TRP channels: a brief overview

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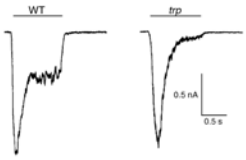
Transient receptor potential (*trp*) in drosophila



•Mutant flies have **transient** rather than sustained current response to light

Minke B Physiol Rev 2002, 82:429

TRP Channels

…A channel class that upholds homeostasis

Homeostasis is the maintenance of equilibrium, or constant conditions, in a biological system by means of automatic mechanisms that counteract influences tending toward disequilibrium. The development of the concept, which is one of the most fundamental in modern biology, began in the 19th century when the French physiologist Claude BERNARD noted the constancy of chemical composition and physical properties of blood and other body fluids. He claimed that this "fixity of the milieu interieur" was essential to the life of higher organisms. The term homeostasis was coined by the 20th-century American physiologist Walter B. Cannon, who refined and extended the concept of self-regulating mechanisms in living systems.

Activation of TRP channels is typically polymodal

Multiple intracellular messengers (integrators)

Activation and modulation overlap

Biophysical stimuli

Ion concentations

Temperature

Exogenous chemicals

Transient Receptor Potential

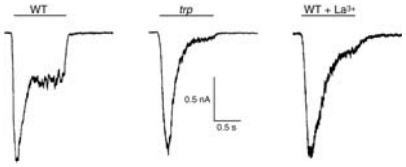
> than 30 cation channels

Cation channels

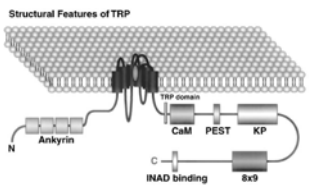
On the basis of sequence homology 7 main subfamilies:

- TRPC (‘Canonical’)
- TRPV (‘Vanilloid’)
- TRPM (‘Melastatin’)
- TRPP (‘Polycystin’)
- TRPML (‘Mucolipin’)
- TRPA (‘Ankyrin’)
- TRPN (‘NOMPC’)

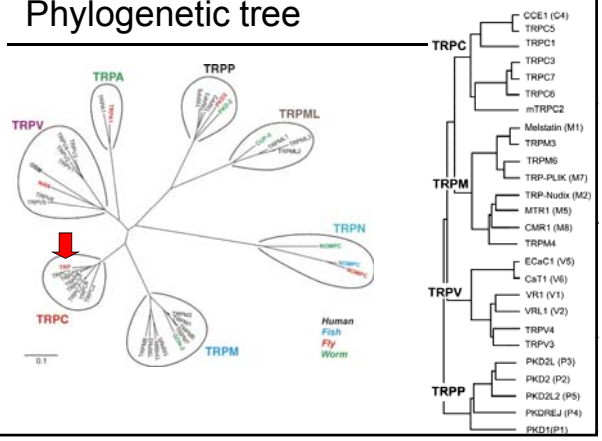
Transient Receptor Potential



From: Minke, B. & Cook, B. *Physiol Rev.* **82**, 429-472 (2002).



Phylogenetic tree

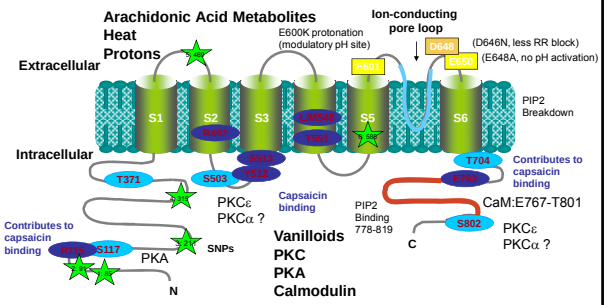


Many names

TRPC channel names		TRPM channel names		TRPV channel names		TRPD channel names	
Current	Previous other	Current	Previous other	Current	Previous other	Current[a]	Previous other
TRPC1	TRP1	TRPM1	Miss1	TRPV1	VR1	TRPP1	PKD1
TRPC2	TRP2	TRPM2	LTRPC2	TRPV2	VRL-1	TRPP2	PKD2
TRPC3	TRP3		TRPC7		GRC-1	TRPP3	PKD2L
TRPC4	TRP4		TRP-Nudix	TRPV3	TRPVL3	TRPP4	PKD-REJ
	CCE1	TRPM3	LTRPM3	TRPV4	VRL-2	TRPP5	PKD2L2
TRPC5	TRP5	TRPM4	LTRPC4		OTCR4		
TRPC6	TRP6	TRPM5	MTR1		VR-OAC		
TRPC7	TRP7	TRPM6	LTRPC6		Trp12		
			ChaK2	TRPV5	ECaC1		
		TRPM7	LTRPC7		CaT2		
			ChaK1	TRPV6	CaT1		
			TRP-PLIK		ECaC2		
		TRPM8	CMR1		CaT-L		
			Trp-p8				

