells	Sensory neurons, brain, skin keratinocytes, testis	Kidney nephron, brain, skin keratinocytes, sensory neurons, respiratory epithelium, smooth muscle	Kidney, small intestine, placenta, pancreas	Small intestine, pancreas, placenta
<b>PHYSIOLOGICAL EFFECTS</b>	Pain sensation, bladder contraction, vasomotor regulation, immunoregulation	Pain sensation, mast cell function,	Pain, warmth sensation	Pain, warmth sensation, osmoregulation, mechanosensation	Calcium absorption	Calcium absorption
<b>DISEASE RELEVANCE</b>	Chronic pain, bladder hyperactivity, inflammatory bowel disease, Prurigo nodularis	Chronic pain	Chronic pain	Chronic pain, diabetes insipidus, asthma	Hypocalcemia	Hypocalcemia

### Abbreviations

**2-APB:** 2-Aminoethoxydiphenyl borate

**BCTC:** N-(4-Tertiarybutylphenyl)-4-(3-chlorophyridin-2-yl)tetrahydropyrazine -1(2H)-carbox-amide

**EGF:** Epidermal growth factor

**GPCR:** G protein-coupled receptor

**SB366791:** N-(3-Methoxyphenyl)-4-chlorocinnamide

**4 $\alpha$ -PDD:** 4  $\alpha$ -Phorbol didecanoate

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