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Transient Receptor Potential Cation Channels in Disease

BERND NILIUS, GRZEGORZ OWSIANIK, THOMAS VOETS, AND JOHN A. PETERS

Department of Physiology, Campus Gasthuisberg, KULeuven, Leuven, Belgium; and Neurosciences Institute, Division of Pathology and Neuroscience, Ninewells Hospital and Medical School, The University of Dundee, Dundee, United Kingdom

Nilius B, Owsianik G, Voets T, Peters JA. Transient Receptor Potential Cation Channels in Disease. *Physiol Rev* 87: 165–217, 2007; doi:10.1152/physrev.00021.2006.—The transient receptor potential (TRP) superfamily consists of a large number of cation channels that are mostly permeable to both monovalent and divalent cations. The 28 mammalian TRP channels can be subdivided into six main subfamilies: the TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), and the TRPA (ankyrin) groups. TRP channels are expressed in almost every tissue and cell type and play an important role in the regulation of various cell functions. Currently, significant scientific effort is being devoted to understanding the physiology of TRP channels and their relationship to human diseases. At this point, only a few channelopathies in which defects in TRP genes are the direct cause of cellular dysfunction have been identified. In addition, mapping of TRP genes to susceptible chromosome regions (e.g., translocations, breakpoint intervals, increased frequency of polymorphisms) has been considered suggestive of the involvement of these channels in hereditary diseases. Moreover, strong indications of the involvement of TRP channels in several diseases come from correlations between levels of channel expression and disease symptoms. Finally, TRP channels are involved in some systemic diseases due to their role as targets for irritants, inflammation products, and xenobiotic toxins. The analysis of transgenic models allows further extrapolations of TRP channel deficiency to human physiology and disease. In this review, we provide an overview of the impact of TRP channels on the pathogenesis of several diseases and identify several TRPs for which a causal pathogenic role might be anticipated.

I. INTRODUCTION

Calcium ions play a central role in many cellular processes including muscle contraction, transmitter release, cell proliferation, gene transcription, and cell death (42). Our knowledge of the molecular players mediating Ca^{2+} entry into cells has increased impressively during the last 10 years, not least due to the discovery of a novel superfamily of channels called "transient receptor potential," or TRP channels. TRP channels contribute to changes in the cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_i$) either by acting as Ca^{2+} entry pathways in the plasma

membrane, or via changes in membrane polarization, modulating the driving force for Ca^{2+} entry mediated by alternative pathways. TRP channels probably also form intracellular pathways for Ca^{2+} release from several cell organelles. Given the unique importance of Ca^{2+} signaling in all cell types, it is not surprising that dysfunctions in Ca^{2+} channels are causal to, or at least involved in, the pathogenesis of several diseases. With regard to the TRP channels, there are at present only a few conditions that can be referred to as a channelopathy, in which a defect in channel functioning is the direct cause of disease. However, in this review we draw upon multiple lines of evidence to provide a comprehensive description of the current state of knowledge that implicates TRP channels in the pathogenesis of several diseases. Taking into account the complexity of TRP channel regulation and their typically polymodal mechanisms of activation, we briefly first describe the main properties of the different TRP family members and subsequently discuss various diseases caused by TRP channel defects, as well as diseases and dysfunctions in which a role of TRP channels has been implicated.

Each TRP channel subunit consists of six putative transmembrane spanning segments (S1–6), a pore-forming loop between S5 and S6, and intracellularly located NH_2 and COOH termini. Assembly of channel subunits as homo- or heterotetramers results in the formation of cation-selective channels. On the basis of amino acid homology, the TRP superfamily can be divided into seven subfamilies (see Fig. 1) (73, 80, 90, 283, 284, 286, 337). The TRPC (canonical) and TRPM (melastatin) subfamilies consist of seven and eight different channels, respectively (i.e., TRPC1–7 and TRPM1–8). The TRPV (vanilloid) subfamily presently comprises six members (TRPV1–6). The most recently identified subfamily, TRPA (ankyrin), has only one mammalian member (TRPA1). The TRPP (polycystin) and TRPML (mucolipin) families, each containing three mammalian members, are relatively poorly characterized, but are attracting increasing interest because of their involvement in several human diseases (see Fig. 1). The TRPN subfamily (NOMP, No mechanopotential) in hearing-assisting sensory neurons in *Drosophila* and zebrafish (*Danio rerio*) has to date only been detected in worm, *Drosophila*, and zebrafish and is proposed to be a mechanostimuli sensing channel (400, 488). Currently available genome information indicates that mammals have no TRPN orthologs.

All functionally characterized TRP channels are permeable to Ca^{2+} with the exceptions of TRPM4 and TRPM5, which are only permeable to monovalent cations. Most Ca^{2+}-permeable TRP channels are only poorly selective for Ca^{2+}, with permeability ratio relative to Na^+ (P_{Ca}/P_{Na}) in the range between 0.3 and 10. Exceptions are TRPV5 and TRPV6, two highly Ca^{2+}-selective TRP channels with P_{Ca}/P_{Na} >100. TRP channels are gated by diverse stimuli that include the binding of intracellular and extracellular messengers, changes in temperature, and chemical and/or mechanical (osmotic) stress. In addition, some TRP channels appear to be constitutively open, whereas others seem to become activated upon depletion of intracellular Ca^{2+} stores, although the latter mechanism remains an issue of intensive discussion (73, 308).

Increases in intracellular Ca^{2+} not only arise upon Ca^{2+} influx, but also upon Ca^{2+} release from internal Ca^{2+} stores, such as the Golgi apparatus, the endoplasmic reticulum (ER) or, specifically in muscle cells, the sarcoplasmic reticulum. A number of recent studies suggest that members of the TRP superfamily may also function

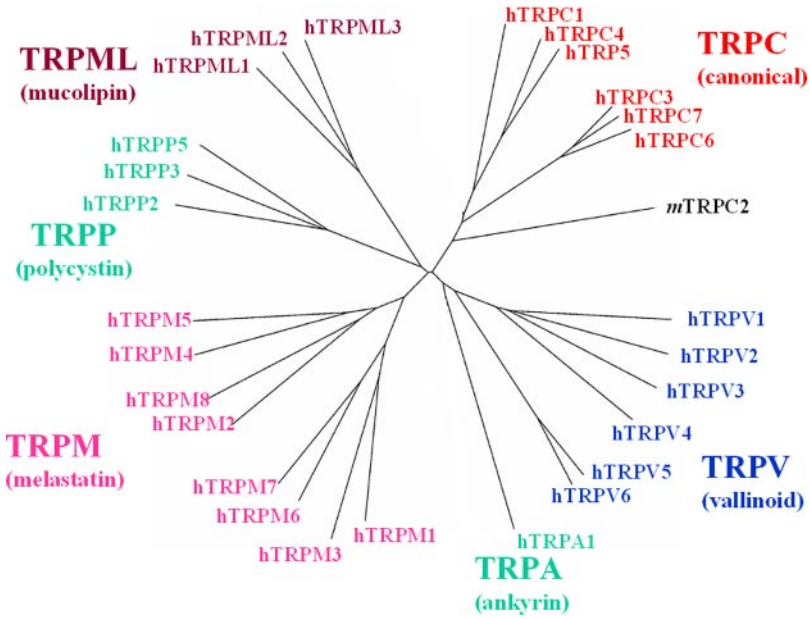


FIG. 1. Phylogenetic tree of the mammalian transient receptor potential (TRP) channel superfamily. TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin), TRPP (polycystin), and TRPML (mucolipin) are the only identified subfamilies in mammals. TRPN (NOMP, NO-mechano-potential) has to date only been detected in worm, *Drosophila*, and zebrafish (400, 488).

as intracellular Ca^{2+} release channels. TRPP2 is partially located in the ER membranes where it acts as a Ca^{2+} release channel (204). Moreover, there are indications that some bona fide plasmalemmal Ca^{2+}-permeable TRP channels (e.g., TRPV1 and TRPM8) can also reside on intracellular membranes where they may function as Ca^{2+} release channels (438, 457, 458, 483, 531).

II. THE TRP SUPERFAMILY

The discovery of TRP channels was related to a channelopathy, albeit in an invertebrate. Phototransduction in the fruit fly, *Drosophila melanogaster*, involves activation of membrane cation channels leading to a depolarizing current. *Drosophila* photoreceptors contain the light-sensitive G protein-coupled receptor rhodopsin, whose activation results in stimulation of phospholipase C-β (PLC-β). Resolving components of the light-induced current (LIC) led to the identification of a *Drosophila* mutant displaying a transient LIC in response to light, in contrast to the sustained LIC in wild-type flies. This mutant strain was termed *trp*, for transient receptor potential. Mutations in this gene led to a disruption of a Ca^{2+} entry channel in the photoreceptors, indicating that TRP, the protein encoded by the *trp* gene, forms all, or part, of a Ca^{2+} influx channel.

A. The "Canonical" TRPCs

The mammalian TRP channels most closely related to *Drosophila* TRP are classified in the TRPC subfamily. The seven mammalian TRPC channels share a structural motif in the COOH-terminal tail, the TRP box, which is located close to the intracellular border of S6 and contains the invariant sequence EWKFAR. TRPC channels also contain three or four NH_2-terminal ankyrin repeats (349). TRPC channels are nonselective, Ca^{2+}-permeable cation channels, but the permeability ratio (P_{Ca}/P_{Na}) varies significantly between different members of the family and somewhat confusingly between reports upon the same channel. For example, estimates of P_{Ca}/P_{Na} for both TRPC4 and TRPC5 expressed in heterologous systems vary between 1 and 9 (326, 347, 381). Such disparate values may reflect contamination of the TRPC4/TRPC5 currents by endogenous conductances and/or the formation of heteromultimeric channels consisting of heterologously expressed and endogenous TRPC monomers. Indeed, several TRPCs, including TRPC1, -4, and -5, can form heteromers, and the current properties are significantly different between TRPC5 and TRPC1/TRPC5 expressing cells. Similarly, TRPC3, TRPC6, and TRPC7 form heteromers (136, 172, 386, 418, 419).

In general, TRPC members can be considered as channels activated subsequent to stimulation of receptors that activate different isoforms of PLC. TRPC3, -6, and -7 are activated by diacylglycerol (DAG), independent of the stimulation of protein kinase C (PKC) (171, 255, 256, 474), suggesting that DAG mediates their physiological activation. In contrast, TRPC1, -4, and -5, which are also activated by receptor-induced PLC, are completely unresponsive to DAG (171, 475). However, the mechanism via which PLC stimulation leads to activation of these channels remains controversial. Surprisingly, one recent study reported that TRPC1 is directly activated by membrane stretch, independent of PLC activity, and that it may be the molecular correlate of the vertebrate stretch-activated cation channel MscCa (262).

Table 1 summarizes some of the key features of the members of the TRPC subfamily (for more detailed reviews, see Refs. 8, 38, 102, 111, 118, 134, 135, 200, 540, 543).

1. Store-operated TRP(C) channels?

In addition to aforementioned functions, all TRPC channels as well as several members of other TRP subfamilies (e.g., TRPV6, TRPM3) have at some point been described as store-operated channels (SOCs), i.e., channels that are activated whenever intracellular Ca^{2+} stores become depleted. Actually, TRP channels were initially considered to be the long-sought molecular correlates of SOCs. However, in many cases, the classification of TRP channels as SOCs is mainly based on the results of Ca^{2+} imaging protocols, in which store-dependent Ca^{2+} influx is estimated from the rise in $[Ca^{2+}]_i$ that occurs in cells to which extracellular Ca^{2+} is readded after artificial store depletion. Such procedures are relatively prone to error, for example, due to the lack of control of the transmembrane voltage (for a more detailed discussion of the problems and pitfalls when identifying a channel as a SOC, see Ref. 308). At present, it remains questionable whether any TRP channel plays a significant physiological role as a store-dependent channel (73, 308, 351, 449). Moreover, as long as the mechanistic link between the filling state of the Ca^{2+} stores and a plasma membrane channel remains unknown, store dependence of a channel should be considered as a phenomenon, not a mechanism.

The search for proteins that form and/or regulate SOCs has recently led to the discovery of two novel types of key players: the stromal interaction molecules (STIMs) and the four transmembrane (TM) proteins ORAIs (also known as CRACMs). First, a number of studies demonstrated that downregulation of the expression of either STIM1 or ORAI1 impairs SOC activation in response to depletion of intracellular Ca^{2+} stores (242, 361, 375, 536). Second, it was found that the absence of Ca^{2+}-release-activated Ca^{2+} (CRAC) channels in T cells from patients with a hereditary form of severe combined immune deficiency (SCID) arises from a homozygous missense muta-

TABLE 1. *Some important properties of the TRPC family members*

Channel and Ensemle Gene Identification Number	Selectivity P_{Ca}/P_{Na}	Conductance, pS	Proposed Activation Mechanisms	Proposed Protein Binding Partners
TRPC1 ENSG00000144935	Nonselective	16	PLC, OAG (weak and only in the absence of extracellular Ca^{2+}), mechanical (stretch), store depletion	TRPC4, TRPC5, TRPP1, TRPC3 (embryo), plasma membrane Ca^{2+}-ATPase, CaM, IP_3R, enkurin, homer, caveolin-1, STIM1
TRPC2 ENSMUSG00000058020	2.7	42	PLC, DAG, store depletion?	CaM, IP_3R, enkurin, junctate
TRPC3 ENSG00000138741	1.6	66	PLC, DAG, OAG, Src, IP_3, intracellular Ca^{2+}, store depletion	TRPC6, TRPC7 CaM, IP_3R, RyR, TrkB, NCX1, caveolin-1, PKG?
TRPC4 ENSG00000100991	1.1–7.7	30–41	PLC, GTPγS, micromolar La^{3+}, store depletion?	TRPC1, TRPC5, CaM, IP_3R, NHERF2, ZO-1
TRPC5 ENSG00000072315	1.8–9.0	38–64	PLC, GTPγS, receptor operated, lysophosphatidylcholine (LPC), micromolar La^{3+} or Gd^{3+}, store depletion? $[Ca^{2+}]_e$, modest elevation of $[Ca^{2+}]_i$, PIP5K, Rac, PI3K, MLCK	TRPC1, TRPC4, NCS-1, CaM, NHERF, enkurin, junctate, stathmin 2, synaptotagmin, MLCK, EBP50 (NHERF1), calcium binding protein calbindin-D28K
TRPC6 ENSG00000137672	5	28–37	PLC, DAG, OAG, src TK, 20-HETE, AIFM flufenamate	TRPC3, TRPC7, CaM, FKBP12, Fyn, MxA
TRPC7 ENSG00000069018	2	75	PLC, DAG, OAG, 20-HETE, store depletion	TRPC3, TRPC6, CaM, FKBP12

Channel names are those suggested from the unified nomenclature for TRPs (283, 284) and recently officially endorsed by NC-IUPHAR (74). Also listed are the assigned numbers from the Ensemble Genome Browser (http://www.ensembl.org/). For further details and references, please refer to the relevant sections in the text. Note that activation by phospholipase C (PLC) refers to G protein coupled receptor (GPCR)-mediated activation of PLC-β and/or RTK-mediated activation of PLC-γ. For further regulatory mechanisms not discussed here, see the excellent guides to TRP channels on the David Clapham laboratory website (http://clapham.tch.harvard.edu/) and the very comprehensive and instructive tables in Ref. 15. For more detailed information see also the Special Issues: "TRP channels: facts, fiction, challenges" *Cell Calcium* 33: 2003; and "Functional role of TRP channels" *Pflügers Arch* 451: 2005; and Refs. 307, 319, 337. For details and references, please refer to the relevant reviews. CaM, calmodulin; DAG, diacylglycerol; OAG, 1-oleoyl-2-acetyl-*sn*-glycerol; RTK, receptor tyrosine kinase; RyR, ryanodine receptor; NCX1, Na^+/Ca^{2+} exchanger isoform 1; FKBP12, immunophilin, 12-kDa FK506 binding protein; PLC, phospholipase C; IP_3, inositol 1,4,5-trisphosphate; PIP5K, phosphatidylinositol 4-phosphate 5-kinase; PI3K, phosphoinositide-3-kinase; 20-HETE, 20-hydroxyeicosatetraenoic acid; PKG, protein kinase G; NHERF, sodium-hydrogen exchanger regulatory factor; NCS-1, neuronal calcium sensor-1.

tion in the *ORAI1* gene and that expression of wild-type ORAI1 in these cells restores CRAC channel function (116). Third, whereas heterologous expression of either ORAI1, or STIM1, alone had little, or no, effect on the amplitude of SOC currents, four independent studies demonstrated that the combined heterologous expression of these two proteins led to a dramatic (up to 100-fold) increase in the amplitude of CRAC-like store-operated Ca^{2+} channels (275, 341, 406, 535). Forth, mutations of conserved acidic residues in S1 and S3 of ORAI1 strongly impair Ca^{2+} influx, enlarge monovalent cation current, and render the channel permeable to Cs^+, providing strong evidence that ORAI1 is a pore subunit of the CRAC channel (356, 523). Although the exact relationship between STIM1 and ORAI1 is currently still unsettled, an appealing hypothesis is that STIM1 acts as a Ca^{2+} sensor in the ER that relocates toward the membrane upon store depletion where it activates ORAI1, which constitutes all, or part of, the CRAC channel (331, 332). Certainly, more studies will be required to establish whether the CRAC channel is formed by ORAI1 alone, or rather in complex with other subunits. Moreover, the role of additional STIMs and ORAIs needs to be further investigated, and the possible interactions of these novel classes of proteins with other (channel) proteins mandates further research. In this context it is interesting to note that two recent independent studies indicate a functional interaction between STIM1 and TRPC1 (177, 251), suggesting that STIM1 may have a more general function in the regulation of Ca^{2+} influx channels, including members of the TRPC subfamily.

B. The TRPV Subfamily

The TRPV family contains six mammalian members: TRPV1-TRPV6, as well as Osm-9 from *C. elegans* (77) and Nanchung (Nan) from *Drosophila* (196) (for a review, see Refs. 40, 76, 152, 222, 235, 301, 327, 350, 443, 485). Members of the TRPV family contain three to five ankyrin repeats in their cytosolic NH_2 termini (49, 185, 190).

TRPV1-TRPV4 are all heat-activated channels that are nonselective for cations and modestly permeable to Ca^{2+}, with permeability ratios (P_{Ca}/P_{Na}) between ~1 and ~10. In addition, TRPV1-TRPV4 also function as chemosensors for a broad array of endogenous and synthetic ligands (7, 15, 49, 71, 72, 185, 190, 271, 285, 321, 322, 430, 470, 484, 486, 496–498, 517, 518). Finally, TRPV4 is acti-

vated upon cell swelling, which is due to the cell swelling-induced formation of the endogenous ligand 5′,6′-epoxyeicosatrienoic acid rather than to mechanosensing by the channel itself (484, 486). Interestingly, these different chemical and physical activatory stimuli mostly have an additive, or even supra-additive, effect on the gating of TRPV channels, which endows these channels with the ability to act as signal integrators. As discussed later in this review, this form of signal integration is of great importance to several pathological states. For example, the thermal hyperalgesia that occurs during inflammation reflects the fact that TRPV1 integrates both thermal and chemical stimuli (i.e., TRPV1-activating compounds in the inflammatory soup), leading to the sensation of noxious heat at innocuous temperatures.

The properties of the two other members of this subfamily, TRPV5 and TRPV6, are quite different from those of TRPV1-TRPV4. They are the only highly Ca^{2+}-selective channels in the TRP family, and both are tightly regulated by $[Ca^{2+}]_i$ (314, 317, 318, 476, 477, 528). Under physiological conditions, these channels exclusively conduct Ca^{2+}, but in the absence of extracellular Ca^{2+}, monovalent cations permeate readily, resulting in anomalous mole fraction behavior similar to that observed in other types of Ca^{2+}-selective channels (169, 318, 476, 477, 528). These properties allow TRPV5 and TRPV6 to play a crucial role as gatekeepers in epithelial Ca^{2+} transport, and as selective Ca^{2+} influx pathways in nonexcitable cells (95, 304, 305). In contrast to the other TRPVs, the temperature sensitivity of TRPV5 and TRPV6 is relatively low.

Table 2 summarizes some of the key features of the members of the TRPV subfamily.

C. The TRPM Subfamily

Members of the TRPM family, on the basis of sequence homology, fall into three subgroups: TRPM1/3, TRPM4/5, and TRPM6/7, with TRPM2 and TRPM8 representing structurally distinct channels. In contrast to TRPCs and TRPVs, TRPMs do not contain ankyrin repeats within their NH_2-terminal domain. An exceptional structural feature of three TRPM members is the presence of entire functional enzymes in their COOH termini: TRPM2 contains a functional NUDT9 homology domain exhibiting ADP-ribose pyrophosphatase activity (209, 344), whereas both TRPM6 and TRPM7 contain a functional COOH-terminal α-kinase (an atypical serine/threonine kinase) (162, 282, 379, 390).