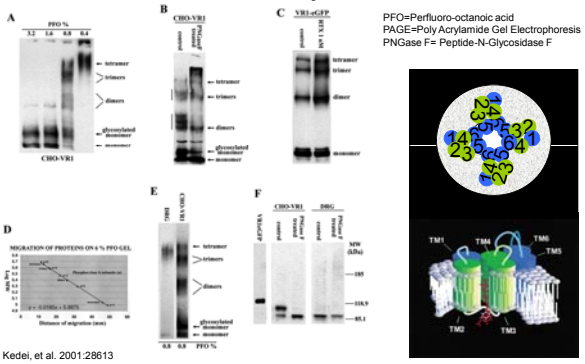
Birnbaumer et al. Cell Calcium 2003:419

6TM channel cartoon



García-Martínez et al. JBC 2000:32552; Jordt et al. PNAS 2000:8134; Premkumar & Ahern Nature 2000: 985; Chuang, et al Nature 2001:957; Numazaki et al. JBC 2002:13375; Bahve et al. Neuron 2002:721; Jung et al. JBC 2002:44448; Olah et al. JBC 2002:35752; Jordt et al. Cell 2002:421; Jung et al. JBC 2003:7048; Numazaki et al. PNAS 2003:8002; Vulcu et al. Pharmacology 2003:38; Zhou et al. J Neurochem 2003:571; Gavva, et al. JBC 2004:20283; Mohapatra & Nau, JBC 2005:13424; Ferrer-Montiel, et al. Eur J Biochem 2004:1820

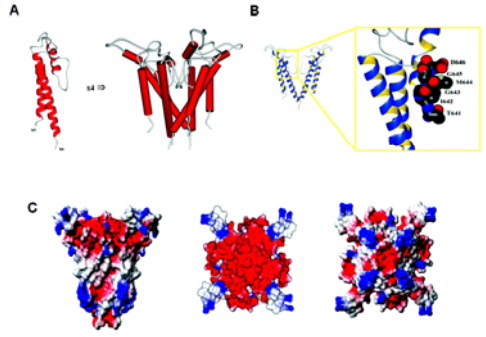
Tetramerization: TRPV1 example



PFO=Perfluoro-octanoic acid
PAGE=Poly Acrylamide Gel Electrophoresis
PNGase F= Peptide-N-Glycosidase F

Kedei, et al. 2001:28613

Hypothesized pore of TRPV1



Permeability

- These are cation channels
- All TRP channels except TRPM4 and TRPM5 are permeable to Ca2+
- Highly Ca2+ selective TRP channels are TRPV5 and TRPV6

Where are they located?

Widespread
- In body
- In animal kingdom

Some very localised

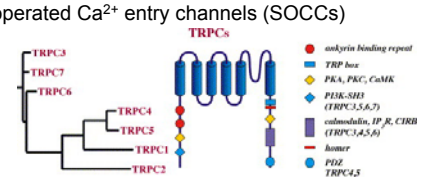
The "canonical" TRPCs

	Selectivity P_{Ca}/P_{Na}	Conductance (pS)	Proposed activation mechanisms
TRPC1	Nonselective	16	PLC, store depletion, OAG (in the absence of extracellular Ca^{2+}, mechanical (stretch)
TRPC2	2.7	42	PLC, DAG, store depletion?
TRPC3	1.6	66	PCL, DAG, OAG, src TK, IP_3, store depletion
TRPC4	1.1	30-41	PLC, GTPγS, micromolar La^{3+}, store depletion?
TRPC5	9	64	PLC, GTPγS, receptor-operated, micromolar La^{3+} or Gd^{3+}, store depletion?, $[Ca^{2+}]_o$, modest elevation of $[Ca^{2+}]_i$, PIP5K, Rac, PI3K
TRPC6	5	28-37	PLC, DAG, OAG, src TK, 20-HETE, AlF_4^-, flufenamate
TRPC7	2	?	PLC, DAG, OAG, 20-HETE, store depletion

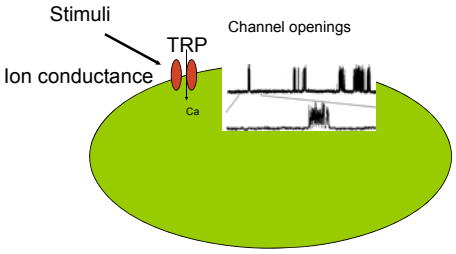
The "canonical" TRPCs

Activated by stimulation of receptors that activate different isoforms of PLC, i.e. PLCβ after activation of GPCRs, and PLCγ after activation of receptor tyrosine kinases (RTKs)

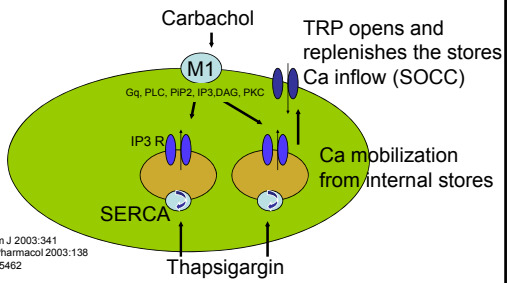
Regulated by the filling status of intracellular Ca^{2+} stores, and consequently to be the elusive molecular candidates for store-operated Ca^{2+} entry channels (SOCCs)



Plasma Membrane activation



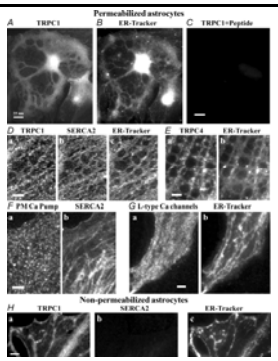
ER function of IP3 mediated Ca signalling



Turner et al. Biochem J 2003:341
Marshall et al. Br J Pharmacol 2003:138
Liu, et al, JBC 2003:5462

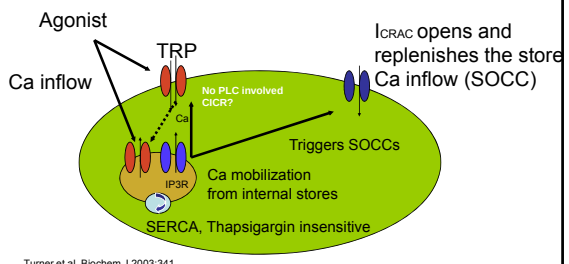
SERCA=Sarcoplasmic/endoplasmic reticulum Ca-ATPase
IP3R=Inositol 3 phosphate receptor
Icrac=Calcium release activated current
M1=Muscarinic GPCR M1 Gq coupled
SOCC=Store operated calcium influx channel

TRPC1 in the ER of astrocytes



Golovina, J Physiol. '2005 May 1;564(Pt 3):737-49

ER function of TRPs?



Turner et al. Biochem J 2003:341
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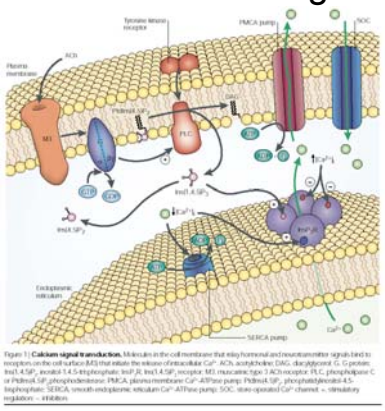
Liu, et al, JBC 2003:5462

SERCA=Sarcoplasmic/endoplasmic reticulum Ca-ATPase
CICR=Calcium induced calcium release
Icrac=Calcium release activated current
M1=Muscarinic GPCR M1 Gq coupled
SOCC=Store operated calcium influx channel

Calcium signaling



GPCR-s:
Angiotensin II
Acetylcholine (M1 M3)
Adrenergic alpha-1
Thrombin
Metabotropic GluR

RTK-s
EGF, NGF, BDNF etc

Other factors
Sperm → oocyte
Light (invertebrates)

From: Clapham, D.E., et al. *Nat. Rev. Neurosci.* **2**, 387-396 (2001).