TABLE 2. *Some important properties of the TRPV family members*

Channel and Ensemle Gene Identification Number	Selectivity P_{Ca}/P_{Na}	Conductance, pS	Proposed Activation Mechanisms	Proposed Protein Binding Partners
TRPV1 ENSG00000043316	~10 (capsaicin-activated current) ~4 (heat-activated current)	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, spermine, 2-APB, OEA, PKA, decreased $PI(4,5)P_2$, inhibited by stretch (short splice variant)	TRPA1, TRPV3?, CaM, PKC, PLC-TrkA, PP2B, calcineurin/cyclosporin, synaptotagmin, synaptogamin, FAF1
TRPV2 ENSG00000154039	1–3	ND	Noxious heat (>53°C), mechanical (stretch, swelling) Growth factors, IGF-I HA, 2-APB	PKA, RGA, ACBD3 (PAR7), dystrophin glycoprotein complex
TRPV3 ENSG00000167723	2.6	190	Heat (23–29°C), camphor, 2-APB, voltage dependent	TRPV1?
TRPV4 ENSG00000111199	6–10	90	Moderate heat (>24°C), cell swelling, shear stress, PKC, anandamide, epoxyeicosatrieonic acids, 4α-PDD, and other phorbols	CaM, MAP7, NHERF2, SGK1, SGK3, signalplex with RyR2, BKCa, glycosylation regulates membrane insertion, CFTR, aquaporin 5, Pacsin 3
TRPV5 ENSG00000127412	>100	75 (for monovalent cations)	Low $[Ca^{2+}]_i$, hyperpolarization, voltage-dependent block by Mg^{2+}	TRPV6, CaM, S100A10, annexin II, NHERF4, calbindin
TRPV6 ENSG00000165125	>100	40–70 (for monovalent cations)	Low $[Ca^{2+}]_i$, hyperpolarization, voltage-dependent block by Mg^{2+}	TRPV5, CaM, S100A10, annexin II

For references as well as channel names, numbering, and additional information, see legend to Table 1. For details and references, please refer to the relevant reviews (see text). ND, not determined; 2-APB, 2-aminoethoxydiphenyl borate; IGF-I, insulin-like growth factor I; OEA, oleoylethanalamide; 4α-PDD, 4α-phorbol 12,13-didecanoate; FAF1, Fas-associated factor 1; PKC, protein kinase C; PKA, protein kinase A; $PI(4,5)P_2$, phosphatidylinositol 4,5-bisphosphate; HA, head activator; TrkA, receptor tyrosine kinase A; PP2B, protein phosphatase 2B; RGA, recombinase gene activator; ACBD3, A kinase-associated protein (previously known as PAP7); MAP7, microtubule-associated protein 7; SGK, serum- and glucocorticoid-inducible kinase; BKCa, big-conductance Ca^{2+}-activated K^+ channel; S100A10, member of the S100 family of Ca^{2+}-binding proteins, dimeric protein, two 11-kDa subunits, also known as P11 adaptor protein.

TRPM channels exhibit highly variable permeability to Ca^{2+} and Mg^{2+}, ranging from Ca^{2+} impermeable (TRPM4 and TRPM5) to highly Ca^{2+} and Mg^{2+} permeable (TRPM6, TRPM7 and specific splice variants of TRPM3)(144, 170, 220, 224, 266, 282, 325, 340, 344, 346, 379, 380, 389, 482, 520, 522). The gating mechanisms of the TRPM subfamily members are equally varied: TRPM2 is activated by intracellular ADP-ribose (ADPR), hydrogen peroxide, and heat, whereas reported activation mechanisms for TRPM3 include cell swelling and sphingosine; TRPM4 and TRPM5 gate upon a rise in intracellular Ca^{2+} and are further strongly activated by heating. Gating of TRPM6 and TRPM7 is regulated by intracellular levels of Mg^{2+} and MgATP. Finally, TRPM8 is activated upon cooling and by cooling agents such as menthol or icilin. As yet, functional characterization of TRPM1 has not been reported (145, 170, 208, 229, 266, 269, 311, 313, 340, 344, 379, 382, 390, 436, 437, 444, 461, 481, 482, 519).

Table 3 summarizes some of the key features of the members of the TRPM subfamily. For more detailed reviews on the TRPM family, see References 2, 69, 205, 208, 272, 369, 382.

D. The TRPML Subfamily

The TRPML family consists of three mammalian members (TRPML1–3) that are relatively small proteins consisting of <600 amino acid residues. TRPML1 is widely expressed and appears to reside in late endosomes/lysosomes (30, 215, 216). It contains a nuclear localization signal and a putative late endosomal/lysosomal targeting signal (423). The loop between S1 and S2 contains a lipase domain of unknown function, although it may be speculated that this region is enzymatically active, or represents a binding site for lipids that could potentially exert a regulatory influence on TRPML1 (30). Recently, TRPML1 has been described as a H^+ channel that may act as a H^+ leak in lysosomes preventing overacidification in these organelles (199, 409). TRPML2 and TRPML3 are as yet not reliably functionally characterized.

Table 4 summarizes some of the key features of the members of the TRPML subfamily. For more detailed reviews, see References 30, 56, 363.

E. The TRPP Subfamily

The TRPP family is very inhomogeneous and can be divided, on structurally criteria, into PKD1-like (TRPP1-like) and PKD2-like (TRPP2-like) proteins.

PKD1-like members comprise TRPP1 (previously termed PKD1), PKDREJ, PKD1L1, PKD1L2, and PKD1L3. TRPP1 consists of 11 transmembrane domains, a very long and complex ~3,000 amino acid extracellular domain, and an intracellular COOH-terminal domain that interacts with the COOH terminus of TRPP2 through a coiled-coil domain (362, 455, 514). The inclusion of PKD1-

TABLE 3. *Some important properties of the TRPM family members*

Channel and Ensemle Gene Identification Number	Selectivity P_{Ca}/P_{Na}	Conductance, pS	Proposed Activation Mechanisms	Proposed Protein Binding Partners
TRPM1 ENSG00000134160	ND	ND	Translocation, MITF-induced expression	TRPM1 short transcript
TRPM2 ENSG00000142185	0.5–1.6	52–80	ADP-ribose, cADPR, NAD, heat, H_2O_2 and other ROS, inhibition of PARP-1	CaM
TRPM3 ENSG00000083067	1.6–2.0	65(Ca^{2+})–130	Cell swelling, store depletion?, D-erythrosphingosine	ND
TRPM4 ENSG00000130529	Selective for monovalent cations	25	Elevated $[Ca^{2+}]_i$, ATP, PKC, decavanadate, voltage dependent; heat, $PI(4,5)P_2$, BTP2	TRPM5, CaM
TRPM5 ENSG00000070985	Selective for monovalent cations	16–25	Elevated $[Ca^{2+}]_i$, $PI(4,5)P_2$, voltage dependent, heat	TRPM4
TRPM6 ENSG00000119121	P_{Mg}/P_{Na} ~6	ND	Decreased $[Mg^{2+}]_i$, 2-APB	TRPM7
TRPM7 ENSG00000092439	3	40–105	Decreased $[Mg^{2+}]_i$, Mg-ATP, $PI(4,5)P_2$, cAMP, G proteins, shear stress, membrane translocation	TRPM6, direct interaction with PLC
TRPM8 ENSG000000144481	1–3	83	Depolarization, cold (8–28°C), menthol, icilin, Ca^{2+}, increased intracellular pH, $PI(4,5)P_2$	Phosphatases, downregulation by PKC-mediated dephosphorylation, PP1

For references as well as channel names, numbering, and additional information, see legend to Table 1. For details and references, please refer to the relevant reviews. Note that TRPM4 data listed are for TRPM4b. ND, not determined. MITF, microphthalmia-associated transcription factor; PARP-1, poly(ADP)ribose polymerase-1; ROS, reactive oxygen species.

TABLE 4. *Some important properties of members of the TRPP and TRPML families, as well as of TRPA1*

Channel and Ensemle Gene Identification Number	Selectivity P_{Ca}/P_{Na}	Conductance, pS	Proposed Activation Mechanisms	Proposed Protein Binding Partners
TRPML1 ENSG00000090674	~1, H^+ permeable	46–83	Increased $[Ca^{2+}]_i$, inhibited by proteolytic cleavage	ND
TRPML2 ENSG00000153898	ND	ND	ND	TRPA1
TRPML3 ENSG00000055732	ND	ND	ND	TRPA1
TRPP2 ENSG00000118762	1–5	40–177	Mechanical stress, $[Ca^{2+}]_i$	TRPP1, type I IP_3R, TRPV4?, TRPC1
TRPP3 ENSG00000107593	4	137	$[Ca^{2+}]_i$	ND
TRPP5 ENSG00000078795	1–5	300	$[Ca^{2+}]_i$	ND
TRPA1 ENSG00000104321	0.8–1.4	40–105	Isothiocyanates, allicin, Δ^9-tetrahydrocannabinol (THC), cinnamaldehyde, prolonged noxious cold?, mechanical stress, voltage dependent, $[Ca^{2+}]_i$ dependent, OAG and arachidonic acid downstream of receptor-mediated PLC activation	TRPML2, TRPML3, CYCL, TRPV1

For references as well as channel names, numbering, and additional information, see legend to Table 1. For details and references, please refer to the relevant reviews mentioned in the text. ND, not determined; CYCL, tumor suppressor protein, ubiquitin hydrolase.

like proteins within the TRP superfamily is at present somewhat tentative and rests upon a degree of structural similarity between TRP channels and the six distal transmembrane domains of at least some PKD1-like members (i.e., PKD1L2, PKD1L3, and PKDREJ) (91, 363). The NH_2-terminal domain of TRPP1 contains numerous structural motifs including several adhesive domains that are likely to participate in cell-cell and cell-matrix interactions. TRPP1-like proteins possess a large extracellular loop, containing conserved "polycystin motifs" of unknown function, between presumed S6 and S7. The latter region is homologous to the loop interposed between the putative S1 and S2 in the TRPP2-like family members (363).

The PKD2-like members structurally resemble other TRP channels in that they are predicted to have intracellular NH_2 and COOH termini, six TM-spanning domains, and a pore region. The members of this grouping comprise PKD2 (TRPP2), PKD2L1 (TRPP3), and PKD2L2 (TRPP5). All PKD2-like members possess a coiled-coil structure in their COOH terminus and form polymodal multiprotein/ion channels complexes (91). TRPP2 and TRPP3 additionally feature a Ca^{2+}-binding EF-hand motif in the COOH terminus. Whether this motif provides the sensor via which Ca^{2+} exerts a regulatory influence on TRPP2 (204) is at present unclear. In heterologous expression systems TRPP2 and TRPP3 form constitutively active cation-selective channels of relatively large conductance (90, 94, 408). Both channels are permeable to Ca^{2+}, with TRPP3 displaying modest selectivity towards the divalent cation (91). Interestingly, TRPP3 has been recently identified as a possible sour taste sensor in mammals (176, 184).

There is considerable evidence that TRPP1 and TRPP2 physically couple to act as a signaling complex at the plasma membrane to which TRPP2 is recruited by TRPP1 (92, 156). Their association suppresses the ability of TRPP1 to activate G proteins (93) as well as the constitutive channel activity of TRPP2 (92). Antibodies directed against an extracellular domain of TRPP1 alleviate such mutual inhibition, simultaneously enhancing channel activity of TRPP2 and G protein activation by TRPP1 (92). Such a mode of activation might mimic the physiological stimulus that activates the complex. TRPP3 and PKD2L3 form a receptor for sour taste (176, 184).

Table 4 summarizes some of the key features of the members of the TRPP subfamily. For more detailed reviews, see References 91, 203, 211, 281, 363.

F. TRPA

The TRPA family currently comprises one mammalian member, TRPA1, which is expressed in dorsal root ganglion (DRG) and trigeminal ganglion (TG) neurons and in hair cells (82, 295, 415). TRPA1 exhibits 14 NH_2-terminal ankyrin repeats (415), an unusual structural feature that may be relevant to the proposed role of the channel as a mechanosensor (221, 295).

Some reports (31, 415) claim that TRPA1 can be activated by noxious cold (−17°C), although such a mode of stimulation has been disputed by others (35, 189, 295). Indirect support for a thermosensitive function of TRPA1 derives from recent reports that antisense knockout of TRPA1 alleviates cold hyperalgesia subsequent to spinal nerve ligation (192) and that the upregulation of the channel in sensory neurons following injury and inflammation contributes to cold hyperalgesia (324). Unfortunately, the recent generation of two independent TRPA1 knockout mouse models has not settled the controversy regarding whether TRPA1 is activated by noxious cold (see below). Chemical activators of TRPA1 include isothiocyanates (the pungent compounds in mustard oil, wasabi, and

horseradish) (31, 189), methyl salicylate (in winter green oil) (31), cinnamaldehyde (in cinnamon) (31), allicin and diallyl disulfide (in garlic) (35, 258), acrolein (an irritant in vehicle exhaust fumes and tear gas) (35), and Δ9 tetrahydrocannabinol (Δ9THC, the psychoactive compound in marijuana) (189). Table 4 summarizes some of the key features of TRPA1. For a more detailed review, see Reference 270.

TRPN is a channel that is closely homologous to TRPA1. It is characterized by 29 ankyrin repeats within the NH_2 terminal. To date, this subfamily comprises only one member in *C. elegans*, *Drosophila*, and zebrafish (400, 488). TRPN1 probably acts as a mechanotransduction channel that is involved in hearing. Mammals apparently lack the TRPN gene (82).

III. THE TRP CHANNEL FAMILY AND DISEASES

A. Introductory Remarks

Defects in ion channel function are widely suspected to be the cause of various diseases, so-called channelopathies. However, of the ~300 ion channels predicted in the human genome (http://www.ncbi.nlm.nih.gov/RefSeq; www.celeradiscoverysystem.com), relatively few have been directly connected to human diseases. Nonetheless, this number is constantly increasing (see the most recent reviews in Refs. 25, 191).

Channelopathies are traditionally defined as diseases coupled with identified defects in the gene encoding the channels. Following this definition, five TRP channel-related channelopathies have been identified to date. However, perturbation of physiological functions mediated by ion channels can also contribute more subtle to the genesis of several diseases. Such effects may be provoked by changes in channel abundance, or channel sensitization, or desensitization, resulting in exaggerated, or diminished, responses to various pathological stimuli. Abnormal endogenous production of various agents during the development of a disease (for example, in inflammation or autoimmune conditions) can affect channel function in a manner that contributes to the progression of the disease. Many members of the TRP superfamily are potential targets for such pathogenic factors. Abnormal regulation of ion channel function is especially interesting in all forms of inflammation and in systemic diseases, such as neurodegenerative, cardiovascular, and respiratory diseases. TRP channels are exceptional in the sense that they are often polymodal, i.e., they are activated by multiple and diverse gating stimuli and act as molecular integrators of these external and/or internal signals.

Unfortunately, our knowledge of the detailed mechanisms through which TRP channels function is still elementary. Such a situation hampers both our understanding of the mechanistic role of TRP channels in human disease and the development of drugs to target TRPs and their specific functions. The more we learn about fundamental TRP channel physiology and the potential role of TRPs in disease, the closer we will come to the development of novel therapies for various disease states. Ion channels are established targets for drugs as witnessed by a variety of therapeutically valuable agents that exert their action through, for example, members of the Cys-loop superfamily of transmitter-gated ion channels, and voltage-activated sodium, potassium, and calcium channel families. However, considering ion channels as a whole, therapeutically useful drugs have been developed for only a handful of targets. The situation is particularly critical for the TRP channel superfamily due to the paucity of selective modulators. To date, the only member of the TRP superfamily that has been targeted is TRPV1: TRPV1 antagonists and compounds that induce fast channel desensitization have been used in the treatment of pain, bladder, and gastrointestinal diseases (see below).

In general, dysregulation of TRP channel function may lead to disease by one or more of the following mechanisms.

Most TRP channels play a role in Ca^{2+} signaling. Given the universal role of Ca^{2+} as a signaling molecule, dysfunctions in Ca^{2+} signaling due to altered TRP channel function can have strong effects on a variety of cellular and systemic processes.

TRP channels can act as general polymodal cellular sensors, measuring changes in the environment to initiate adequate cell organ and behavioral response. Mistuning in these sensory inputs may cause multiple forms of cellular and somatosensory dysregulation.

Some TRP channels function as gatekeepers for the selective (re)absorption of ions such as Mg^{2+} and Ca^{2+}. Dysfunction will lead to general disturbances in Mg^{2+} and Ca^{2+} homeostasis.

Some TRP channels are present on intracellular membranes, where their malfunctioning may lead to disturbed organelle function. One clear example is the dysregulation of lysosome function due to mutations in TRPML1 (30).

Several TRP channels are involved in the control of cell proliferation and growth. Dysfunctions may lead to growth disturbances, altered organogenesis, or cancer.

Some TRP channels play an important role in the trafficking of interacting proteins. Mistargetting of these binding partners may underlie a variety of pathological conditions.

TRP channels have the potential to modulate the electrical activity of excitable cells, e.g., in brain and heart. Investigating the consequences of TRP channel dysfunction on electrically complex cell functions such as

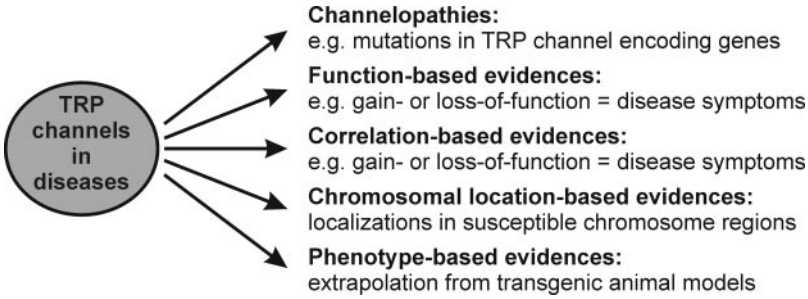


FIG. 2. TRPs and disease. Overview of the various extrapolations of a possible involvement of TRP channels in the pathogenesis of diseases.

generation of spontaneous electrical activity is an important challenge for future research.

In the sections that follow we describe established TRP channelopathies and draw upon a number of lines of evidence that are suggestive of the involvement of TRP channels in disease (Fig. 2). The expanding generation of TRP channel null-mutant mice and other transgenic models will allow the extrapolation of observed perturbations, at least to a certain extent, to human physiology and disease (96, 122, 123). An important caveat in such approaches is that the absence of a phenotype in knockout mice does not preclude an important function of the targeted channel, because compensatory mechanisms may mask a deficit. We will also consider the following: *1*) function-based evidence (where changes in TRP channel function may be associated with symptomatology), *2*) genetic evidence (where genes encoding TRP channels reside within vulnerable chromosomal regions), and *3*) correlation-based evidence (where a disease state appears to be associated with changes in the abundance of individual TRP channels). Finally, the established, or potential, contribution of individual TRP channels to various disease groups is summarized in Table 5.

B. Dysfunctions in TRP Channelopathies

Genetic defects in four TRP channels (TRPC6, TRPM6, TRPP2, and TRPML1) have been identified as the direct underlying cause of hereditary diseases. In addition, a variation in TRPM7 has been associated with an increased risk for two neurodegenerative diseases.

1. TRPC6 and focal segmental glomerulosclerosis

Six mutations of the *TRPC6* gene have very recently been linked to the human proteinuric kidney disease focal and segmental glomerulosclerosis (FSGS) of the late-onset type (370, 507). In this disease, which is distinct from the early-onset form of FSGS, the podocyte foot processes and the glomerular slit diaphragms of the glomerular filter are initially well developed and functional but lose their integrity between childhood and late adulthood (207, 370, 507). Three of the identified mutations of the *TRPC6* gene are missense mutations that result in enhanced signaling (gain of function) by TRPC6 via specific amino acid substitutions. The P112Q substitution enhances plasma membrane expression of heterologously expressed TRPC6 and increases both inward current responses and the $[Ca^{2+}]_i$ transient evoked by G protein-coupled receptors (GPCRs) that signal through PLC-β (507). Similarly, TRPC6 R895C and E897K mutants display enhanced activity following GPCR activation, but neither the remaining missense mutations (N143S, S270T) nor the truncated mutant K874X give evidence of perturbed function (370).