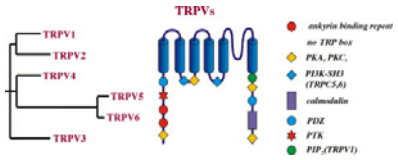
The TRPV subfamily

	Selectivity P_{Ca}/P_{Na}	Conductance (pS)	Proposed activation mechanisms
TRPV1	~10	35–80	Depolarization, heat (≥43 °C), low pH (≤5.9), vanilloids, endovanilloids, PKC, anandamide, 12-(S)-HPETE, 15-(S)-HPETE, 5-(S)-HETE, leukotriene B_4, 2-APB, OEA, PKA, decreased $PI(4,5)P_2$, voltage dependent
TRPV2	1-3	n.d.	Noxious heat (>53 °C), mechanical (stretch, swelling) growth factors, IGF-1, HA, 2-APB
TRPV3	2.6	190	Heat (>33 °C), camphor, 2-APB, voltage dependent
TRPV4	6	90	Moderate heat (>24 °C), cell swelling, shear stress, PKC, anandamide, 5',6'EET, 4α-PDD and other phorbols
TRPV5	>100	75	Low $[Ca^{2+}]_i$, hyperpolarization, voltage dependent block by Mg^{2+}
TRPV6	>100	40-70	Low $[Ca^{2+}]_i$, hyperpolarization, voltage dependent block by Mg^{2+}

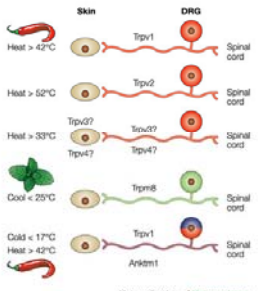
The TRPV subfamily

TRPV1-4 is activated by temperature changes, but can also be activated by numerous other stimuli

TRPV5-6 are tightly controlled by intracellular calcium



TRPs in Sensory Nerves



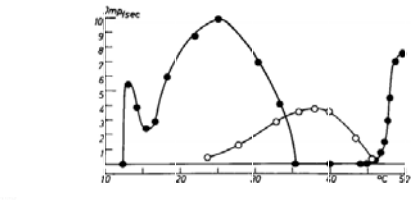
Patapoutian et al. Nat Rev 2003:529

A relatively young channel class

	TRPV1	TRPV2	TRPV3	TRPV4	TRPV5	TRPV6
First cloned	**1997**	**1999**	**2002**	**2001**	**1999**	**1999**
First tools	**Capsaicin RTX Camphor**	**-**	**Camphor**	**Bisandro-graphol ide**	**-**	**-**
KO paper	**2000**	**-**	**2005**	**2003**	**2003**	**-**

1997 → 2007

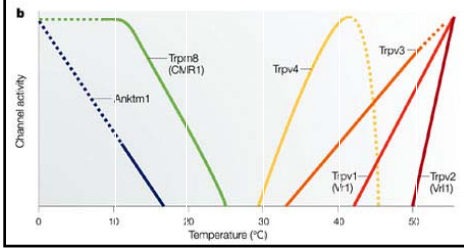
Conv E Phys | Opus Xpress | PX | IW Quatro



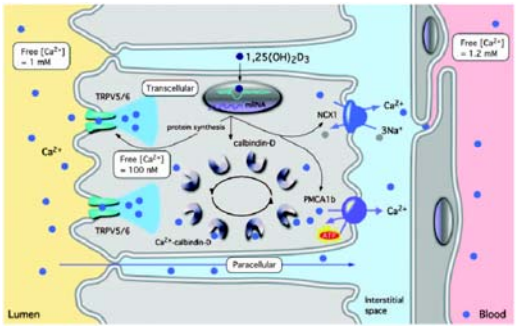
Normothermic environment

Warm environment

Cold environment

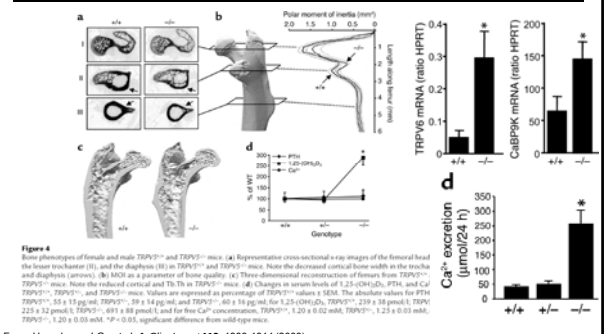


Epithelial calcium channels



From: Hoenderop, J.G., et al. *Physiol Rev.* **85**, 373-422 (2005).

The TRPV5 Knockout mouse



From: Hoenderop, J.G., et al. *J. Clin. Invest* **112**, 1906-1914 (2003).