Among other sites in the nephron, TRPC6 is expressed in the podocytes in the kidney glomerular filter (Fig. 3) (370, 507). Podocyte foot processes and the glomerular slit diaphragm form the glomerular filter and are an essential part of the permeability barrier in the kidney, which is defective in FSGS (108, 207). A lack of nephrin, a transmembrane protein of the immunoglobulin superfamily and a central component of the slit diaphragm, induces increased TRPC6 expression in podocytes and leads to an altered localization of TRPC6 (370). The defect in the filter function results in proteinuria and progressive kidney failure leading to end-stage renal failure (148, 207, 489). It is uncertain how mutations in TRPC6 translate into the development of FSGS, but at least for those mutations that result in gain of function there are some logical possibilities. Enhanced Ca^{2+} entry may constitute a pathogenic trigger, such as a Ca^{2+} overload of the podocyte that initiates cell death by apoptosis, or causes dysregulation that compromises the integrity of the permeability barrier (370). Notable in this regard is the renoprotective action in FSGS of agents that reduce the activity of the renin-angiotensin-aldosterone system, including angiotensin coverting enzyme (ACE) inhibitors and competitive antagonists of the angiotensin-1 (AT_1) receptor (507, 508). As mentioned above, activation of GPCRs signaling through PLC-β in podocytes, for example, through activation of the AT1 receptor, evokes exaggerated $[Ca^{2+}]_i$ influx in cells expressing the TRPC6 P112Q mutant. Alternatively, mutations in TRPC6 may impair the ability of the podocyte to adapt to the normal physiological demands of maintaining the functional glomerular filter, such as responding to changes in glomerular filtra-

TABLE 5. *Proposed functions of TRPs and possible relationships to diseases*

			Possible Disease Connections		
	Proposed Function	Channelopathy	Functional evidence *(transgenic mouse models)*	Genetics and genetic mapping evidence (OMIM*)	Reference Nos.
TRPC1 3q22-3q24	Via coupling to metabotrobic mGlu1 mediates slow EPSCs, mechanosensor, growth cone guidance	ND	Asthma, bronchial hyperresponsiveness, COPD, defective immunresponse in B cells, T cells (NFAT), heart hypertrophy, Duchenne muscular dystrophy, neurodegenrative disorders	Myotonic dystrophy type 2, hypertension, Seckel syndrome	52, 210, 364, 428, 491, 505
TRPC2 pseudogene	Pheromone sensing in mice, acrosome reaction	ND	*Gender recognition defect behavioral defects*	ND	227, 416, 543
TRPC3 4q27	BDNF-mediated neuronal differentiation, vasomotor function, resistance vessel, airway regulator, antigene stimulation of lymphocytes, growth cone guidance	ND	Pulmonary disease, idiopathic pulmonary arterial hypertension (IPAH), heart hypertrophy, essential hypertension	ND	245, 527
TRPC4 13q13.1-q13.2	Vasomotor function, microvascular permeability, GABAergic input lateral geniculate nucleus	ND	COPD, *impairment of endothelium-dependent vasorelaxation and endothelial barrier function*	Breast cancer, atopic dermatitis	121, 122, 292, 439
TRPC5 Xq23	Growth cone morphology, growth cone guidance, brain development	ND	COPD	Coronary heart disease, X-linked mental retardation, migraine	139, 143, 233
TRPC6 11q21-q22	Vasomotor function, smooth muscle, platelet aggregation, mechanosensor	Proteinuric kidney disease focal and segmental glomerulosclerosis (FSGS, OMIM 603965)	IPAH, heart hypertrophy, mucus hypersecretion in COPD, Duchenne muscular dystrophy, neurodegenerative disorders, *defective vasomotor control, sensitized myogenic response (TRPC3 upregulation)*	COPD, lung cancer	225, 230, 231, 328, 370, 508, 527
TRPC7 5q31.2	Role in immune response	ND	ND	ND	239
TRPV1 17p13.3	Sensing spicy (hot) peppers, pain sensation, noxious temperature sensing, sensor bladder distension	ND	Thermal hyperalgesia, allodynia, functional bowel disease (FBD), inflammatory bowel disease (Crohn, OMIM 266600), vulvodynia, osteoarthritis, pancreatitis, GRD (gastroesophageal reflux disease), bladder disease, cystitis, asthma, migraine, schizophrenia, pain in general (tooth pain)	Breast cancer, myasthenic syndrome, non-insulin-dependent diabetes mellitus	10, 22, 131, 132, 263, 298, 299, 333, 350, 441, 459, 524
TRPV2 17p11.2	Sensing thermal pain, mechanosensing	ND	Muscular dystrophia (disruption dystrophin-glycoprotein complex), cardiomyopathy, *cardiac hypertrophy*	Central areolar choroidal dystrophy, myasthenic syndrome, prostate cancer	16, 126, 185
TRPV3 17p13.3	Warm sensing, osmosensing	ND	*Defective environmental thermosensation. Hairlessness and* atopic dermatitis	Breast cancer, myasthenic syndrome, non-insulin-dependent diabetes mellitus	24, 285
TRPV4 12q24.1	Osmosensing (CNS), warm sensing, nociception, pressure sensing (DRG)	ND	Hypotonic hyperalgesia, allodynia, thermal hyperalgesia, asthma, bronchial hyperresponsiveness, neuropathic pain, ADNSHL (autosomal nonsyndromic hearing loss), impairment of osmoregulation, hypertension, *defective environmental themosensation*	Central hypoventilation syndrome, cardiopathy	13, 14, 21, 124, 237, 238, 432, 440
TRPV5 7q35	Ca^{2+} reabsorption kidney (absorption in duodenum), vitamin D sensitive	ND	Defective Ca^{2+} reabsorption, *hypercalciuria, osteoporosis, Zucker diabetic fatty rats*	Renal tubular acidosis, cancer	166, 186, 304, 469

TABLE 5—*Continued*

	Proposed Function	Channelopathy	Possible Disease Connections: Functional evidence *(transgenic mouse models)*	Possible Disease Connections: Genetics and genetic mapping evidence (OMIM*)	Reference Nos.
TRPV6 7q33–34	Ca^{2+} absorption duodenum (reabsorption in kidney)	ND	Increased in prostate cancer, *Ca^{2+} malabsorption, decreased fertiliy, alopecia, Ca^{2+} wasting, reduced bone*	Renal tubular acidosis, cancer	304, 342, 509, 541
TRPM1 15q13-q14	Tumor suppressor	ND	Downregulation in malignant melanomas	Lymphoma, hypertension	107
TRPM2 21q22.3	Oxidant stress sensor in immune cells, glia in brain, respiratory bursts in neutrophils, temperature dependent, Ca^{2+} entry in pancreatic β-cells	ND	BP-I, -II (bipolar disorder), nonsyndromic hereditary deafness neuronal cell death	Epilepsy, leukemia; holoprosencephaly HPE1 (OMIM 236100), Knobloch syndrome (OMIM 267750)	294, 504, 515, 525
TRPM3 9q21.11	Ca^{2+} absorption in kidney osmosensor, mechanosensor	ND	Defective Ca^{2+} reabsorption	Candidate genes for amyotrophic lateral sclerosis with frontotemporal dementia (OMIM 105550), early-onset pulverulent cataract (OMIM 605749), hemophagocytic lymphohistiocytosis (HLH, OMIM 603552), infantile nephronophthisis (OMIM 602088)	224
TRPM4 19q13.32	Ca^{2+} oscillation in T lymphocytes, mast cells, pneumocytes type II, macula densa cells, negative-feedback regulator for Ca^{2+} entry, Bayliss effect, slow waves in sleep, memory function in entorhinal cortex, mechanosensor, temperature dependent	ND	Hyperresponsiveness in immune cells, induction of proinflammatory conditions, allergy, defective surfactant secretion in pneumocytes type II-, defective Bayliss effect, trigger for paroxysmal depolarization shift (PDS), spreading depression hypoxic depolarization, stroke	Diabetes mellitus, prostate cancer, leukemia, lymphoma	219, 385, 403
TRPM5 11p15.5	Sweet, bitter, umami taste, temperature dependent	ND	Taste dysfunction	Beckwith-Wiedemann syndrome (BWS, OMIM 602131, 602631), diabetes mellitus, breast, bladder and lung cancers	357
TRPM6 9q22	Mg^{2+} (re)absorption duodenum, kidney	Autosomal-recessive, hypomagnesemia with secondary hypocalcemia (HSH/HOMG 1; OMIM 602014)	Defective Mg^{2+} reabsorption	Spastic paraplegia, deafness, amyotrophic lateral sclerosis with frontotemporal dementia	389, 487
TRPM7 15q21	Mg^{2+} homeostasis, cell cycle regulation, entry pathway for trace metals	Amyotrophic lateral sclerosis-Parkinsonism/dementia complex (ALS-G/PD-G Guam disease; OMIM 105500)	Target for exitotoxicity in brain, neuronal cell death, defective vacscular remodelling, hypertension, stroke, *defective ossification (zebrafish model)*	Spinocerebellar ataxia, colorectal adenoma and carcinoma, susceptibility to dyslexia	1, 113, 163, 447
TRPM8 2q37.1	Cold sensing, pain pathway, sensor	ND	Cold hyperalgesia, upregulated in tumors of prostate, breast, colon, lung, skin, painful bladder syndrome	Chronic obstructive pulmonary disease, Parkinson's disease	289, 454, 456, 532
TRPP2 4q21–23	Cardiac and skeletal muscle and kidney development, tubulogenesis, mechanosensation in primary cilia, sperm movement	Autosomoal dominant polycystic kidney disease (ADPKD; OMIM 173910)	Cardiac septal defects, disturbances left-right axis, organ localization, possibly associated with Bardet-Biedl syndrome, some connection with ARPKD (autosomal recessive polycystic kidney disease)	Neutropenia, susceptibility to psoriasis	232, 343, 408, 424
TRPP3 10q24-q25	Kidney development, retinal development, sour taste	ND	ARPKD, *krd mouse with kidney-retina defects and in severe cases with brain defects, relation to pax2*	Renal hypoplasia, optic nerve coloboma with renal disease, epilepsy, Alzheimer's desease	153, 154, 329, 511
TRPP5 7p13-p12	ND	ND	ARPKD	Epilepsy, allergy and asthma susceptibility, muscular dystrophy, inflammatory bowel disease	511
TRPA1 8q13	Activation by pungent painfull stimuli (mustard oil, wasabi, horseradish, garlic, onions, ⋯), activated by bradykinin (PLC dependent), mechanotransduction channel, noxious cold	ND	Inflammatory pain, cold hyperalgesia, *cold hyperalgesia, mechanical pain, mechanical hypersensitivity, inflammatory pain*	Spastic paraplegia, sensorineural deafness, convulsions	31, 35, 189, 214, 295

TABLE 5—*Continued*

	Proposed Function	Channelopathy	Possible Disease Connections: Functional evidence *(transgenic mouse models)*	Possible Disease Connections: Genetics and genetic mapping evidence (OMIM*)	Reference Nos.
TRPML1 19p13.3-13.2	Intracellular protein sorting/transport, role in late endosomal pathway, endocytosis	Mucolipidosis IV (ML IV, OMIM 252650)	ND	Alzheimer's disease, liposarcoma, mental retardation	29, 199, 405, 409
TRPML2 1p22	ND	ND	Candidate gene for neurosensory disorders, *associated with varitint-waddler (Va)*	ND	99, 195
TRPML3 1p22.3	Maturation of hair cells, retina, intracellular trafficking	ND	Candidate gene for neurosensory disorders, *associated with varitint-waddler (Va) mouse*	ND	99, 195

For details and references, see text. Functional evidences of possible disease connections obtained from transgenic mouse models are in italics. ND, not determined; EPSC, excitatory postsynaptic current; BDNF, brain-derived neurotrophic factor; DRG, dorsal root ganglion; NFAT, nuclear factor of activated T cells. * For more possible associations, see http://www.ncbi.nlm.nih.gov/entrez/query.fcgidb-OMIM.

tion pressure. Possibilities also include a role for TRPC6 in the guidance of proteins such as nephrin and podocin, which are required to maintain the filtration barrier (508). Further functional characterization of the disease-causing mutations and their interactions with components of the glomerular filter is required to answer these questions. In addition, the development of a transgenic mouse model for FSGS, for example, by replacing wild-type TRPC6 by one of the disease-causing mutants or even by inducing overexpression of wild-type TRPC6, would be instrumental in further unraveling the role of TRPC6 in kidney function and FSGS.

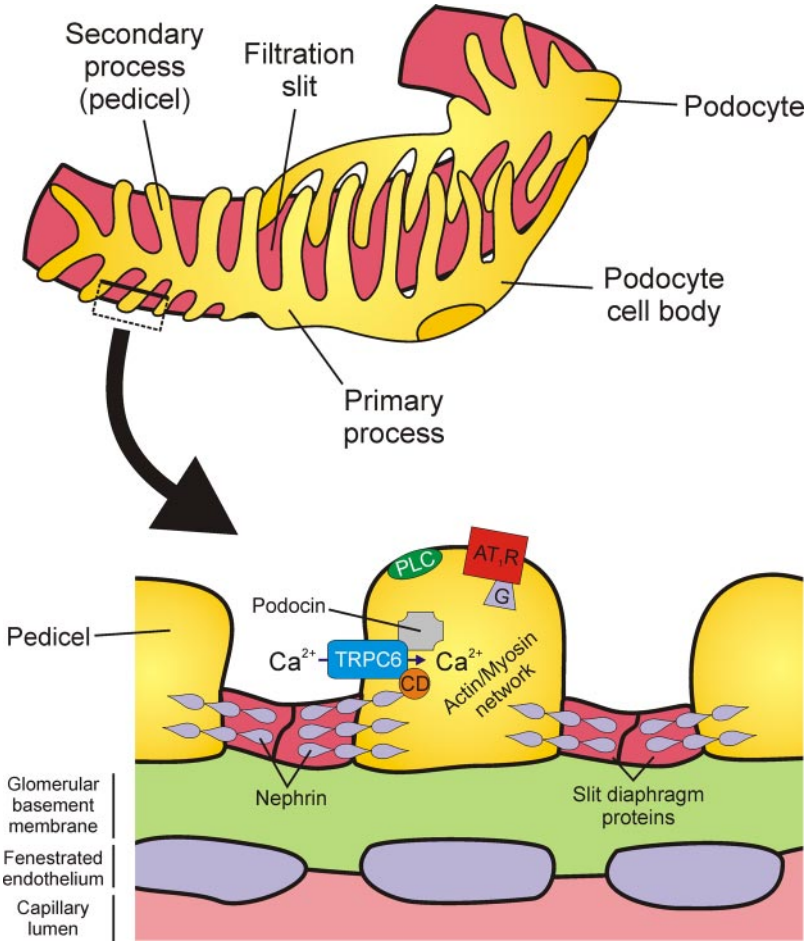


FIG. 3. The glomerular filtration barrier. Two podocyte foot processes bridged by the slit membrane, the glomerular basement membrane, and the porous capillary endothelium are shown. The surfaces of the podocytes and of the endothelium are covered with a negatively charged glycocalyx containing the sialoprotein podocalyxin. The glomerular basement membrane is composed mainly of collagen IV, laminin 11, and the heparan sulfate proteoglycan agrin. The slit membrane is a porous proteinaceous membrane composed of (as far as is known) nephrin (Neph1, -2, and -3), P-cadherin, and FAT1. The slit membrane proteins are joined to the cytoskeleton by various adaptor proteins, including podocin, zonula occludens protein 1 (ZO-1; Z), CD2-associated protein (CD), and catenins. TRPC6 associates with podocin, CD, and nephrin at the slit membrane. Among the many surface receptors, only the angiotensin II (AT) type 1 receptor (AT1) is shown (for more detailed information, see Ref. 207).

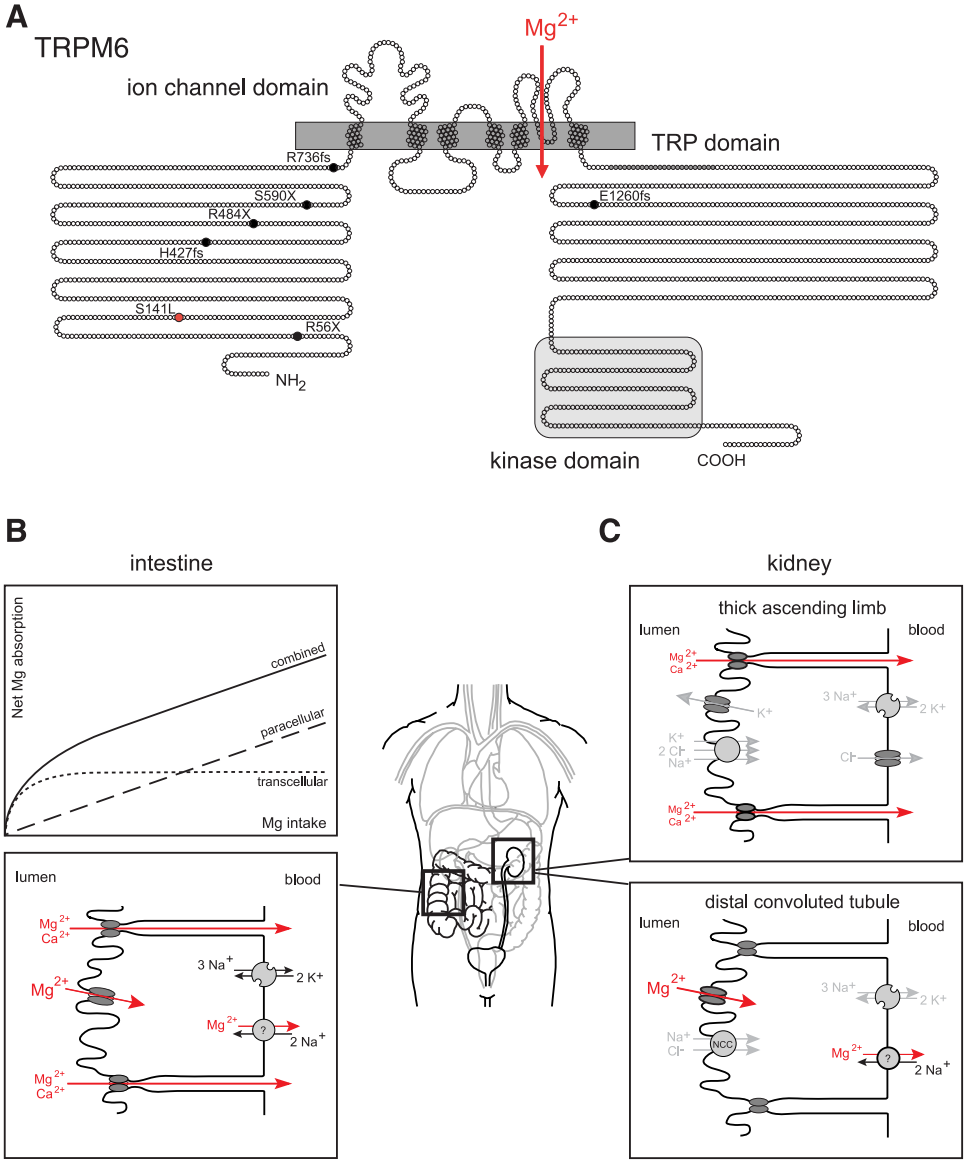


FIG. 4. TRPM6 and Mg^{2+} reabsorption. *A*: the TRPM6 protein is a cation channel region with six transmembrane domains, a pore region, a long NH_2 terminus conserved within the TRPM family, the TRP domain of unknown function located COOH-terminally of the ion channel domain, and a COOH-terminal kinase domain with sequence similarity to the atypical α-kinases. The mutations identified in hypomagnesemia with secondary hypocalcemia (HSH) patients are shown. Note that only one single point mutation S141L (red) was identified. *B*: epithelial magnesium transport in intestine and kidney. The intestinal absorption demonstrates curvilinear kinetics resulting from the summation of two transport mechanisms: a saturable transcellular transport (dotted line), which is of functional importance at low intraluminal concentrations, and a paracellular passive transport (dashed line) rising linearly with intraluminal Mg^{2+} concentrations. TRPM6 is a component of the active transcellular pathway, but HSH patients are able to compensate for their genetic defect by high oral magnesium intake. *C*: in the thick ascending limb (TAL), Mg^{2+} is reabsorbed via the paracellular route. A specific tight junction protein between the cells of the TAL, namely, paracellin-1, or claudin-16, permits the selective paracellular flux of Ca^{2+} and Mg^{2+}. Defects in paracellin-1 lead to combined calcium and magnesium wasting. *D*: the distal convoluted tubule (DTC) reabsorbs Mg^{2+} in a transcellular fashion, consisting of an apical entry into the DCT cell through the Mg^{2+}-selective ion channel TRPM6 and a basolateral extrusion of unknown molecular identity (69; see also Ref. 202). [Adapted from Schlingmann and Gudermann (387).]

2. *TRPM6 and hypomagnesemia with secondary hypocalcemia*

Most TRP channels are involved in Ca^{2+} signaling. Much less is known about Mg^{2+}, although it constitutes the third most common cation in the intracellular fluid ($[Mg^{2+}]_i$ = 0.5–1.0 mM) and the Mg^{2+} entry mechanism is incompletely understood. Mg^{2+} homeostasis demands precise regulation of the plasma concentration of Mg^{2+}, which is generally within the range of 0.9–1.0 mM and dependent on a balance between intestinal absorption and renal excretion (69, 202). Heterologously expressed TRPM6 forms a Mg^{2+}-permeable channel, and TRPM6 is primarily expressed in the brush-border membrane of the small intestine and in the apical membrane of the renal distal convoluted tubule (DCT), which both contain highly specialized cells responsible for Mg^{2+} absorption and reabsorption (Fig. 4) (482). TRPM6 provides an important influx pathway for Mg^{2+} and other divalent cations and is at the same time tightly regulated by the intracellular concentration of Mg^{2+} (482). One subsequent study contested this view and reported that TRPM6 can only form a functional cation channel in combination with TRPM7 (70). However, recent data confirm that TRPM6 can indeed form functional homotetrameric Mg^{2+}-permeable channels, although TRPM6 + TRPM7 heterotetrameric channels are also functional (229).

The *TRPM6* gene has been mapped to chromosome 9q21.13, an area identified as the "HSH-critical region." Defects in this chromosomal locus have been associated with the disease hypomagnesemia with secondary hypocalcemia (HSH; or HOMG) (Fig. 4) (389, 487). HSH is an autosomal-recessive disorder that is characterized by

very low serum levels of Mg^{2+} and Ca^{2+}. The primary defect is attributable to impaired intestinal Mg^{2+} absorption in the presence of an additional renal Mg^{2+} leak. The defect in intestinal transport distinguishes HSH from all other known forms of hereditary hypomagnesemia. Patients with HSH display a multitude of neurological symptoms, including seizures and muscle spasms during infancy. HSH progression may result in death if untreated. Life-long dietary Mg^{2+} supplementation can widely suppress the symptoms and therefore allows higher life expectancy, even though serum Mg^{2+} levels often remain subnormal (0.5–0.6 mM). Detailed analysis of the HSH-critical region revealed a variety of mutations in the *TRPM6* gene in all tested HSH patients, which emphasizes the importance of functional TRPM6 transcripts in Mg^{2+} homeostasis. Most mutations result in a truncated protein through the introduction of stop codons, although single point mutations, frame-shift mutations, exon deletions, and mutations affecting alternative splicing have also been described (388, 389, 487).

Intestinal Mg^{2+} uptake in the brush-border epithelia occurs in a curvilinear manner and is regulated by two independent pathways: *1*) passive paracellular absorption, which rises linearly with increasing luminal Mg^{2+} concentrations, and *2*) transcellular transport, driven by secondary active transport, reaching saturation at high luminal Mg^{2+} levels (Fig. 4) (202). TRPM6 represents an essential molecular component of the active transcellular Mg^{2+} uptake at the apical membrane. The significance of saturation at high luminal Mg^{2+} concentrations is to prevent the cell being overloaded with Mg^{2+}. This feedback mechanism is provided by TRPM6 itself, which is highly regulated by the intracellular concentration of Mg^{2+} (482). Electrophysiological studies on TRPM6 in heterologous expression systems revealed that both Mg^{2+} and Ca^{2+} block TRPM6 currents in a voltage-dependent manner, with higher affinity for Mg^{2+} (482). On the basolateral aspect of the epithelial cell, a yet unidentified Na^+/Mg^{2+} exchanger accounts for onward transport of Mg^{2+} into the interstitial space and blood. The situation in HSH, where the transcellular pathway is not functional, requires utilization of the paracellular pathway to allow Mg^{2+} absorption. This effect can only be achieved by increasing the luminal Mg^{2+} concentration with a high-Mg^{2+}-containing diet [up to 16-fold higher than the normal recommended daily intake (78)] to generate a stronger driving force for the passive Mg^{2+} uptake. Unfortunately, such high luminal levels of Mg^{2+} act as an osmotic laxative and frequently result in severe diarrhea.

The situation in the DCT of the nephron is different. Although most reabsorption of Mg^{2+} in the nephron occurs via a paracellular pathway in the thick ascending limb of the loop of Henle, it is the DCT that determines the final reabsorption of filtered Mg^{2+} from the lumen to the blood and thus the final urinary Mg^{2+} excretion. In the DCT, paracellular transport of Mg^{2+} does not occur, and TRPM6, located on the apical membrane of the epithelial cells, is the obligate pathway for the active reabsorption of Mg^{2+}. If this pathway is defective, as in HSH, no further Mg^{2+} can be reabsorbed, resulting in the urinary Mg^{2+} leak that has often been observed in HSH patients.

Interestingly, colorectal cancer can be successfully treated with an antibody (cetuximab) directed against the epithelial growth factor receptor (EGFR) (391). However, unwanted side effects often observed in these patients are the typical HSH syndromes (i.e., hypomagnesemia and secondary hypocalcemia). It will be of high interest to investigate whether the EGFR has a modulatory influence on TRPM6 function.

3. TRPP2 and autosomal dominant polycystic kidney disease

Although the functional analysis of the TRPPs (polycystins) is not yet as developed as for most other TRP subfamilies, their involvement in human disease has been studied most extensively. Mutations in either TRPP1, or TRPP2, lead to polycystic kidney disease (PKD), which is characterized by the progressive development of large fluid-filled cysts in the kidney. Cysts can occupy much of the mass of the abnormally enlarged kidneys, thereby compressing and destroying normal renal tissue and impairing kidney function. Approximately 50% of patients with the primary form of PKD will progress to kidney failure, or end-stage renal disease (ESRD) (141). PKD is the most common inherited cause of kidney failure.

Autosomal dominant PKD (ADPKD) is by far the most prevalent, inherited, form of PKD accounting for ~90% of cases. The symptoms of ADPKD usually develop between the ages of 30 and 40, but they can commence earlier, even during childhood. In most instances, ADPKD arises from mutations in the *TRPP1 (PKD-1)* or *TRPP2 (PKD-2)* genes (Fig. 5) (424). Mutations in TRPP1 (56 disease-causing mutations are known, 384 single nucleotide polymorphisms, SNPs) account for 85% of ADPKD and are associated with a more severe disease (appearing earlier) than that caused by TRPP2 mutations (45 disease causing mutations being known, 186 SNPs) (see also Ref. 514). The survival time of patients with TRPP2 mutations is longer than for those with TRPP1 defects. The cysts are not confined to the kidney, but also occur in hepatic tissue, brain tissue, and pancreatic ductal tissue. It is assumed that cystic tissue lacks functional TRPP1/TRPP2 (90, 94, 408). Other abnormalities associated with TRPP1 mutations include valvular defects in the heart, cerebral and aortic aneurysms, diverticulae in the colon, and inguinal hernia. TRPP2 mutations are also related to structural defects in the heart, e.g., defective septum formation. Mutations in TRPP2 in mice recapitulate all the cystic abnormalities, cardiac septum defects, and lead to

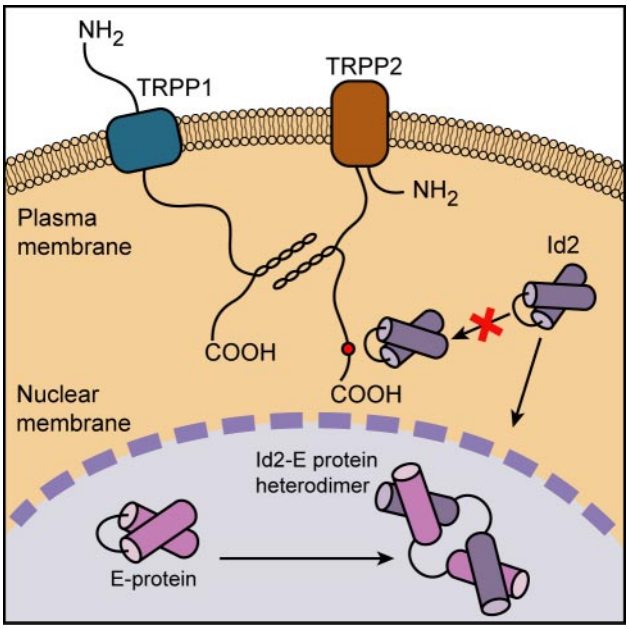


FIG. 5. Model of the mechanisms of TRPP2 action. TRPP2 sequesters Id2 in the cytoplasm. Normally, phosphorylated TRPP2, associated with TRPP1, prevents nuclear translocation of Id2 by binding it to the COOH terminus. TRPP1/TRPP2 mutations allow Id2 to dissociate and trasnlocate into the nucleus (arrow) where it binds to E-protein family members. E-proteins activate growth supressor genes. If Id2 binds to E-proteins, the activity of growth suppression proteins is switched off and genes activating G_1-S progression (e.g., Cdk2) are activated. This mechanism may explain the hyperproliferative feature of autosomal dominant polycystic kidney disease (ADPKD). [Adapted from Gomez (139) and Li et al. (232).]

embryonic whole body edema, renal failure, and early death (513).

ADPKD is the result of a two-hit mechanism whereby somatic inactivation of the normal allele in individual polarized epithelial cells results in loss of heterozygosity and initiates cyst formation (408). Early cyst formation, which can occur in any segment of the nephron, is associated with an increase in the number of cells in the circumference of already dilated renal tubules (50). Normally, lengthening of tubules is associated with mitotic orientation of cells along the tubule axis. This process is lacking in epithelial cells from PKD models (117).

Recently, it was shown that both basal and EGF-stimulated kidney cell proliferation are upregulated in cells that lack TRPP2, indicating that it acts as a negative regulator of cell growth. A possible explanation of that effect has been recently proposed (39, 232). TRPP1 and TRPP2, when localized in the cell membrane, inhibit the transfer of the helix-loop-helix (HLH) protein Id2, a crucial regulator of cell proliferation and differentiation, into the nucleus. Phosphorylation of the COOH terminus of TRPP1, which probably recruits TRPP2 to the cell membrane and forms a receptor-ion channel complex, is necessary for Id2 binding. When this binding is defective, for example, in ADPKD, Id2 can enter the nucleus and activate G_1-S progression. Correspondingly, renal epithelial cells from ADPKD patients demonstrate a clearly enhanced nuclear localization of Id2 (232). This could be a mechanism for the hyperproliferative phenotype in ADPKD and may cause cyst formation. Interestingly, the above mechanism involving Id2 could be important for other proliferative disorders.

TRPP2 is important for cilia movement and for the development of heart, skeletal muscle, and kidney. It probably also acts as a channel in the membranes of intracellular organelles. The current view is that TRPP2 (and possibly also TRPP3 and TRPP5) requires TRPP1, or TRPP1-like proteins, to function as plasma membrane receptors. The latter complexes may form mechanosensors in primary cilia and are involved in the development of a variety of organs, especially in tubulus formation. This mechanosensory complex is most likely indispensable for regulation of embryonic fluid movement. During embryogenesis, TRPP2 is active in node monocilia and plays a role in the establishment of left-right asymmetry (see below).

The autosomal recessive form of PKD (ARPKD) is a much more rare hereditary disease, with an estimated incidence of 1 in 20,000 live births (530). This disease is not related to defects in TRPP subfamily members but caused by mutations in the *PKHD1* gene, which encodes for fibrocystin (also known as polyductin), a protein of >4,000 amino acids (530). Interestingly, fibrocystin colocalizes with TRPP2 at the basal bodies of primary cilia (41, 533). It will be of great interest to investigate whether TRPP2 and fibrocystin interact functionally, and whether this interaction is related to the pathology of PKD.

4. TRPML1 and mucolipidosis type IV

TRPML1 (or mucolipin 1, MLN1) is a high-conductance, nonselective,Ca^{2+}-permeable cation channel encoded by the *MCOLN*1 gene (368). TRPML1 probably assembles into complexes that demonstrate variable single-channel conductance. Channel activity is reduced at low pH probably due to an assembly defect (56). The protein contains a serine-lipase domain in the amino part of the protein between the first two transmembrane domains that might function either enzymatically as a lipase, or as a binding domain or a transporter of lipids that might act as channel regulators (Fig. 6) (363).

Mutations in *MCOLN*1 cause mucolipidosis type IV (MLIV), an autosomal recessive, neurodegenerative lysosomal storage disorder. MLIV is clinically characterized by severe psychomotor retardation, ophthalmologic abnormalities including corneal opacity, retinal degeneration, strabismus, agenesis of the corpus callosum, blood iron deficiency, and achlorohydria (30). The disease normally presents within the first year of life and progresses slowly, with patients remaining in an apparent steady

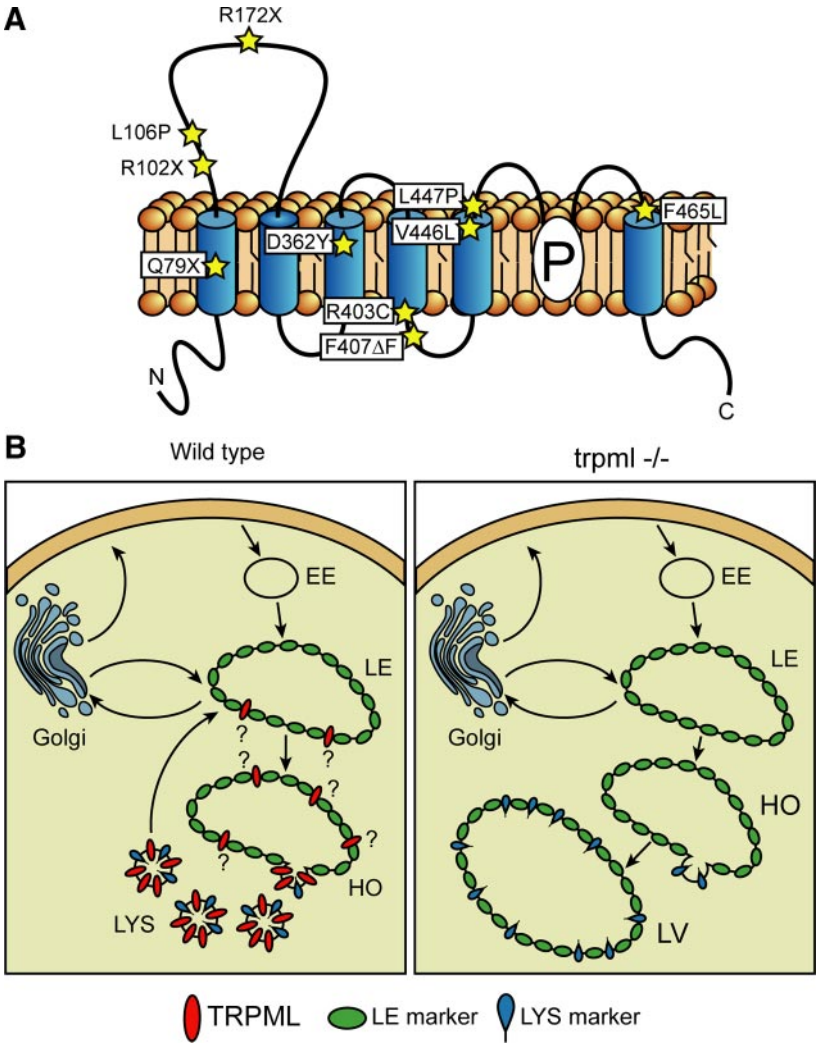


FIG. 6. A model for the pathogenesis of mucolipidosis IV (MLIV). *A*: mutations causing MLIV (for details, see Refs. 29, 30). [Adapted from Fig. 3 in Altarescu et al. (17).] *B*: a model adapted from *Caenorhabditis elegans*. In WT, solutes and membrane are internalized and delivered to the early endosome (EE). Molecules from the endocytic and biosynthetic pathways are then delivered to late endosomes (LE). Lysosomal hydrolases and the solutes and internal vesicles destined for degradation are condensed in membrane structures budding off from these late endosomes (hybrid organelles; HO). The scission of the budding vesicles yields primary lysosomes (L). In defective TRPML1 channels, the maturation/scission of lysosomes budding from hybrid organelles is defective. These endosomes continue to receive membrane and solutes from the endocytic and biosynthetic pathways and hence increase in size (for details, see Ref. 450).

state for two to three decades. MLIV is found in a relatively high frequency (carrier frequency 1:90–1:100) among Ashkenazi Jews (29, 30, 405).

The pathological mechanisms underlying MLIV are not fully understood. Abnormal storage of amphiphilic lipids (phospholipids, gangliosides, neutral lipids, and mucopolysaccharides) and membranous materials in multiconcentric lamella together with granulated, water-soluble substances in late endosomes and lysosomes have been visualized by electron microscopy (Fig. 6) (29). However, there is considerable variability in the composition of the stored materials between different organs and tissues. Such abnormal storage has been hypothesized to be due to altered membrane fusion and fission events in the late endocytic pathway (63).

TRPML1 channel disease-causing mutations (i.e., V446l and ΔF408) retain channel function, but unlike wild type, TRPML1 are unaffected by pH changes, suggesting that these mutations somehow affect control of clustering and complexing of TRPML1 (368). There is no defective hydrolytic activity, but rather a defective endocytic process in MLIV. An elevation of ~1 pH unit was determined in the storage vacuoles of affected cells, which is typical of late endosomes and prelysosomal vacuoles (Fig. 6) (254, 264).

Defective TRPML1 channels induce changes in the endocytotic transport of membrane components, such as block of the endocytotic route to the final lysosome. In cells from MLIV patients, disturbed Ca^{2+} signaling has been described. In addition, large acidic organelles appeared consisting of late endosomes and lysosomes. It would appear that the Ca^{2+}-dependent fusion between late endosome/lysosome hybrid vesicles is defective. TRPML1 could play a key role in Ca^{2+} release from the endosome/lysosome hybrid, which triggers the fusion and trafficking of these organelles. Perhaps TRPML1 is important in decreasing the intravesicular concentration of Ca^{2+} (215, 216).

The *C. elegans cup-5* (coelomocytes uptake defective) mutant is the homolog of human mucolipin-1 gene. Interestingly, CUP-5 is essential for viability and required for lysosome biogenesis. Mutations in *cup-5* cause the

accumulation of large vacuoles in coelomocytes, resulting in increased cell death and embryonic lethality (450, 485).

Recently, a novel pathomechanism has been proposed for the development of mucolipidosis. Measurement of lysosomal pH revealed that the lysosomes in TRPML1-deficient cells obtained from patients with MLIV are overacidified. Because TRPML1 can function as a proton channel, the increased lysosomal acidification in TRPML1-deficient cells is likely to be due to a loss of function of TRPML1 channels resulting in a reduced H^+ leakage. In addition, there is a marked reduction in lipid hydrolysis in *MCOLN1*$^{(-/-)}$ cells, attributable to a decreased lipase activity (199). The accumulation of lipids and membranous material in intracellular organelles such as lysosomes, which is a typical characteristic of MLIV, might thus be due to decreased lipase activity (409). Alternatively, TRPMLs might be involved in correct compartmentalization. Traffic of TRPML3 to lysosomes is required for the normal function of the mucolipidosis inducing TRPML1. However, it is not clear yet whether mutants of TRPML1 causing MLIV disrupt also TRPML3 translocation and might induce a decreased number of TRPML1 channels in the patient's lysosomes (473).

5. *TRPM7 and Guamanian amyotrophic lateral sclerosis/Parkinsonism dementia*

TRPM7 is the closest homolog of TRPM6, with which it shares most basic functional features (293, 379). In contrast to the rather restricted expression pattern of TRPM6, TRPM7 is ubiquitously distributed in most cells and tissues, providing an ion channel pathway for entry of Mg^{2+}, Ca^{2+}, and trace metal ions (282). TRPM7 is therefore believed to be the molecular correlate of the ubiquitous Mg^{2+}-nucleotide-regulated metal ion channel/Mg^{2+}-inhibited ion channel (MagNuM/MIC) (382). Mg^{2+} influx through TRPM7 has been shown to be indispensable for cellular viability: targeted deletion of TRPM7 in DT-40 chicken B lymphocytes causes rapid cell growth arrest followed by cell death within 2–3 days (293). However, viability can be maintained and the arrest of cell proliferation reversed by supplementation of the culture medium with excess Mg^{2+} (~10 mM), or reintroduction of wild type, or functional mutants, of TRPM7 (293, 390). These results illustrate the essential role of Mg^{2+} in cell cycle progression and cell proliferation (377), for which a hypothetical scheme, the "membrane magnesium mitosis" (MMM) model of proliferation control, has been proposed. "Membrane perturbation" evoked by a variety of growth factors is postulated to increase $[Mg^{2+}]_i$ via the release of Mg^{2+} from negatively charged binding sites on the inner leaflet of the plasma membrane, thus providing both free Mg^{2+} and Mg-ATP^{2-} for protein and DNA synthesis (377). The data obtained with TRPM7 suggest that regulated influx of Mg^{2+} through a membrane pore, rather than release from an intracellular "store" is more likely to be the pivotal event.

Given the important role of Mg^{2+} in cell proliferation and viability, it can be expected that disturbance of the cellular Mg^{2+} homeostasis, which depends on TRPM7, can have severe pathological consequences. Indeed, two diseases in humans have been linked to mutations in TRPM7: Guamanian amyotrophic lateral sclerosis (ALS-G) and Guamian Parkinsonism dementia (PD-G). These related neurodegenerative disorders are found with a relatively high incidence on the Pacific Islands Guam and Rota (352). The etiology of these disorders remains elusive, but evidence suggests a complex interplay of genetic and environmental factors (353). A TRPM7 variant, T1482I, which is located between the channel and the kinase domain, has been found in a subgroup of both ALS-G and PD-G patients but not in matched control subjects (163). Although the T1482I variant has no detectable alteration in α-kinase activity, it displays a somewhat higher sensitivity to inhibition by intracellular Mg^{2+} within the physiologically relevant range. The incidence of both ALS-G and PD-G is increased in environments that are deficient in Ca^{2+} and Mg^{2+}, such as the west Pacific. Thus increased sensitivity of TRPM7 to inhibition by Mg^{2+} could aggravate the Mg^{2+} homeostasis in an Mg^{2+}-deficient environment, leading to a reduced intracellular Mg^{2+} concentration, which could in turn contribute to the etiology of the neurodegenerative diseases (163, 390).

At this point, it seems premature to classify ALS-G and PD-G as real TRP channelopathies. First, the functional charaterization of the T1482I variant is still quite incomplete. The difference in Mg^{2+} sensitivity between wild-type and T1482I channels is relatively mild, and the influence of this variation on the sensitivity of TRPM7 to other known regulators [e.g., Mg-ATP, cAMP, phosphatidylinositol 4,5-bisphosphate (PIP_2)] is currently unknown. Given that all ALS-G or PD-G patients that carried the T1482I allele also carried a wild-type allele, it is unclear whether the reduced Mg^{2+} sensitivity has any consequence in vivo. Second, only a relatively small number of brain samples were tested in this study and only 5 of 22 ALS-G or PD-G patients carried the T1482I variation (163). Whether the samples included close relatives is not clear. Notably, analysis of a SNP database revealed that 40% of the Japanese in Tokyo carry at least one T1482I allele (4.5% being homozygous for the mutation) (163), indicating that this mutation is also quite common in healthy subjects. However, we foresee that natural variation in the coding regions of TRP channels, leading to mild functional consequences similar to the TRPM7 T1782I variant, may play an important role in sensitivity to environmental conditions and the predisposition to certain diseases.