The TRPM subfamily

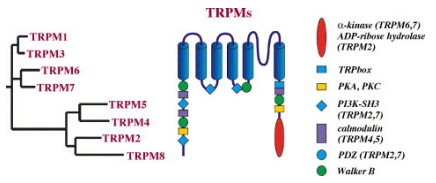
	Selectivity P_{Ca}/P_{Na}	Conductance (pS)	Proposed activation mechanisms
TRPM1	n.d.	n.d.	Translocation
TRPM2	0.5-1.6	52-80	ADP-ribose, NAD, H_2O_2 and other ROS
TRPM3	1-2	65 (Ca^{2+})–130	Cell swelling, store depletion? d-erythrosphingosine
TRPM4	none	25	Elevated $[Ca^{2+}]_i$, ATP, PKC, decavanadate, voltage dependent
TRPM5	none	16–25	Elevated $[Ca^{2+}]_i$, $PI(4,5)P_2$, voltage dependent
TRPM6	P_{Mg}/P_{Na} ~6	n.d.	Decreased $[Mg^{2+}]_i$
TRPM7	3	40–105	Decreased $[Mg^{2+}]_i$, Mg-ATP, $PI(4,5)P_2$, cAMP, G-proteins
TRPM8	1-3	83	Cold (8–28 °C), menthol, icilin, Ca^{2+}, pH, $PI(4,5)P_2$, voltage dependent

The TRPM subfamily

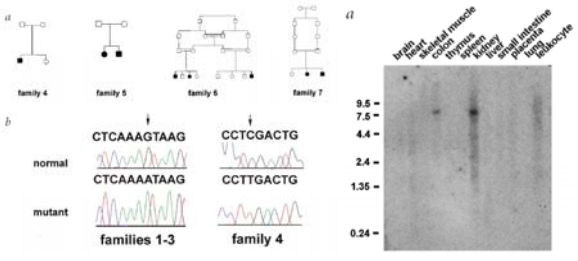
Both TRPM6 and TRPM7 contain an atypical serine/threonine protein kinase within the C-terminal domain.

The TRPM sequence does not contain ankyrin repeats

A cold sensitive channel



Mutation of *TRPM6* causes familial hypomagnesemia with secondary hypocalcemia



From: Walder, R.Y., et al. *Nat. Genet.* **31**, 171-174 (2002).

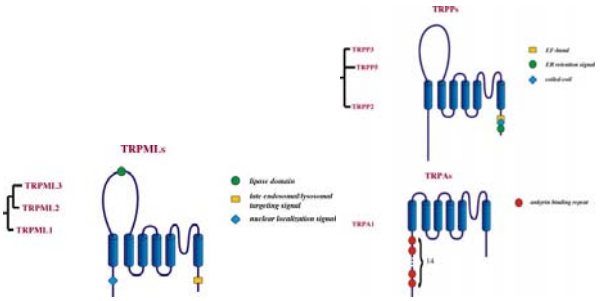
Hypomagnesemia, Hypocalcemia, Seizures: caused by impaired intestinal Mg^{2+} absorption abnormal renal Mg^{2+} excretion

Can be overcome by high-dose Mg^{2+} supplementation

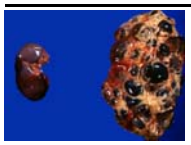
TRPP, TRPML, TRPA

	Selectivity P_{Ca}/P_{Na}	Conductance (pS)	Proposed activation mechanisms
TRPML1	~1	46-83	Increased $[Ca^{2+}]_i$
TRPML2	n.d.	n.d.	n.d.
TRPML3	n.d.	n.d.	n.d.
TRPP2	1-5	40-177	Mechanical stress, $[Ca^{2+}]_i$
TRPP3	4	137	$[Ca^{2+}]_i$
TRPP5	1-5	300	$[Ca^{2+}]_i$
TRPA1	0.8-1.4	40–105	Isothiocyanates, allicin, Δ^9-tetrahydrocannabinol (THC), cinnamaldehyde, bradykinin, noxious cold?, mechanical stress, voltage dependent, $[Ca^{2+}]_i$

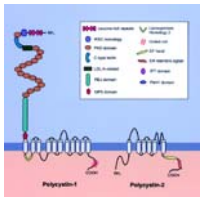
TRPP, TRPML, TRPA



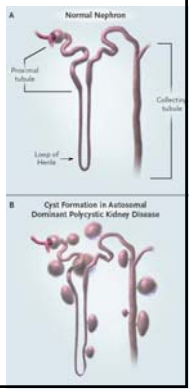
Polycystic Kidney Disease



http://peir.path.uab.edu/iplab/messages/598/467.html?1002303218



From: Igarashi, P. & Somlo, S. *J. Am. Soc. Nephrol.* **13**, 2384-2398 (2002).