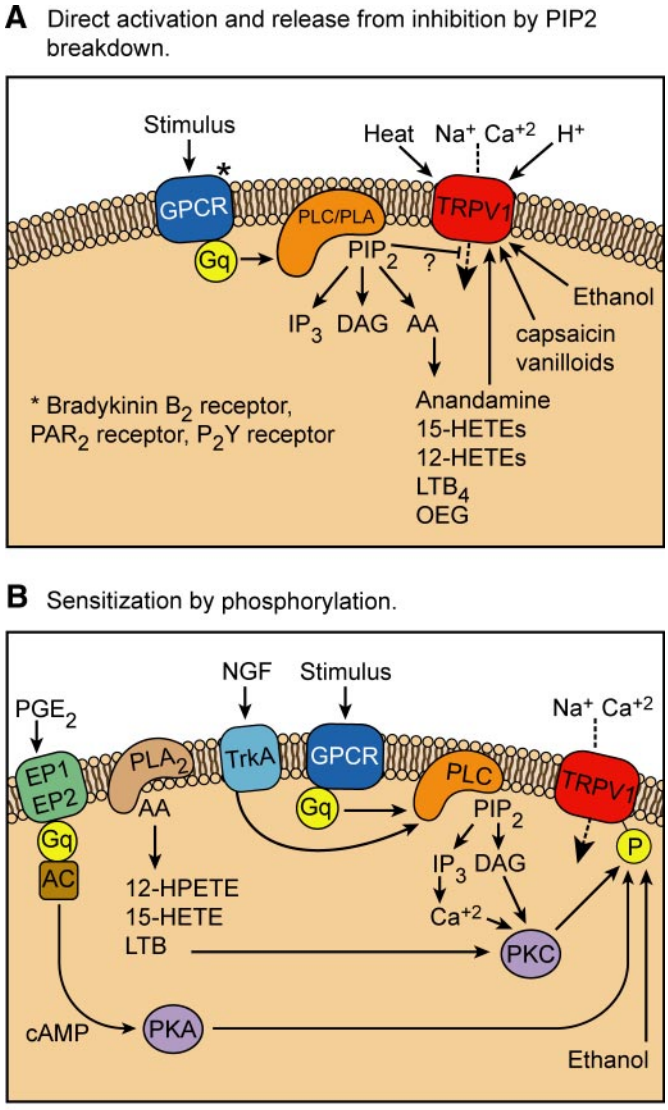
C. TRPs and Pain

According to the International Association for the Study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual, or potential, tissue damage or described in terms of such damage. Depending on its origin, pain can be classified as follows: pain caused by the stimulation of nociceptive receptors and transmitted over intact neural pathways is termed nociceptive pain; pain caused by damage to neural structures that disrupts the ability of the sensory nerves to transmit correct information to the brain is termed neuropathic pain; finally, pain with no clear physiological origin can be termed psychological pain. In addition, based on its timing, pain can be classified as acute, when the pain is directly correlated with its cause and has a clear warning function, or chronic, when pain persists much longer that the painful stimulus by which it was evoked.

1. TRP channels in acute nociceptive pain

Growing evidence implicates several members of the TRP superfamily in the detection of acute noxious thermal, mechanical, and chemical stimuli. Note that acute nociceptive pain, despite its unpleasantness, is a critical component of the body's defense system as part of a rapid warning relay that instructs the motor neurons to minimize physical harm and should not be considered as a disease condition. However, a short survey of the involvement of TRP channels in normal pain will be provided to better understand their involvement in pain related to pathological conditions. Indeed, it has become increasingly clear that the hypersensitivity and pain that occurs under various pathological conditions is often due to upregulated expression and/or increased sensitivity of TRP channels.

The first evidence for the involvement of TRP channels in the pain pathway came with the cloning of the vanilloid receptor TRPV1, which is arguably the most extensively studied member of the entire TRP superfamily (58). Its expression in DRG, TG, and nodose ganglion (NG) neurons, particularly in association with nociceptive afferent fibers, together with its activation by heat (>43°C), acid, and pungent vanilloid compounds strongly indicated that the TRPV1 plays an important role in the detection and integration of noxious stimuli (Fig. 7) (60, 442). Analysis of *TRPV1* gene knockout mice confirmed that the channel contributes to the detection of acute painful chemical and thermal stimuli (59, 87). In particular, *trpv1*$^{(-/-)}$ mice showed reduced responses to noxious heat stimuli and complete indifference to pungent vanilloids. A number of subsequent studies using gene knockout, or knockdown, strategies have highlighted the role of other TRP channels in detection of particular



C TRPV1/4 activation

STIMULUS	*RECEPTOR*
NGF	TrkA (*via PKC*)
Bradykinin	BK (*via PKC*)
ATP	P_2Y (*via PKC*)
Serotonin	5-HT (*via PKC*)
PGE_2	$EP_{1,2}$ (*via PKA*)
H^+	TRPV1
Lipids	TRPV1/4
Heat	TRPV1/4
Pressure	TRPV4

FIG. 7. Diversity of mechanisms activating TRPV1 and their relation to pathogenic stimuli. *A*: direct activation of TRPV1 and activation via PLC and PLA_2 pathways that produce endogenous activating lipids. *B*: sensitization of TRPV1. Schematic diagram of some of the stimuli and intracellular pathways that contribute to the sensitization TRPV1 function in terminals of primary sensory neurons (for more information, see Ref. 131). *C*: a synopsis of stimuli causing TRPV1 and TRPV4 activation and their respective receptors.

painful stimuli by nociceptive neurons. The *trpv3*$^{(-/-)}$ mice exhibit deficits in innoxious and noxious heat perception (285). The *trpv4*$^{(-/-)}$ mice present a phenotype that includes a reduced sensitivity to pressure exerted on the tail (426). Moreover, the induction of osmotic and mechanical hyperalgesia is absent in *trpv4*$^{(-/-)}$ mice (12). In one study, *trpa1*$^{(-/-)}$ mice displayed a reduced aversive reaction and pain in response to mustard oil, as well as reduced sensitivity to noxious cold and to punctate mechanical stimuli (214). However, in a second independent study of a different *trpa1*$^{(-/-)}$ mouse strain, altered cold and mechanosensitivity were not evident (35). In addition, TRP channel null mutations in invertebrate model systems, such as the *painless* mutant of *Drosophila* (homologous to TRPA1) and the *OSM-9* mutant of *C. elegans* (homologous to TRPV4) display reduced avoidance reactions to noxious thermal, chemical, and osmotic stimuli (485). Thus it seems well established that TRP channels play an important and evolutionary conserved role in the detection of noxious stimuli, which is essential for survival.

TRPV1, TRPA1, and TRPM8 are all expressed in sensory neurons in the DRG, TG, and NG. More than 50% of DRG neurons express TRPV1, largely in association with substance P (SP), calcitonin gene-related peptide (CGRP), and the high-affinity nerve growth factor (NGF) receptor TrkA. A subset of TRPV1-containing neurons also expresses TRPA1, whereas TRPM8 seems to be present in neurons that express neither TRPV1 nor TRPA1. Importantly, the sensory nerves that innervate the maxillary molar teeth also express TRPV1, TRPM8, and TRPA1. Activation of these channels may underlie the temperature sensitivity of teeth and may contribute to tooth pain (333).

In addition to their normal role as detectors of harmful stimuli, several pathological conditions lead to changes in the expression level and/or sensitivity of "pain" TRP channels. This can lead to exaggerated pain, when the experienced pain overestimates the harmfulness of the stimulus, or chronic pain, when the pain persists after the noxious stimulus has terminated. Below, we first review the mechanisms that are known to regulate expression and sensitivity of TRP channels in the pain pathway, followed by an overview of pathological states characterized by TRP-dependent pain.

2. *Mechanisms altering the sensitivity of "painful" TRP channels*

Many pathological conditions are characterized by hyperesthesia, i.e., enhanced sensitivity to sensory stimuli. With respect to pain, a distinction can be made between allodynia, when pain is experienced in response to nonnoxious stimuli, and hyperalgesia, when exaggerated pain is experienced in response to noxious stimuli.

Mechanisms leading to allodynia and hyperalgesia are best described for TRPV1. The *trpv1*$^{(-/-)}$ mice are not only less sensitive to acute painful thermal and chemical stimuli, but they are also defective in developing inflammatory thermal hyperalgesia (59, 87). Several mechanisms have been elucidated that contribute to the increased sensitivity of TRPV1 during inflammation. Sensitization can arise from phosphorylation of TRPV1 at multiple sites via PKC and PKA, downstream of activation of GPCRs by transmitters such as bradykinin, ATP, NGF, CGRP, and prostaglandins (Fig. 7). In addition, TRPV1 is subject to tonic inhibition by phosphatidylinositol 4,5-bisphosphate (PIP_2) (68) providing an additional biochemical pathway through which the activity of the channel can be regulated by inflammatory substances, such as bradykinin and NGF (for a concise overview, see Ref. 15). Ethanol is a very efficient sensitizer of TRPV1 (453). Sensitization by PKC also appears to involve increased exocytotic delivery of TRPV1 to the plasma membrane (287). Similarly, insulin and insulin-like growth factor I (IGF-I) increase the TRPV1 translocation to the plasma membrane via activation of receptor tyrosine kinases, which leads to phosphatidylinositol 3-kinase and PKC activation (467). Neurotrophic factors, such as NGF, glia-derived growth factor (GDGF), and neurotropin 3 (NT-3) also increase the number of TRPV1 expressing neurons in sensory ganglia, elevate TRPV1, and increase the response to capsaicin in single DRG neurons. This neurotrophic factor-induced gain of TRPV1 function may contribute to the pain experienced during tissue repair and growth (19). Similarly, in mice generated to release the neuronal survival factor artemin from skin keratinocytes, increased levels of TRPV1 (and TRPA1) transcripts in DRG nociceptive neurons were detected, an event associated with an increase in the sensitivity of nociceptive C fibers to heat and a reduced threshold to heat in behavioral studies (112). Moreover, in mice, mRNA encoding artemin is profoundly upregulated in response to inflammation induced by hindpaw injection of complete Freud's adjuvant (CFA) and hindpaw injections of artemin (particularly with concurrent administration of NGF) cause prolonged thermal hyperalgesia (260).

In addition, TRPV1 is sensitive to transmembrane potential. Activation of the channel occurs in a voltage-dependent manner upon strong depolarization, and changes in temperature result in graded shifts of the voltage dependence of activation, leading to inward TRPV1 currents at physiological values upon sufficient heating (481). Other factors that activate/stimulate the channel, such as capsaicin, protons, or PKC activation, also shift the voltage-dependent activation curve towards negative voltages, which may be the general mechanism whereby the temperature sensitivity of TRP channels can be modulated. Moreover, the voltage dependence of TRPV1 implies that depolarized neurons will have a lower

threshold for heat activation, which may contribute to heat allodynia/hyperalgesia (481). Recently, Fas-associated factor 1 (FAF1) has been identified as a regulatory protein of TRPV1, which binds to the channel in sensory neurons. FAF1 reduces TRPV1 activation by agonists, heat, and protons and may form part of a TRPV1 receptor complex (signalplex) (197).

Given the well-established role of TRPV1 in the pain pathway, much effort has been expended in the development of TRPV1-selective desensitizing agonists and antagonists as new therapeutic options in the treatment of clinical pain (206). One example of a novel approach in pain treatment refers to the role of TRPV1 in the generation of pain caused by bone sarcomas. Osteoclast activation induces bone reabsorption and acidosis, thereby activating TRPV1 in bone sensory fibers. In an in vivo model of bone cancer pain, treatment of mice with the selective TRPV1 antagonist JNJ-17203212 led to a significant decrease in movement-evoked nocifensive behavior (132). Similarly, another selective TRPV1 blocker, A-425619, was shown to cause effective antinociceptive effects in several models of pathological nociception and thermal hyperalgesia (265). Most recently, SB-705498 was reported as a TRPV1 antagonist with good oral bioavailablity and effectiveness in reducing hyperalgesia and allodynia in animal models (365, 366). These examples illustrate the potential of TRPV1 antagonists in the treatment of diverse forms of pain in humans. In addition, the induction of desensitization of TRPV1 by dephosphorylation via calcineurin provides an alternative mechanism of antihyperalgesia, as recently demonstrated with the CB1 receptor agonist WIN55,212–5 (335). In a similar vein, the potentiation of TRPV1 receptor activity by adenylate cyclase, as occurs in response to protaglandins in inflamed tissue, can be suppressed by morphine acting through μ-opioid receptors (480).

Whereas the role of TRPV1 in pain is widely recognized and accepted, the involvement of other TRP channels is probable but far less established. TRPV2, which is activated by very noxious temperatures and is expressed, among other locations, in DRG ganglia in medium-sized neurons, is involved in pain reception. Intraplantar injection of CFA in the rat induces overexpresion of TRPV2, which is connected to peripheral sensitization during inflammation and thermal hyperalgesia (398). Results obtained using *trpv4*$^{(-/-)}$ mice indicate that this channel is also involved in development of thermal hyperalgesia induced by intraplantar carrageenan injection (440).

Recent studies conducted upon two independent *trpa1*$^{(-/-)}$ mouse models (35, 214) point to an important role for TRPA1 in the pain response to endogenous inflammatory mediators and to diverse exogenous irritants, including mustard oil, acreolin in tear gas (and a metabolite of cyclophosphamide and ifosfamide, which are widely used chemotherapeutic agents), and allicin in garlic and onions (Fig. 8). In wild-type mice, topical application of mustard oil constitutes an acute noxious stimulus and evokes neurogenic inflammation causing thermal and mechanical hyperalgesia. In contrast, in *trpa1*$^{(-/-)}$ mice, the acute effects of mustard oil (e.g., paw licking and flinching) are abolished (35), or reduced (214), and hypersensitivity is either absent (35) or blunted (214). Of considerable significance, the algesic peptide bradykinin activates TRPA1 in a G protein-dependent manner (31), and in *trpa1*$^{(-/-)}$ mice, the development of hyperalgesia in response to injections of bradykinin is greatly reduced (35, 214).

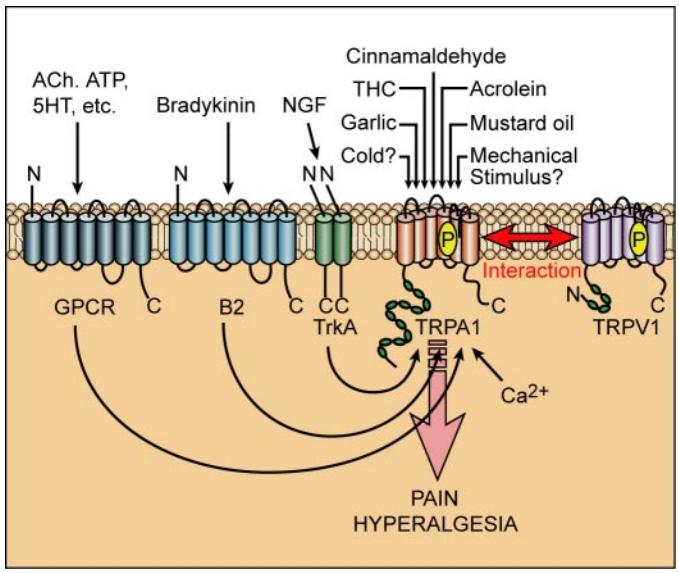


FIG. 8. TRPA1 function: overview of the possible role and activation mechanism of TRPA1 in sensory signal transduction, especially in pain response and generation of hyperalgesia. Note that TRPA1 is probably functionally coupled to TRPV1 and that both channels are regulated by similar PLC-dependent sensitization pathways (35, 270).

As noted previously, TRPA1 has been proposed to be activated by temperatures that are perceived as noxiously cold (31, 415), although this mode of activation has not been confirmed in other studies (35, 189, 295). In this respect it is interesting that a small subpopulation of DRG neurons that express neither TRPA1 nor TRPM8 nonetheless respond to cold with a large and rapidly adapting inward current (27). Analysis of TRPA1 knockout mice has not resolved this significant discrepancy. In one study, *trpa1*$^{(-/-)}$ animals displayed no obvious deficits in cellular, or behavioral, responses to acute cold (35). However, in a second study performed upon a different *trpa1*$^{(-/-)}$ line, behavioral deficits to cold were detected (214). Both groups employed the cold-plate test and evaporative cooling by topically applied acetone as cold stimuli. It is conceivable that subtle differences in the scoring of the "cold-evoked" behaviors studied might have contributed to the discrepancy between the two studies (414). In addition, there may be the potential for the contribution

of a gender bias, as only female animals demonstrated a robust deficit in the avoidance of noxious cold in the study of Kwan et al. (214). However, the two studies also differ in an additional aspect. Bautista et al. (35) report that the disruption of the *trpa1* gene impacts on the withdrawal response to noxious mechanical stimuli, whereas Kwan et al. (214) maintain that the threshold of mechanically induced pain is increased, indicating that TRPA1 might be involved in mechanical hyperalgesia (see also Refs. 31, 414) (see Fig. 8). Importantly, because of similar activation and sensitization pathways, for example, by endogenous messengers, TRPA1 can functionally interact with the nociceptor function of TRPV1.

3. TRPs in neuropathic pain

In humans, neuropathic pain tends to be chronic and debilitating and occurs during conditions such as trigeminal neuralgia, diabetic neuropathy, postherpetic neuralgia, late-stage cancer, amputation, or physical nerve damage. Neuropathic pain is usually perceived as a steady burning and/or "pins and needles" and/or "electric shock" sensations. This is due to the fact that a neuropathy often results in the firing of both nociceptive and nonnociceptive (touch, warm, cool) sensory nerves in the same area, producing signals that the spinal cord and brain do not normally receive. Several lines of evidence point to the involvement of members of the TRPV family, especially TRPV1 and TRPV4, in the etiology of neuropathic pain. Thermal allodynia and hyperalgesia arise from hypersensitivity of TRPV1 due to release of inflammatory messengers, low pH and activation of PKC, the protease-activated receptor 2 (PAR_2), and phosphoinositol 3-kinase (18, 131, 226, 441, 542). Moreover, a painful peripheral neuropathy induced by taxol can be treated by gene silencing of TRPV4 (13).

TRPA1 has been linked to cold hyperalgesia, a symptom of inflammatory and neuropathic pain. Inflammation and nerve injury both increase the expression of TRPA1 in DRG neurons without affecting the abundance of the cold-sensing channel TRPM8 (192). Such overexpression, which appears to be driven by NGF engaging the p38 mitogen-activated protein kinase (MAPK) pathway, contributes to injury-induced cold hyperalgesia because TRPA1 knock down by siRNA strategies suppresses cold hyperalgesia in a rat nerve injury model (324). Therefore, TRPA1 may represent a new target for treatment of cold hyperalgesia caused by inflammation and by nerve damage.

Recently, it has been shown that activation of TRPM8 in sensory afferents of neuropathic and chronic pain rat models by either cutaneous or intrathecal application of pharmacological agents or by modest cooling causes inhibition of sensitized pain responses (360). The analgesic effect of TRPM8 activation relies on group II/III metabotropic glutamate receptors (mGluRs) that very likely respond to glutamate released from TRPM8-containing neurons to suppress nociceptive inputs. Interestingly, the analgesic profile of TRPM8 activators seems to be different from the pronociceptive profile of TRPA1 activators and merits further investigation of a potential relationship between TRPM8-mediated analgesia and TRPA1-related cold hyperalgesia in different subpopulations of sensory neurons. Understanding of these two antagonistic cold-activated mechanisms could result in novel strategies for intervention in chronic sensitized pain states.

4. TRPs in pain related to the gastrointestinal tract

TRPV1 is greatly overexpressed in painful gastrointestinal diseases such as inflammatory bowel disease, Crohn's disease, and ulcerative colitis (131, 524). Mechanical hypersensitivity of the colon contributes to chronic abdominal pain in patients with bowel disease. In mice, colon afferent fiber action potential discharge evoked by circumferential colon stretch occurs, in part, via the activation of TRPV1 as evidenced by reduced mechanosensitivity in $trpv1^{(-/-)}$ mice and a similar effect of the antagonist capsazepine. Importantly, stretch-evoked fiber responses were enhanced by inflammatory mediators in wild-type but not in $trpv1^{(-/-)}$ mice. Such experimental evidence suggests that TRPV1 contributes to mechanosensitivity and nociception and that it is sensitized during bowel disease and acute inflammation (188, 524). Accordingly, antagonists of TRPV1 have been demonstrated to reduce experimentally induced colitis (173, 174). However, the potential use of TRPV1 antagonists in bowel diseases may be limited by the fact that TRPV1 also plays a protective role in the gastroduodenal region of the gastrointestinal tract, where its activation contributes to the maintenance of the mucosal barrier (131, 174).

Direct experimental evidence supports a role of TRPV1 in the pathogenesis of pancreatitis, a severe inflammatory disease associated with mid and upper abdominal pain that frequently radiates to the back, causing frequent vomiting, and in severe cases shock due to pancreatic bleeding (Fig. 9). Large amounts of fluid are lost into the abdominal cavity due to massive local vasodilatation and plasma extravasation. This is largely a result of ischemia, production of free radicals, and inflammatory mediators such as SP and CGRP, which are released by a pathological activation of sensory neurons. Factors that directly stimulate sensory Aδ and C fibers are protons, heat, leukotrienes (e.g., leukotriene B_4), arachidonic acid metabolites (e.g., anandamide), bradykinin, and proteases such as trypsin. Many of the mediators that participate in the generation of acute pancreatitis, including protons, leukotrienes (e.g., leukotriene B_4), arachidonic acid metabolites (e.g., anandamide), and bradykinin, act on TRPV1 to cause depolarization of the sensory fibers, increased neuronal firing (which also induces SP release in

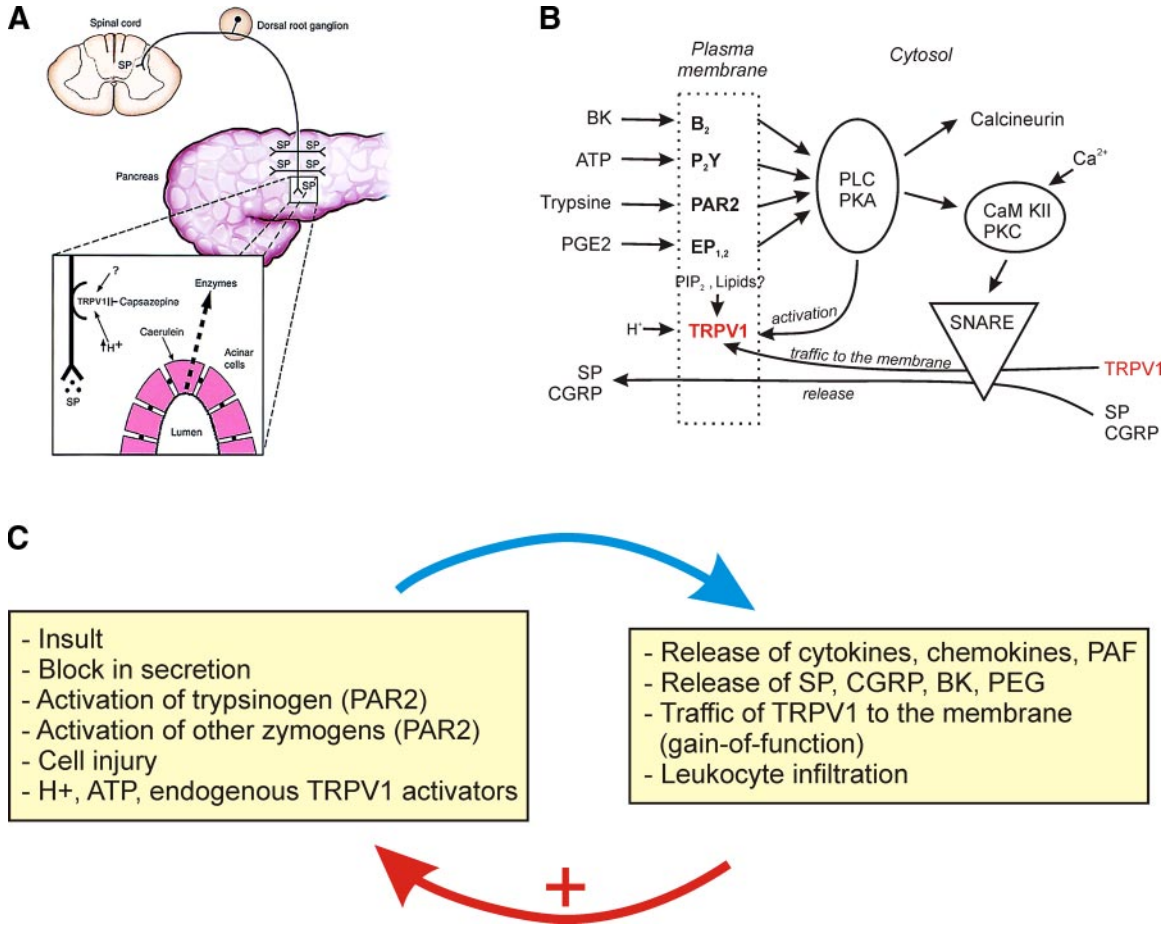


FIG. 9. Involvement of TRPV1 in the pathogenesis of pancreatitis. *A*: a schematic synopsis of the proposed signaling pathway for TRPV1 in substance P (SP) release in the cerulein-pancreatitis model. In this model, cerulein causes intra-acinar activation and release of digestive enzymes. Subsequent tissue acidification, H^+, or release of an endogenous TRPV1 ligand stimulates the channels on primary sensory neurons inducing antegrade and retrograde depolarization. Efferent release of SP leads to pancreatic tissue neutrophil infiltration and necrosis. [Modified from Fig. 6 in Nathan et al. (297).] *B*: intracellular pathways involved in TRPV1 activation, neuropeptide release, and probably also increased plasma membrane incorporation of TRPV1 under inflammatory conditions. Bradykinin, nerve growth factor (NGF), and prostaglandin E_2 stimulate G protein-coupled receptors that signal to PLC, PKA, PKC, and Ca^{2+}/calmodulin kinase II (CaMKII) pathways to increase TRPV1 channel activity and also release Ca^{2+} to the cytosol. Increased $[Ca^{2+}]_i$ activates PKC and CaMKII, which apart from modulating TRPV1, act by increasing SP and calcitonin gene-related peptide (CGRP) release that are all involved in the pathogenesis of inflammation, e.g., pancreatitis. The block diagram below shows the positive pathogenic feedback mechanisms from a pancreatic insult to necrotic pancreatitis.

the dorsal root), Ca^{2+} entry, and exocytosis of SP and CGRP from sensory nerve endings (40, 152, 234), all of which aggravate the disease causing factors and pain (Fig. 9). Therefore, inhibition of TRPV1 should ameliorate the symptoms and progression of pancreatitis. Indeed, in experimental pancreatitis induced by the frog toxin cerulein, application of the TRPV1 anatagonist, capsazepine, protects against tissue damage and causes reductions in protease secretion, pancreatic myeloperoxidase activity (which is a marker of inflammation), and the release of SP (297, 298). Interestingly, one of the most frequent causes of pancreatitis is excessive consumption of ethanol, which is well known as a sensitizer of TRPV1 (see also Refs. 84, 453).

Intraperitoneal injection of L-arginine causes necrotizing pancreatitis in rodents. It is now known that this inflammation activates TRPV1 in sensory nerves causing release of CGPR and SP, both centrally and peripherally (502, 503). In this model, enhanced c-*fos* activity in laminae I and II of the spinal cord (presumably indicative of increased nociceptive input) was reduced by intrathecally administered antagonists of SP and CGRP and also by systemic capsazepine. The latter also suppressed the incidence of spontaneous abdominal contractions, suggesting a decreased severity of referred pain.

A clear example illustrating the implications of TRPV1 activation by diverse stimuli has been shown in patients with gastroesophageal reflux disease (GRD). These patients suffer heartburn and chest pain. TRPV1 is expressed in sensory nerves within the mucosa of the esophagus, and its expression is upregulated in esophagitis patients (263). TRPV1 is activated by heat and acid pH,

and its activation is sensitized by ethanol, which all trigger the burning pain characteristic of GRD. However, although TRPV1 immunoreactivity has been found to correlate with the duration of acid exposure in the lower esophagus, symptom score and duration do not (44). Nonetheless, in the conditions enumerated above and in other functional bowel disorders, TRPV1 is a potential target for novel therapies (173, 174, 383).

5. Neurogenic inflammation

TRPV1 is a key player in neurogenic inflammation, characterized by vasodilation, plasma extravasation, edema, inflammatory pain, and thermal and mechanical hyperalgesia. Neurogenic inflammation is provoked by overstimulation of peripheral nociceptor terminals subsequent to injury, or by nonneurogenic inflammation (350). Such overstimulation results in an increased release of neurotransmitters, particularly peptides, from peripheral and central nociceptor terminals, or in the case of tissue injury, ATP and protons from damaged cells. Most inflammatory diseases such as allergic rhinitis, asthma, dermatitis, vulvodynia, bowel disease, and pancreatitis include a neurogenic component. The major neuropeptides involved in neurogenic inflammation are SP, CGRP, and neuropeptide Y (NPY). Proalgesic, proinflammatory mediators include NGF, protons, histamine, cytokines, chemokines, glutamate, and ATP. The macrophage-derived chemokine CCL3, which activates the GPCRs CCR1, -3, and -5, also sensitizes TRPV1 (534). In addition, elevated extracellular concentrations of cations, such as Na^+, Ca^{2+}, and Mg^{2+} sensitize and activate TRPV1, and such modulation may occur at physiological levels in the context of inflammation (6). The key role of TRPV1 mainly resides in its ability to integrate multiple noxious stimuli. As noted above, TRPV1 is activated by leukotriene B_4 (LTB_4) and other lipoxygenase metabolites of arachidonic acid, and as a consequence of this action contributes to the development of neurogenic inflammation, as for example in *Clostridium difficile* toxin A-induced ileitis (273). Inflammatory actions of LTB_4 via TRPV1 would be anticipated to reinforce the well-established proinflammatory role of LTB_4 that occurs through GPCR (i.e., the two receptors for LTB_4, BLT1 and BLT2)-mediated processes such as neutrophil activation and degranulation and leukocyte migration into the bloodstream (433). Compounds that block both LTB_4 and TRPV1 may thus represent a novel class of highly effective anti-inflammatory drugs, and such agents have recently been identified in preclinical studies (267).

6. TRPs in pain related to the urogenital tract

Vulvodynia coupled to vulvular vestibulitis gives rise to a painful burning sensation, allodynia, and hyperalgesia in the vulval vestibulus and is correlated with TRPV1 overexpression in vulvodynia tissues (459). Consequently, capsaicin has been used to desensitize TRPV1. Indeed, patients suffering from vulvular vestibulitis who applied capsaicin cream topically once daily showed a clear positive therapeutic effect: they reported significantly reduced dyspareunia and had more frequent sexual relations (412).

Activation of TRPV1 by the endogenous agonist anandamide, the bladder tissue content of which is increased in experimentally induced inflammation, evokes painful hemorrhagic cystitis accompanied by increased bladder reflex activity. Such symptoms can be antagonized by the selective TRPV1 antagonist capsazepine applied onto the serosal surface of bladders. Interestingly, activation of TRPV1 by anandamide does not induce desensitization, in that anandamide applied onto the serosal surface of naive bladders increased the reflex activity in a persistent and concentration-dependent manner (106). In addition, cystitis is accompanied by increased expression and function of TRPV1 in the dorsal root ganglia, indicating the important role of TRPV1 in the development of pain and hyperalgesia under these conditions (105, 106, 395).

In bladder specimens from patients with painful bladder syndrome (PBS), idiopathic detrusor overactivity (IDO), but not asymptotic microscopic hematuria, marked increases in the number of TRPM8 immunoreactive sensory nerve fibers of small caliber are evident in the absence of any change in urothelial TRPM8 immunoreactivity. Thus TRPM8 may provide a novel target for painful and overactive bladder diseases (289).

7. TRPs in pain related to bone

Overexpression, or de novo expression, of TRPV1 has been described in the synovia of joints and may contribute to the pathogenesis of the painful disease osteoarthritis. In rat models of chronic osteoarthritis evoked by CFA, or intra-articular iodoacetate injection, overexpression of TRPV1 and increased CGRP release have been reported (67, 115). In wild-type mice, CFA injection induces decreased mechanonociceptive thresholds, mechanical allodynia, and marked arthritic changes in tibiotarsal joints. All such changes were significantly less in *trpv1*$^{(-/-)}$ mice (429). In agreement, CFA-induced swelling of the knee joint and associated hypersensitivity are reduced, though not abolished, in *trpv1*$^{(-/-)}$ mice compared with wild-type controls (34). In joints, synoviocytes abundantly express TRPV1, TRPV4, and TRPA1. The functional role of these channels in articular surfaces and their involvement in pathological changes, e.g., arthritic inflammation, is still a matter of intensive research (201).

8. Itch

Itch (pruritus) is an irritating skin sensation causing a desire to scratch and is a symptom of various skin

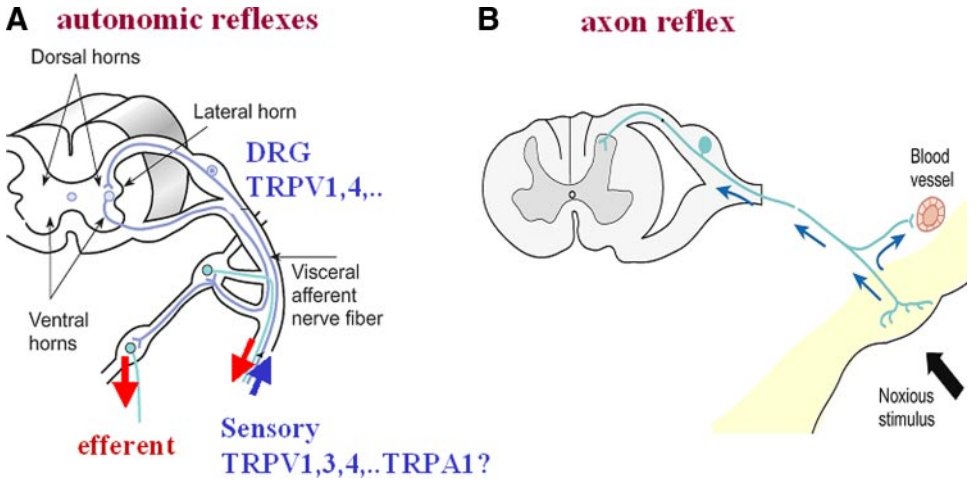


FIG. 10. Involvement of TRP channels in autonomic and axon reflexes. *A:* autonomic reflex initiated by activation of TRPV1, -3, -4, and TRPA1 (and probably more candidates that are not illustrated). *B:* stimulation of TRP channels shown in *A* in skin and in epithelial cells in internal organ can initiate axonal reflexes that signal to blood vessels to induce changes in local blood flow and additionally, via the dorsal horns, other reflexes. [Adapted from Figs. 10.1 and 8.15 in Pocock and Richards (355).]

disorders such as psoriasis, eczema, sunburn, and allergy, but also infections of lice, scabies, and worms. Recent research indicates that TRPV1 is not only involved in pain transmission but also plays an important role in the initiation of itch (280) (for a recent review, see Ref. 336). The well-known alleviation of itch by cooling could involve inhibition of TRPV1. Itching sensation might be also related to the activation of other temperature-sensitive TRPs expressed in the skin, sensory fibers, and keratinocytes (TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, TRPM8). Moreover, eicosanoids, which are known puritogenic compounds, can potently activate TRPV1 and TRPV4 (497). The use of TRPV1 activators, such as capsaicin or resiniferatoxin, to desensitize TRPV1 is therefore promising as antipruritic agents. In addition, activation of TRP channels in nonsensory cells may also contribute to itch. For example, activation of TRPV2 in mast cells causes degranulation and subsequent release of histamine, which causes itch (413).

D. TRP Channels in Systemic Diseases

The following sections summarize the evidence and indications for involvement of TRP channels in the pathophysiology of different organ systems. To understand the complex role of TRP channels in the pathogenesis of diseases, their polymodal activation must be appreciated. This is best understood for TRPV1 and has been considered in some detail above. TRPV1 activation causes firing of action potentials in sensory fibers that is relayed to the spinal cord and can trigger efferent signals, for example, autonomous reflexes (Fig. 10). Activation of sensory fibers can also be directly translated via axon reflexes into vegetative responses, such as vasodilatation. Thus TRP channels can interfere via multiple pathways with organ function. The interplay between sensitization and desensitization may cause an especially complex pattern of the interference of TRP channels under pathophysiological conditions, e.g., via autonomous, or axon, reflexes some organ functions can be potentiated, or attenuated (Fig. 10).

1. Immune system

As described above, the sensitivity of TRP channels in nociceptors can be greatly modulated in inflamed tissue, contributing to hyperalgesia and allodynia. In addition, several different TRP channels, in particular members of the TRPC and TRPM subfamilies, are involved in many inflammatory processes. TRPC1 is involved in antibody recognition in B lymphocytes. Suppression of TRPC1 results in reduced B-cell antigen receptor (BCR)-mediated oscillations in $[Ca^{2+}]_i$ and consequently depressed activation of the nuclear factor of activated T cells (NFAT) (288, 364). TRPC1 is also expressed in monocytes and leukocytes and might play a fundamental role in these cells, which are involved in immune defense. Interestingly, mutations in TRPC3 induce a reduction of T-cell receptor activation-induced Ca^{2+} entry in T lymphocytes, which may parallel the defective immune responses from patients with severe combined immunodeficiency (SCID) (348).

TRPM2 is highly expressed in granulocytes and cells of the monocytic lineage, including neutrophils and macrophages (345, 346). Such cells are exposed to oxidative stress and produce, when activated, reactive oxygen species (ROS) themselves. This process is known as the respiratory burst. An involvement of ROS in the fight against invading pathogens has been postulated (28). Ca^{2+} signaling via TRPM2 could play an important role during this process: activation of TRPM2 by ROS-induced Ca^{2+} entry, which in turn potentiates activation of this channel, leads to a positive feedback mechanism. Similar to the situation in lymphocytes, the oxidant-induced activation of the transcription factors NFκB and AP-1 is thought to be of importance in the production of cyto-

kines in macrophages (180). Death of hematopoietic cells through activation of caspases and PARP cleavage is mediated by TRPM2. Thus strategies to inhibit TRPM2 function, or to reduce TRPM2 expression, antagonize cell death in immune responsive blood cells (537).

Recently, TRPM4 was identified as an essential element in the regulation of the Ca^{2+} oscillations of T-lymphocyte activation, which is required for NFAT-dependent interleukin (IL)-2 production (219). TRPM4 acts as an inhibitor of excessive T-cell stimulation, and downregulation of TRPM4 induces a dramatic increase in $[Ca^{2+}]_i$ and IL-2 production after stimulation with phytohemagglutinin (PHA) (219). The mechanism via which TRPM4 exerts control over $[Ca^{2+}]_i$ in T cells is by maintaining a relatively depolarized membrane potential, which limits the driving force for Ca^{2+} entry (219). A similar effect has been observed in mast cells, where TRPM4 deletion results in excessive increases in $[Ca^{2+}]_i$ after antigen stimulation (R. Vennekens, B. Nilius, V. Flockerzi, and M. Freichel, unpublished data). Very recently, the immunosuppressantcompoundYM-58483{*N*-[4–3,5-bis(trifluromethyl)pyrazol-1-yl]-4-methyl-1,2,3-thiadiazole-5-carboxamide} has been shown to enhance the activity of TRPM4 in T cells, thereby markedly suppressing the production of IL-2 (435). It seems likely that defects in the function of TRPM4 will result in inappropriate release of cytokines triggering immunological hyperresponsiveness, proinflammatoty conditions, or allergy.

TRPV1 has been recently shown to be involved in the progression of allergic contact dermatitis (ACD). Oxazolone-induced ACD in wild-type mice was less pronounced than in *trpv1*$^{(-/-)}$ mice. Interestingly, the apparently protective role of TRPV1 in ACD appeared to be independent of major inflammatory neuropeptides such as SP and CGRP (32).

2. Cardiovascular system

Nearly all TRP channels are expressed in the cardiovascular system (for reviews covering the cardiovascular system, see Refs. 36, 37, 181, 183, 309, 310, 522).

An intriguing, although still very hypothetical, connection between TRPC channels and heart hypertrophy has been suggested. The most important trigger for heart hypertrophy is Ca^{2+}-mediated activation of calcineurin, which in turn mediates the hypertrophic response via its downstream transcriptional effector NFAT. NFAT transcription factors are necessary and sufficient for the induction of cardiac hypertrophy (159). Translocation of NFAT into the nucleus occurs via calcineurin-dependent dephosphorylation of conserved serines at the NH_2 terminus. Calcineurin is a phosphatase activated by increased levels of $[Ca^{2+}]_i$. Thus the crucial event in cardiac muscle is an elevation in $[Ca^{2+}]_i$, potentially via Ca^{2+} influx through TRPC1 and TRPC3 (505). Indeed, a gain-of-function phenotype of TRPC3 induces an increased NFAT activation in vivo, cardiomyopathia, and increased hypertrophy after pressure overload, which could be blocked by disruption of the calcineurin Aβ gene (296). Interestingly, downregulation of heart SERCA2, or deletion of SERCA2a, causes a concentric cardiac hypertrophy with impaired cardiac contractility and relaxation (396, 478). Notably, SERCA downregulation correlated with an upregulation of TRPC4 and TRPC5 (396).

Occlusive vascular disease, often leading to myocardial infarction and stroke, can be caused by the switch in smooth muscle cell phenotype to an invasive and proliferative mode, leading to neointimal hyperplasia. This condition is often a lethal complication in myocardial infarction, stroke, atherosclerosis, and clinical procedures such as angioplasty and grafting in bypass surgery. TRPC1 causes switching of vascular smooth muscle cells to an invasive and proliferative mode and initiates neointimal hyperplasia, which are all associated with enhanced calcium entry and cell cycle activity. Importantly, a specific E3-targeted (pore blocking) antibody to TRPC1 reduced neointimal growth in human veins, indicating that this might be a new avenue in the treatment of occlusive vascular diseases (210, 466).

Studies in rats suggest that TRPC1 and TRPC6 are involved in the development of hypoxic pulmonary hypertension. Chronic hypoxia induces pulmonary vasoconstriction due to increased store-operated Ca^{2+} entry, probably via TRPC1, into the pulmonary artery smooth muscle cells (PASMCs) (491, 500).

TRPC6 has been described as a protein interacting with other members of the TRPC subfamily, namely, TRPC3 and TRPC7. TRPC6 is highly expressed in the pulmonary system and is abundantly expressed in vascular tissues. Using an antisense oligonucleotide strategy, TRPC6 was found to mediate membrane depolarization and subsequent vasoconstriction induced by elevated intravascular pressure, the important myogenic constriction response in small arteries and arterioles (182, 501). Somewhat paradoxically, *trpc6*$^{(-/-)}$ mice display elevated blood pressure associated with enhanced basal and agonist-induced cation entry into smooth muscle cells, a more depolarized membrane potential, and increased smooth muscle contractility. This unexpected finding has been explained by a compensatory increase in the expression of the constitutively active TRPC3 channel in smooth muscle cells obtained from *trpc6*$^{(-/-)}$ mice (103). Such constitutive activity of TRPC3 has also been demonstrated in rabbit ear artery myocytes (11). Interestingly, TRPC3 is abnormally abundant and active in spontaneously hypertensive rats, suggesting that the channel might be involved in the pathogenesis of essential hypertension (245) (for a review, see Ref. 246).