From: Wilson, P.D. *N. Engl. J. Med.* **350**, 151-164 (2004).

TRPN

A single member, found in *C. elegans*, *Drosophila* and zebra fish

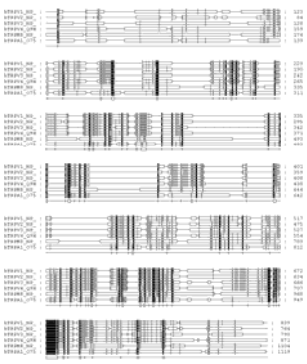
The mammalian genome appears to lack the TRPN gene

The *Drosophila* TRPN1 was named:
no mechanoreceptor potential C (NOMPC)

TRPN1 is selectively expressed in mechanosensitive cells, including ciliated mechanosensory organs in *Drosophila*, mechanosensory neurons in *C. elegans*,
the hair cells of zebra fish ear.
Similar to TRPA1

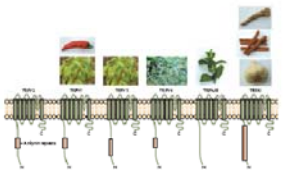
Temperature sensor?

What would it look like?



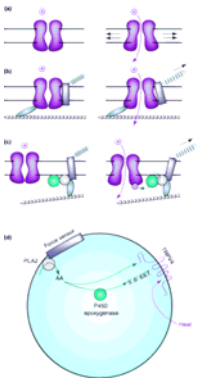
ILLLNMLI?

Naturally occuring agonists



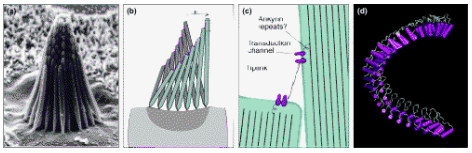
Capsaicin from Chili Pepper
Resiniferatoxin from Latex of the perennial Euphorbia Resinifera Berg (cactus)
Camphor from Camphor Laurel Tree: Cinnamomum Camphora
Bisandrographolide from Chinese Herbal Plant: Andrographis Paniculata
Menthol from Green mint
Isothiocyanates from horseradish
Cinnemaldehyde from Cinnamon
Allicin from garlic

Mechanosensors?



Various mechanisms for activation of ion channels (violet) by mechanical stimuli. **(a)** Direct activation by force conveyed through lipid tension. **(b)** Direct activation by force conveyed through structural proteins. Linking proteins might be intracellular, or extracellular, or both, and force might be parallel or normal to the membrane. **(c)** Indirect activation by force conveyed to a mechanically sensitive protein that does not form the channel. A second messenger carries the signal to a ligand-activated channel. **(d)** Various activation pathways for TRPV4. Current evidence suggests that a force sensor responding to membrane tension activates phospholipase A2 (PLA2), producing arachidonic acid (AA). AA can directly activate TRPV4 or be metabolized to 5′,6′-EET by P450 epoxygenase to activate the channel. TRPV4 is also activated by temperature, probably directly.

TRPA1 (V4?) involved in hearing?



Mechanotransduction by vertebrate hair cells. **(a)** A single hair bundle from a frog vestibular hair cell. Stereocilia heights increase uniformly towards the kinocilium. **(b)** Positive deflection of the hair bundle increases the distance between adjacent stereocilia tips. **(c)** Transduction apparatus in the stereocilia tips. The tip link, probably composed of cadherin 23, extends between adjacent membranes and is associated with one or two transduction channels at each end. The transduction channel, probably incorporating TRPA1, is elastically linked to the actin cytoskeleton. (Reproduced with permission from Sotomayor *et al*. 2005) **(d)** The crystal structure of a polyankyrin domain similar to that in TRPA1, in this case with 24 ankyrin repeats. Molecular dynamics modeling suggests that it is an elastic element.

Perspectives

- Multifunctional sensors of environmental cues in the form of physical and chemical stimuli
- Widely expressed in the CNS and peripheral cell types
- Involved in numerous fundamental cell functions
- An increasing number of important pathological conditions are now being linked to TRP dysfunction

TRPV1 may be involved in

- Pain
- Irritable Bowel Syndrome
- Diabetes Type 1

TRP dysfunction in diseases

- TRPC6: Focal segmental glomerulosclerosis
- TRPM6: Hypomagnesemia with secondary hypocalcemia
- TRPP2: Polycystic kidney disease
- TRPML1: mucolipidosis type IV
- TRPM7: ALS-G