TRPC channels play a role in idiopathic pulmonary arterial hypertension (IPAH), a fatal disease leading to failure of the right heart. The crucial event for IPAH is an

excessive pulmonary artery smooth muscle cell proliferation, which is connected to overexpression of TRPC3 and TRPC6 (527). This overexpression probably correlates with the cell cycle suggesting that, at least for TRPC6, the transition from quiescent pulmonary smooth muscle cells to mitotic cells is favored. Inhibition of TRPC6 with small interfering mRNA attenuated cell proliferation, suggesting that the targeting of this channel could be a promising approach for interfering with pulmonary arterial smooth muscle cell proliferation in IPAH patients. TRPC6 is also involved in angiotensin-induced heart hypertrophy. ANG II induces NFAT activation, and cardiac hypertrophic responses have been correlated with TRPC6 activity (328).

Recently, another mechanism linking TRP channels with pulmonary hypertension was described. Contraction and proliferation of PASMC is caused by chronic hyperoxia and precedes pulmonary hypertension and right ventricular failure. This mechanism requires the expression of hypoxia inducible factor 1 (HIF-1). In a rat model, TRPC1 and TRPC6, but not TRPC4, became overexpressed under hypoxic conditions as well as upon overexpression of HIF-1 under normoxic conditions. Thus both channels may contribute to the development of hypoxic pulmonary hypertension, and this response seems to be mediated by HIF-1 (492).

TRPV1 is expressed in cardiac spinal sympathetic sensory fibers (529). Afferent (Aδ and C) fibers expressing TRPV1 are essential for the sympathoexcitatory reflex during cardiac ischemia, which is associated with chest pain, increased blood pressure, and enhanced sympathetic nerve activity (392, 529). By an ischemia-induced direct activation of sensory nerve endings in the heart, which probably involves increased tissue levels of bradykinin, TRPV1 participates as a sensor of tissue ischemia (330). However, TRPV1 does not merely act in a sensory capacity because its activation also causes the release of SP, neurokinin A (NKA), and CGRP from peripheral nerve terminals in the epicardial surface of the cardiac ventricle and around coronary blood vessels (493). These neuropeptides induce vasodilation and negative inotropic and chronotropic effects and thus mitigate the effects of ischemia and reperfusion injury (51). In this sense, TRPV1 exerts a cardioprotective role. Indeed, TRPV1 gene deletion decreases the release of SP in response to ischemia/injury and impairs the recovery of cardiac function after the insult. The protective effect of TRPV1 is most likely mediated by enhanced NK1 receptor function in response to TRPV1-mediated release of SP (493). Clearly, the potential exists for antagonists of TRPV1 to produce unwanted cardiac effects, particularly in patients with angina. Interestingly, TRPV1 has also been implicated in the cardioprotective effect associated with alcohol consumption. At concentrations encountered after modest imbibement, ethanol causes coronary artery dilation and, by a mechanism that involves the release of CGRP from perivascular sensory nerve terminals, mediated by activation of TRPV1 (128).

Agonists of TRPV1 are also known to constrict resistance arteries, and this effect is attenuated in anandamide-pretreated vessels. It has been proposed that anandamide causes phosphorylation-dependent desensitization of TRPV1, thereby suppressing capsaicin-dependent vasoconstriction (249). Relatedly, a study in which capsaicin was employed to desensitize TRPV1 suggests that the channel contributes to the Bayliss myogenic constriction in resistance arteries (394). In this scenario, activation of TRPV1 is thought to occur through an increase in the local concentration of 20-HETE in response to increased intraluminal pressure. SP release from C-fiber afferents subsequently drives the myogenic response (394).

Administration of capsaicin to neonatal rats causes the degeneration of sensory neurons that express TRPV1. Such animals display an exaggerated increase in blood pressure following salt loading, suggesting a role for TRPV1 in the development of hypertension. It is probable that a reduced release of CGRP and SP, both of which are both potent vasodilators that sensitize TRPV1, underlies the hypertension observed in capsaicin-treated animals (462, 490). Additional support for a role of TRPV1 in opposing hypertension evoked by salt loading has been provided by a comparison of Dahl salt-sensitive and Dahl salt-resistant rats maintained on high- or low-salt diets for a period of 3 wk. In the salt-resistant animals, high salt intake was found to activate and upregulate the expression of TRPV1, whereas in salt-sensitive animals the expression and function of the channel were impaired (495).

Endocannabinoids, potent TRPV1 activators, induce several effects on endothelial cells and seem to be involved in endothelium-dependent vasorelaxation. Two derivatives of arachidonic acid, 2-arachidonoyl-glycerol (2-AG) and anadamide (AEA; arachidonyl-ethanolamide), induce Ca^{2+} influx and phosphorylation of vasodilator-stimulated phosphoprotein (VASP) through activation of both TRPV1 and of the cannabinoid receptors CB_1 and CB_2, all of which are expressed in the endothelium (138). Nitric oxide (NO) release from endothelial cells triggered by activation of Ca^{2+} influx through TRPV1 has also been described (354). Thus TRPV1 (see below) as well as CB_1 and CB_2 receptors are likely to be implicated in various endothelial cell functions (367).

Anandamide also acts as a TRPV1 receptor agonist in the trigeminovascular system, eliciting channel activation that promotes CGRP release and causes excessive vasodilation. The latter occurs independently of CB_1 receptor activation, which has in fact been shown to inhibit trigeminovascular neurons and prevent vasodilation. It is possible that CGRP release mediated by TRPV1 is related to migraine (10, 129). In the same vein, TRPV1, expressed in nociceptive afferent fibers of the encephalic dura ma-

ter, contributes to dural vasodilation and could therefore play a role in menigeal nociception (109). TRPV1 activation also results in an acute disruption of the blood-brain barrier following ischemia and reperfusion. Such an increase in cerebrovascular permeability mediated by TRPV1 is blocked by NK1 receptor antagonists (175).

TRPV2 seems to be activated by myocyte stretch and is translocated to the plasma membrane in response to growth factors (190). Once in the membrane, TRPV2 may act as a mechanosensitive channel causing an increased Ca^{2+} influx that is involved in myocyte degeneration caused by disruption of the dystrophin-glycoprotein complex. Consistent with this pathophysiological role, cardiomyopathy, left ventricular dilation, decreased systolic performance, disorganized myocyte arrangement, and interstitial fibrosis are observed in transgenic mouse models with a specific overexpression of TRPV2 in the heart (185).

TRPV4 is downregulated by WNK kinases (with no K), a small group of serine/threonine kinases with unique catalytic domains that lack the lysine residue used by other kinases to coordinate ATP (124). Several WNK kinases, in particular WNK4, have been put forward as candidate genes for essential hypertension, familial hyperkalemia and hypertension (FHH or Gordon's syndrome, or pseudohypoaldosteronism type II, PHA-II). The causal link is the downregulation of the expression of the Na^+-Cl^- cotransporter in the kidney by WNK kinases. However, this effect is missing in some disease-causing mutants (79, 506, 521). It is intriguing to hypothesize that the osmoregulatory channel TRPV4 might also be involved in the pathogenesis of hypertension.

TRPM4 and TRPM5 are two closely related proteins that are both activated by an increase in $[Ca^{2+}]_i$ and are both impermeable to Ca^{2+}. Therefore, they are depolarizing channels that reduce the inward driving force for Ca^{2+}. TRPM4-like currents have been observed in many tissues, such as cardiomyocytes (149–151). TRPM4 is overexpressed in cardiomyocytes from spontaneously hypertensive rats, which also show cardiac hypertrophy, kidney sclerosis, and increased bone calcification and are characterized by cardiac arrhythmias caused by delayed afterdepolarization (R. Guinamard, personal communication). TRPM4-like channels are also involved in the myogenic constriction response in small arteries (110). This probably occurs via activation of TRPM4 by vessel stretch, resulting in depolarization, activation of voltage-dependent Ca^{2+} channels, and feedback activation of TRPM4, which may then sustain the myogenic response. Defects in TRPM4 function would presumably attenuate the Bayliss effect.

TRPM4 may also affect blood vessel tone indirectly by virtue of its expression in the endothelium. Agonist stimulation of endothelial cells activates a nonselective cation channel with characteristics strikingly similar to those of TRPM4 (312, 315, 422). Interestingly, within the endothelium this channel is regulated by NO and ATP. NO donors such as *S*-nitroso-*N*-acetylpenicillamine (SNAP) and 3-morpholinosydnonimine (SIN-1) inhibit TRPM4. In contrast, inhibitors of NO synthases potentiate the TRPM4-like current, whereas superoxide dismutase (SOD), which inhibits the breakdown of NO, causes inhibition. This mechanism indicates a role for TRPM4 in sensing the metabolic state of the cell and NO in endothelial cells (421, 422).

A novel role for TRPM6 and TRPM7 in vascular dysfunction has recently been shown. It is well documented that an increased $[Mg^{2+}]_i$ in vascular smooth muscle cells (VSMCs) causes vasodilation and reduces agonist-induced vasoconstriction. In contrast, low $[Mg^{2+}]_i$ contributes significantly to increased vascular tone, enhanced responses to vasoconstrictors, defective vasodilatation and vascular remodelling, and elevated blood pressure (445, 446). Increased $[Mg^{2+}]_i$ is also involved in cell cycle activation and growth of VSMCs (448). The influence of $[Mg^{2+}]_i$ on VSMCs appears to be tightly connected to Mg^{2+} influx via TRPM7 (158). Both ANG II and aldosterone upregulate TRPM7. Long-term effects are an increase in $[Mg^{2+}]_i$ and growth of VSMC. These effects are attenuated when TRPM7 is knocked down. However, short-term application of ANG II and aldosterone causes a decrease in $[Mg^{2+}]_i$, probably via activation of Mg^{2+} efflux by a Na^+/Mg^{2+} exchanger. $[Mg^{2+}]_i$ is significantly reduced in VSMCs isolated from spontaneous hypertensive rats (SHR) in comparision to normotensive Wistar-Kyoto (WKY) rat controls. Basal levels of expression of TRPC6 in WKY rats and SHR are similar, but those of TRPC7 are significantly reduced in the latter (447). Furthermore, although ANG II enhances the expression of both TRPM6 and TRPM7 in WKY rats, such an effect is limited to TRPM6 in SHR rats. These results suggest that downregulation of TRPM7 in SHR contributes to the abnormally low $[Mg^{2+}]_i$ in VSMCs of SHR and to hypertension. More generally, they indicate an important role for TRPM7 in blood pressure regulation and VSMC growth.

TRPM7 has recently been described as a mechanosensitive channel. It is translocated to the plasma membrane by shear stress. High levels of expression of TRPM7 have been found in VSMCs that are normally cushioned from shear stress by an intact layer of endothelial cells. However, transmission of shear stress to VSMCs via myoendothelial connections will be increased at sites of increased shear stress. In particular, VSMCs will be directly affected by high shear stress in regions of vascular damage due to ruptured atherosclerotic plaques, or invasive vascular techniques. In such cells, TRPM7 activation may be potentiated leading to an increased influx of Ca^{2+} that in turn may trigger cell proliferation, support formation of atherosclerotic plaques, and finally induce cell death (323).

In addition to activation by shear stress and stretch, TRPM7 has been connected to some unexpected functional features that might be especially important for endothelial dysfunction. Overexpression of TRPM7 induces cell rounding and loss of matrix adhesion and, vice versa, silencing of TRPM7 strengthens cell adhesion and increases the number of adhesion complexes. This function is coupled to Ca^{2+} permeation through the channel but does not involve its kinase activity (420). However, in another report TRPM7 has been shown to phosphorylate the myosin IIA heavy chain, supposedly via a direct interaction between the TRPM7 COOH terminus and the myosin molecule. Thus low overexpression of TRPM7 induces cell spreading, adhesion, and the formation of focal adhesions (75). Activation of TRPM7 induces focal adhesion transformation into podosomes by a kinase-dependent mechanism. However, both reports clearly indicate that TRPM7 is involved in the regulation of cell adhesion, probably by different pathways.

TRPP2 seems to be important for the stability of the vessel wall (100). It has long been known that ADKPD patients suffer not only from kidney cysts, but also from aneurisms resulting from thinning of the arterial wall with ensuing rupture and internal bleeding (384).

3. Respiratory system

It has been reported that TRPC1 plays a role in asthma and chronic obstructive pulmonary disease (COPD). In proliferating airway smooth muscle cells, TRPC1 is upregulated (427, 428). Therefore, it has been speculated that TRPC1 is a target to prevent the fibrosis that is a symptom of COPD in the peripheral airways. TRPC4 and -5 are also expressed in airway tracheal and bronchial smooth muscles and along with TRPC1 are considered as possible candidates in the pathogenesis of asthma and COPD (83, 230, 231). TRPC6 may contribute to mucus hypersecretion, another feature that is characteristic of COPD (230, 231).

TRPV1 is involved in several respiratory diseases (130). Exposure to air-borne particulate matter (PM) is epidemiologically associated with increased morbidity and mortality and is thought to initiate and exacerbate respiratory disorders such as asthma, cardiovascular complications, and allergy-related immune responses (Fig. 11). Capsazepine inhibits and even prevents PM-induced apoptosis in airway epithelium. Binding of PM to the cell membrane induces a capsazepine-sensitive increase in $[Ca^{2+}]_i$ and cAMP, which can in turn induce apoptosis of epithelial cells, possibly via sensitization of TRPV1 (3, 4). In this context, it worthwhile noting that

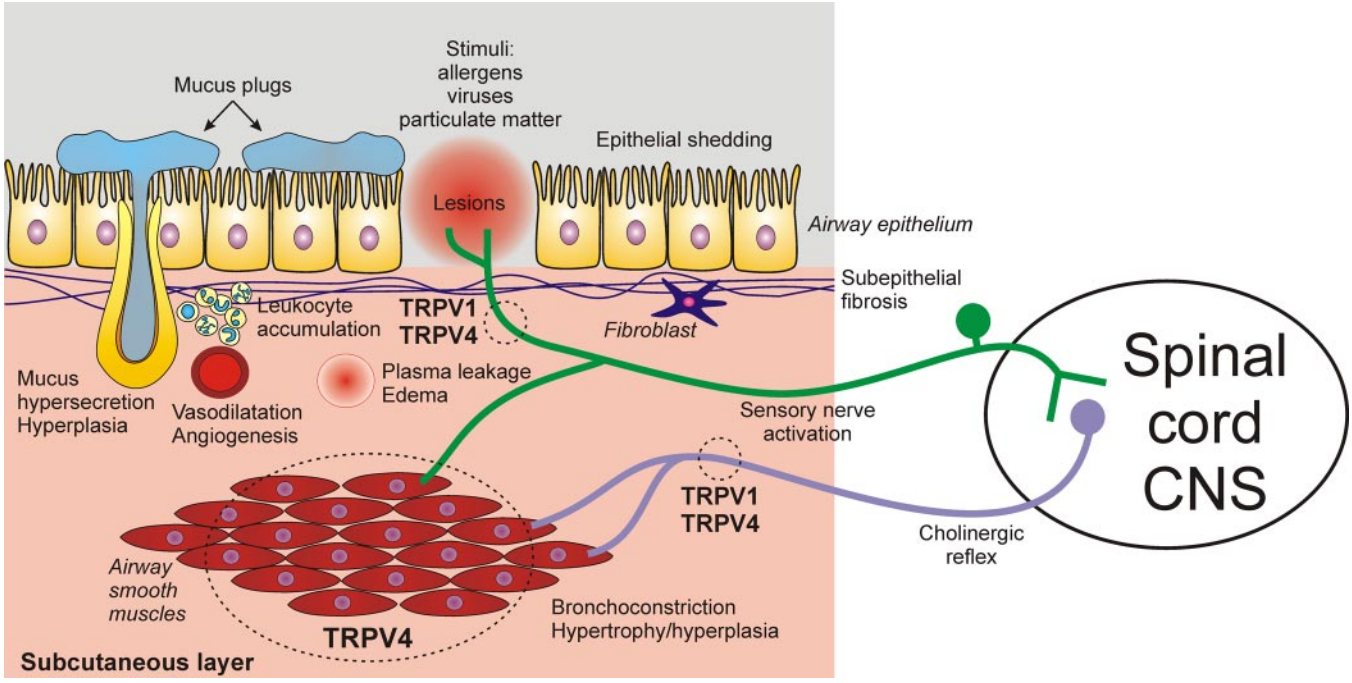


FIG. 11. TRPV1 and TRPV4 in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD). Respiratory epithelium is stimulated by lesions and various inflammatory triggers including allergens, viruses, and particulate matter. Subsequently, TRPV1 and TRPV4 are activated in sensory nerves which in turn initiate efferent cholinergic reflexes. The latter, apart from driving bronchoconstriction, can contribute to goblet cell hyperplasia, rarefied bronchial epithelial cells that tend to transdifferentiate to squamous cell epithelial cells, thickening of basement membrane, proliferation of myofibroblastoid cells between the basement membrane and the smooth muscle cells that are hypertrophic and hyperplastic, excess of luminal mucus, epithelial and luminal eosinophils, submucosal lymphoid cells and mast cells, mucous gland hypertrophy, and vasodilation of submucosal small vessels (for more details, see Ref. 238).

nicotine, inhaled during cigarette smoke, directly sensitizes TRPV1 without the participation of nicotinic acetylcholine receptors and in the absence of any change in the temperature sensitivity of the channel (248). Interestingly, ethanol is known to trigger attacks of asthma in predisposed individuals, an effect that could conceivably be related to its sensitizing action on TRPV1 (452).

TRPV4 is widely expressed in the airway system and seems to be involved in bronchial hyperresponsiveness, which is a hallmark of asthma (Fig. 11) (187, 238). Asthma is accompanied by a denudation of the epithelial lining of the bronchi and bronchioli. This occurs within a pathophysiological framework described as "airway remodelling." Under such conditions, bronchial smooth muscles as well as nerve endings can become exposed to the hypotonic bronchial fluid, which could contribute to bronchial hyperresponsiveness through activation of TRPV4. TRPV4 might also be coupled to the regulation of cilia activity in bronchial epithelial cells. Activation of TRPV4 increases cilia beat frequency in oviductal cells, an effect that can be counteracted by loading of such cells with an antibody directed against the channel. By extrapolation, TRPV4 may play a role in mucocilary transport and airway function/dysfunction (21). A model for the role of TRPV1 and TRPV4 in asthma and COPD is illustrated in Figure 11.

Interestingly, aquaporin-5 (AQP5), a water-permeable channel expressed in lung, cornea, and various secretory glands, is downregulated in hypotonic media. In mouse lung epithelial cells, the downregulation of AQP5 requires extracellular Ca^{2+} causing an increase in $[Ca^{2+}]_i$ and can be blocked by pharmacological inhibitors of TRPV4. This increase in $[Ca^{2+}]_i$ is linked to a hypotonic activation of TRPV4, suggesting that this channel is involved in the water and osmolyte homeostasis in various epithelial cells of the lung (399).

2-Aminoethoxydiphenyl borate (2-APB), an activator of TRPV1, TRPV2, and TRPV3, elicits cardiorespiratory reflexes (e.g., apnea, bradycardia, and hypotension) via an intense discharge in vagal pulmonary C fibers when administered as an intravenous bolus to spontaneously breathing anesthetized rats. The stimulation of C fibers by 2-APB was attenuated, but not abolished, by concentrations of capsazepine sufficient to completely suppress the excitatory effect of capsaicin, indicating that in addition to TRPV1, other 2-APB-sensitive channels participate in C-fiber excitation. Consistent with this, ruthenium red, which blocks all TRPV family members, totally suppressed excitation evoked by 2-APB. Such data are compatible with a role for TRPV1, TRPV2, and TRPV3 in the regulation of cardiorespiratory functions (146).

We have already described the functional impact of TRPM4-like channels in several cell types in some detail. Within the airways, TRPM4-like channels may induce a feedback inhibition in type II pneumocytes, which are important for production, storage, and secretion of the pulmonary surfactant via exocytosis of lamellar bodies (259).

4. Gastrointestinal system

Liver cells express a Ca^{2+}-impermeable, ATP-sensitive cation channel, with characteristics that closely resemble those of TRPM4. This channel is activated by free radicals, and such regulation significantly contributes to liver cell necrosis (33, 404). Mechanistically, activation of the TRPM4-like channel by hydroxyl radicals may generate inwardly directed movement of cations and accompanying H_2O leading to cell swelling and necrosis.

The endogenous fatty acid oleoylethanolamide (OEA), which is synthesized and released from the intestine upon feeding, participates in the regulation of food intake over a period of hours and acts as a satiety factor via a mechanism that appears to involve the activation of TRPV1 downstream of PKC (5, 371). In wild-type mice, OEA excites the peripheral terminals and soma of vagal sensory nerves, an effect that is blocked by capsazepine. Moreover, intraperitoneal administration of OEA at higher concentrations evokes visceral pain-related behavior (accompanied by acute suppression of food intake) that is inhibited by capsazepine. Neither the pain-related behaviors, nor the anorexigenic effect of OEA, were observed in *trpv1*$^{(-/-)}$ mice (494). In addition, it has been demonstrated by comparisions of tissues excised from *trpv1*$^{(+/+)}$ and *trpv1*$^{(-/-)}$ mice that the sensitivity of jejunal afferent fibers to jejunal distension, or intraluminal acid, is decreased in the absence of TRPV1 (374). Collectively, such findings indicate further important roles for TRPV1 in gastrointestinal function and dysfunction.

5. Bladder

An important role of TRPV1 has been recognized in bladder diseases (Fig. 12) (46). Overactive bladder symptoms due to various etiologies have been successfully treated with capsaicin or resiniferatoxin due to their desensitizing effects on TRPV1, which is detected in all human genitourinary tract tissues (55, 61, 194, 526). In the urinary bladder, TRPV1 (and also TRPV4; T. Gevaert and B. Nilius, unpublished data) is expressed on sensory nerve terminals and in the epithelial cells (urothelium) lining the bladder lumen (47). Analysis of *trpv1*$^{(-/-)}$ mice indicates that TRPV1 participates in normal bladder function (48). Mice lacking TRPV1 display a higher frequency of low-amplitude (spontaneous low-volume spotting) nonvoiding bladder contractions compared with wild-type animals. This gain of function was accompanied by reduction in both spinal cord signaling and reflex voiding during bladder filling. TRPV1 is required for bladder stretch detection, which involves stretch-evoked release

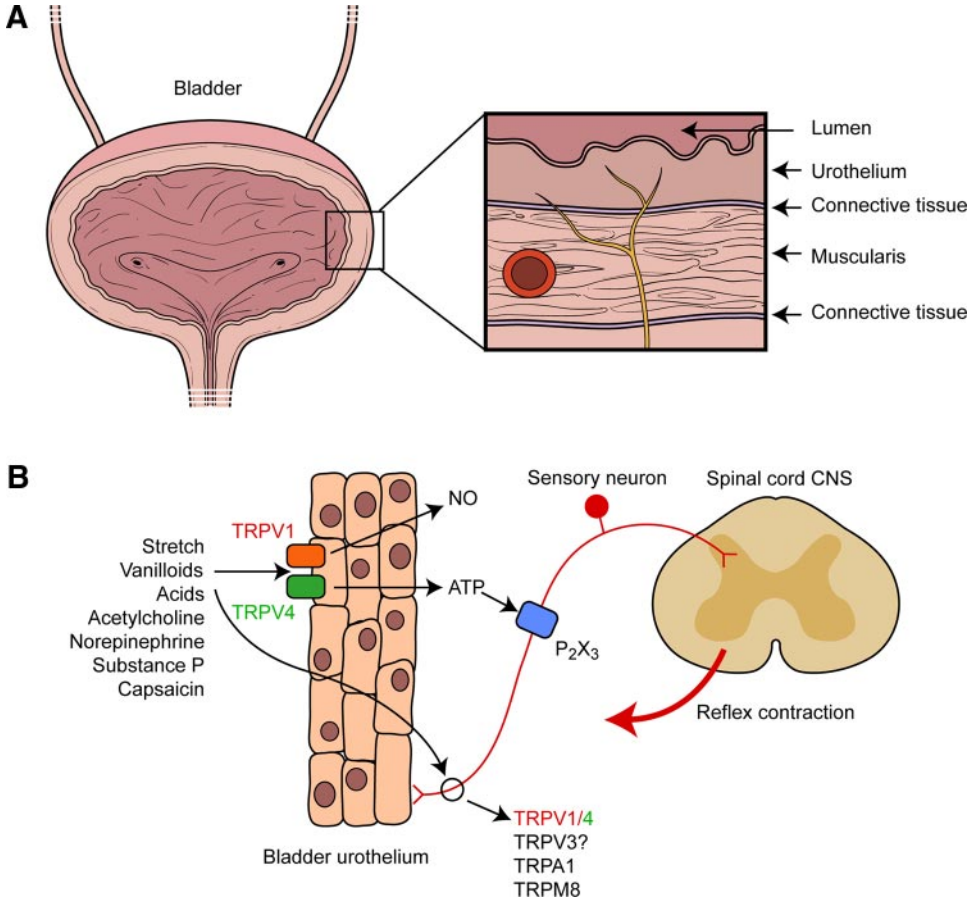


FIG. 12. Involvement of TRPV1 and TRPV4 in regulation of bladder contraction. *A*: illustration of the composition of the bladder wall. *B*: TRPV1 and TRPV4 are both expressed in the urothelium and can be directly activated by the stimuli shown at the *left*. Moreover, these substances can also activate both channels in sensory fibers in the urothelium and the muscularis, which can cause, via the spinal cord, contraction of the bladder and pain. Stimulation of TRPV1 and TRPV4 in the urothelium induces release of ATP and nitric oxide. ATP can also activate the sensory fibers via P_2X_3 receptors.

of ATP and also NO (Fig. 9). Release of both mediators is reduced in bladders excised from *trpv1*$^{(-/-)}$ mice. These findings indicate that TRPV1 participates in normal bladder function and is essential for normal, mechanically evoked purinergic signaling from the urothelium to sensory afferent fibers (47, 48). Moreover, the *trpv1*$^{(-/-)}$ mouse does not develop bladder overactivity during acute bladder inflammation, indicating that TRPV1 is involved in bladder hyperreflexia in inflammation (401).

A role for TRPV1 in bladder overactivity is also supported by clinical observations. In patients suffering from neurogenic detrusor overactivity (NDO), TRPV1 immunoreactivity in the urothelium and the number of nerve fibers expressing TRPV1 are increased (22, 23, 53). For those patients who benefited from intravesicle resiniferatoxin (RTX) therapy, TRPV1 urothelial immunoreactivity decreased after treatment. In addition, in biopsies from the same patients, suburothelial TRPV1-expressing nerve fibers were reduced in number following therapy with RTX. Apparently, successful therapy using RTX leads to a reduced TRPV1 expression in both urothelial and neuronal cells (22).

An intriguing example of the role of TRPM8 in bladder function has recently been explicitly postulated (456), although experimental observations predictive of such a role date back to the early 1990s (241). Filling of the bladder with ice-cold water induces a rapid detrusor reflex and voiding in patients with supraspinal lesions, but such an effect occurs neither in patients with peripheral lesions nor in normal subjects. This forms the basis of the diagnostic icewater test to determine whether disturbances of bladder function involve a neurogenic component. The reflex is dependent on stimulation of sensory C fibers in the bladder, which express TRPM8 (289). In cats (241) and guinea pigs (456), inclusion of menthol within an intravesicular infusion of cold saline greatly facilitates the detrusor reflex, presumably by sensitization of TRPM8. Indeed, Lindstrom and Mazieres (241) commented with great prescience that "(the effect of menthol) could be described as a shift of the temperature-response curve for the cooling reflex towards higher temperatures."

Interestingly, several families have been identified with nocturnal enuresis/incontinence. Four linkages to chromosomal regions were described, two of which refer to the location of TRP channel genes, namely, TRPC4 (13q13) and TRPV4 (12q) (250).

6. *Reproductive system*

The functional importance of TRPC channels in sperm activation has been documented (for a review,

see Ref. 114). TRPC1, -2, -3, -4, and -6 are expressed in mammalian sperm (TRPC2 in mice only), along with TRPP2. In mouse sperm, TRPC6 localizes to the postacrosomal region and may be involved in the acrosome reaction. In contrast, TRPC1 and TRPC3 are confined to the flagellum and might, in concert with other Ca^{2+}-entry channels, be involved in the process of sperm activation as mature sperms are released from the caudal epididymis. However, TRPC channels are probably not crucial to hyperactivation, (i.e., the increased amplitude in flagellar beating that enables sperm to penetrate the zona pellucida of the oocyte), which requires the sperm-specific channels CatSper1 and CatSper2 (74, 86, 451). In human sperm, the distribution of TRPC channels differs in detail from that described for the mouse, but TRPC1, -3, -4, and -6 have all been detected within the flagellum, suggestive of a role in motility (57). Pharmacological suppression of TRPC channel activity causes impairments in the motility of human sperm, with the caveat that the agents employed exhibit rather poor pharmacological selectivity (57). TRPC3 also plays a role in fluid formation in the epididymis (66). Integration of data on TRPC channels in sperm will increase our understanding of sperm function and dysfunction. While transient increases in $[Ca^{2+}]_i$ via T-type Ca^{2+} channels might be necessary to trigger sperm capacitation, the acrosome reaction requires sustained Ca^{2+} entry, which may occur via TRPC channels.

Interestingly, TRPC1, -2, and -5, but not TRPC3, bind to a protein called enkurin, which may link these channels to the signaling complex for the acrosome reaction. Enkurin functions as a Ca^{2+} sensor and is coupled to PI 3-kinase and SH3 proteins (425). Another binding protein for TRPC2 and TRPC5 is junctate, an IP_3R-associated protein. TRPC activation might involve modification of the interaction with junctate and the IP_3R probably affecting activation by store depletion (410). The first functional role for TRPP2 in sperm concerned germ cell differentiation (513). Targeted disruption of a *trpp2* homolog in *Drosophila*, *pkd2*, which is expressed in the head and the tail of the sperm, resulted in male infertility without an effect on spermatogenesis. Instead, the mutant sperms, although motile, were unable to reach the sperm storage organ in the females (seminal receptacles and spermathecea) (127). A similar deficit in directional movement is observed following targeted disruption of a second *Drosophlia trpp2* homolog termed, most appropriately, "almost there" (*amo*) that localizes to the distal tip of the flagellum (499). It is intriguing those sensory functions of TRPP2 homologs are conserved across evolution in both motile (flagellum) and nonmotile (monocilium) axonemal-containing structures.

7. Kidney

TRPC1, -3, and -6 are expressed in the kidney. TRPC1 colocalizes with AQP-1 in the proximal tubule. TRPC3 and -6 are predominantly found in the glomeruli but are also detectable in podocytes (137). An analysis of renal function in *trpc1*$^{(-/-)}$ knockout mice has not yet been reported. Kidney tissues also demonstrate high levels of expression of TRPM3, especially in the medullary ray, the renal corpuscle, and the epithelium of the collecting tubule, where it may be involved in the reabsorption of Ca^{2+}, or other divalent cations (224). TRPM4-like channels are present in macula densa cells in the kidney juxtaglomerular apparatus where they might exert a negative influence over renin exocytosis (217). Indeed, intact TRPM4 seems to be a ubiquitously required negative-feedback component for many Ca^{2+}-dependent mechanisms.

The most Ca^{2+}-selective channels, TRPV5 and TRPV6, seem to play an essential role in maintenance of a constant extracellular Ca^{2+} concentration. The important role of TRPV5 and TRPV6 in the processes of transcellular Ca^{2+} reabsorption is well established. TRPV5 is mainly expressed in the apical membrane of kidney DCT2, CNT cells, bone, and intestine, whereas TRPV6 is widely expressed in the brush border of the apical membrane in intestine but also in kidney (164–166, 169, 304). TRPV5 null-mutant mice exhibit a diminished Ca^{2+} reabsorption, which causes a severe hypercalciuria. However, compensatory hyperabsorption of dietary Ca^{2+} was measured in *trpv5*$^{(-/-)}$ knockout mice (166). The urine produced by *trpv5*$^{(-/-)}$ mice is much more acid than in wild-type animals, which might be a defense mechanism against kidney stone formation. Compensatory mechanisms that possibly ameliorate TRPV5 deletion include the upregulation of TRPV6 in the intestinal brush border and the duodenal overexpression of calbindin-D_9K, which results in Ca^{2+} hyperreabsorption. It is, however, intriguing that TRPV5 dysfunction could be involved in diseases such as osteoporosis (166). A potential candidate for a TRPV5 channelopathy is autosomal dominant idiopathic hypercalciuria (290). Although the coding sequence of the TRPV5 gene is not affected in this disease, three SNPs were detected in the 5′-flanking region.

The following Ca^{2+}-related disorders most probably involve TRPV5 and TRPV6 (463): *1*) vitamin D-deficiency rickets type I (VDDR-I). This autosomal recessive disease is characterized by low 1,25-dihydroxyvitamin D_3 levels, hypocalcemia, rickets, osteomalacia, growth retardation, and failure to thrive. Both Ca^{2+} reabsportion channels, TRPV5 and TRPV6, are downregulated consistent with a pathogenetic role in this disease. *2*) In postmenopausal osteoporosis, estrogen has stimulatory effects on TRPV5 and TRPV6 expression. This type of osteoporosis is coupled to estrogen deficiency and decreased Ca^{2+} reabsorp-

tion via both channels. *3*) The autosomal disease idiopathic hypercalciuria (IH) is either caused by excessive intestinal Ca^{2+} reabsorption or defective renal Ca^{2+} reabsorption. Both forms increase the risk of kidney stone formation. So far, it is unknown whether mutations in TRPV5, or TRPV6, are involved in the pathogenesis of this disorder. What is known, however, is that SNPs in the Ca^{2+} sensing receptor (CaSR) increase the risk for IH. *4*) In parathyroid hormone (PTH)-related disorders, reduced serum PTH levels downregulate TRPV5 expression, which contributes to the hypocalcemia. *5*) For tacrolism, immunosuppressant drugs, like tacrolimus, also induce an increased bone turnover with hypercalciuria. Renal Ca^{2+} wasting is probably due to decreased TRPV5 expression (302). *6*) Thiazide diuretics increase Ca^{2+} reabsorption and cause hypocalciuria. A similar phenotype occurs in mutations of the Na^+/Cl^- cotransporter (NCC) leading to Gitelman syndrome. An upregulation of TRPV5 has been excluded (306). However, an increased paracellular reabsorption of Ca^{2+} has been measured (303). In addition, in Gitelman's syndrome a clear downregulation of TRPM6 has been observed. *7*) Glucocorticoids, like prednisolone, used as anti-inflammatory and immunosuppressive agents, reduce bone mineral density as a side effect due to a diminished duodenal expression of TRPV6 and calbindin D9K (178).

Inactivation of the TRPV6 channels causes decreased intestinal Ca^{2+} reabsorption (45). However, the exact role of these channels in Ca^{2+} signaling remains to be elucidated.

TRPV5 and TRPV6 play an important role during immunosuppression. FK506 (tacrolimus, an immune suppressor inhibiting the protein phosphatase 2B, or calcineurin) is a potent immunosuppressant but induces, as an unwanted effect, hypercalciuria and hypomagnesemia. These disturbances occur via a dramatic downregulation of TRPV5 and also calbindin D(28K), which is important for intracellular transport of Ca^{2+} from the apical reabsorption site to the basolateral membrane, and also TRPM6, a Mg^{2+}-permeable channel (see below). Such downregulation of specific Ca^{2+} and Mg^{2+} transport proteins provides a molecular mechanism for FK506-induced hypercalciuria and hypomagnesemia (302).

So far, TRPM6 and TRPM7 are the best-described players in Mg^{2+} homeostasis. Many publications have reported that disturbances in Mg^{2+} homeostasis cause cardiac arrhythmia, diabetes, and chronic alcoholism. These diseases are associated with diminished levels of plasma and parenchymal Mg^{2+}. Hypomagnesemic disorders develop in critically ill patients often due to kidney failure, or medication side effects, and are mostly life-threatening (179). TRPM6 is downregulated by thiazide-induced hypocalciuria, an effect that also occurs in NCC−/− mice (a model for the Gitelman syndrome) (306).

8. Skeletal muscle and bone

TRPV5 is localized in the ruffled membrane of osteoclasts and is absent from the osteoblast. Importantly, *trpv5*$^{(-/-)}$ mice exhibit significant disturbances in bone structure, with a reduced trabecular network and diminished thickness of cortical bone.

TRPV4 is expressed in chondrocytes and in osteoblasts. Four-week-old TRPV4-deficient mice demonstrate deformed chondrocytic columns and irregularly shaped bone trabeculae. Thus TRPV4 has been implicated in the regulation of chondrocyte polarity, chondrocytic differentiation, and endochondral ossification (278). TRPV4 has also been proposed as a sensor of mechanical stress in bone. In tail suspension experiments, which are used as a model for unloading and decreased gravity, control mice respond with a dramatic loss of trabecular bone volume, an effect not manifested in TRPV4-deficient animals (277).

Recently, in a very elegant study on zebrafish, it has been shown that mutations in TRPM7 cause severe growth retardation and general alterations in skeletal development (113). With respect to bone growth, endochondral ossification is accelerated whereas intramembraneous ossification is delayed during the larval to adult transition. Skeletal deformation and a dramatically reduced growth of the mutant animals are observed. Additional abnormalities evident in the mutants comprise embryonic melanophore defects, touch response impairment, and the development of kidney stones. The entire spectrum of defects is caused by TRPM7 mutations, some of which (i.e., melanophore defects) could be rescued by dietary supplementation of Mg^{2+}. Whether TRPM7 plays a similar role in growth and skeletogenesis in mammals remains to be investigated (113).

Given the emerging role of TRP channels as mechanosensors, TRPC1 and TRPV2 have been considered in the pathogenesis of stretch-induced muscle damage in normal and in dystrophic muscles. Both channels, when activated by stretch, can induce increased Ca^{2+} entry, which contributes to reduced force production, increased protein breakdown, and a malfunction of membrane permeability (16). TRPC3 has recently been shown to play a role in remodeling events in skeletal muscle. Conversion of fast into slow skeletal muscle requires an upregulation of NFAT. This upregulation is connected to an overexpression of TRPC3, indicating that skeletal muscle conversion may proceed via the Ca^{2+} influx-calcineurin-NFAT pathway (376).

Increased Ca^{2+} influx, probably via an upregulation of TRPC1 and TRPC6, has been reported to be involved in Duchenne muscular dystrophy (126, 468). It is known that disruption of the dystrophin-glycoprotein complex caused by genetic defects in dystrophin, or sarcoglycans, induces muscular dystrophy and cardiomyopathy. Interestingly, the expression of TRPV2 is increased in the

sarcolemma of skeletal/cardiac muscle in dystrophic patients and also in an animal model (the BIO14.6 strain of the Syrian hamster) that lacks functional δ-sarcoglycan and displays reduced abundance of dystrophin (185).

9. Endocrine system

TRPC1 (and probably also TRPC3) are activated by the peptide hormone orexin A via the GPCR OX_1 (218). This activation mode may link TRP channels to important physiological functions, because orexin regulates sleep/wakefulness states, alertness, and food intake (appetite). In addition, the orexin knockout mouse is a very useful model of human narcolepsy, a disorder that is characterized primarily by rapid-eye-movement sleep dysregulation.

Another interesting, but not yet understood, function of TRPV5 concerns its role in pancreatic β-cells. TRPV5, but not TRPV6, is highly expressed in β-cells and may play a role in the regulation by Ca^{2+} of insulin secretion. In Zucker diabetic fatty rats, a model for diabetes mellitus type 2, the progression of diabetes is correlated with a downregulation of TRPV5 (186).

10. Brain

In principle, TRPC channels could be important in the development of many neurological diseases. This is because TRPC channels seem to be crucially involved in the signaling via metabotropic glutamate receptors (198) and actions of brain-derived neurotrophic factor (BDNF) (228) that include netrin-1 and BDNF-mediated growth cone guidance (43, 139, 143, 233, 286, 397).

Recent studies indicate a potential link between TRPC1 and neurotoxicity induced by the exogenous agent 1-methy-4-phenylpyridium (MPP^+). The latter causes selective nigral dopaminergic lesions and induces Parkinson disease-like syndromes. When applied to human dopaminergic SH-SY5Y neuroblastoma cells, MPP^+ causes decreased expression and plasma membrane localization of TRPC1. In an opposite manner, TRPC1 overexpression reduces the neurotoxicity of MPP^+, inhibits cytochrome *c* release by MPP^+, and decreases Bax and Apaf-1 protein levels, indicating an inhibition of degenerative apoptosis involved in Parkinson's disease (52). Thus TRPC1 may execute a neuroprotective role in dopaminergic neurons.

Some indications suggest a role for TRPC6 in Alzheimer's disease. Mutations in the presenilin (PS) genes are linked to the development of early-onset Alzheimer's and transient expression of presenilin mutants (N141I, M239V) along with TRPC6 in HEK-293 cells results in a strong inhibition of agonist-induced Ca^{2+} entry (225). This effect does not result from an increased secretion of amyloid β-peptides into the medium, and TRPC6 itself remains functional as evidenced by unchanged direct activation by OAG. Interestingly, the loss-of-function PS mutant D263A augments the activity of TRPC6.

TRPV1 is widely expressed in the brain (276) and, in addition to its role as an intergrator of noxious stimuli in the periphery, is probably involved in higher order phenomena such as satiety regulation, cognition, and motor control (431). TRPV1 may also be involved in neurodegenerative mechanisms occurring during stroke (changes in brain temperature, pH, modulation of glutamate release) (261). In this context, TRPV1 agonists that promote fast desensitization and TRPV1 antagonists have been proposed to exhibit neuroprotective properties. In a model of global cerebral ischemia in gerbils, capsaicin reduced ischemia-induced hyperlocomotion, memory impairment, and electroencephalogram changes and improved survival of CA1 pyramidal cells in the hippocampus measured at various time points after the insult. Such protective effects were reduced by capsazepine (338). In a subsequent study employing the same model, the CB_1 receptor antagonist rimonabant was also found to exert neuroprotective effects that, on the basis of antagonism by capsazepine, were at least partially attributed to the involvement of TRPV1 (339). One proposed mechanism is that block of CB1 by rimonabant promotes TRPV1 activation by endogenously generated compounds, such as anandamide, which in turn cause TRPV1 desensitization (339). However, much of the argument for the involvement of TRPV1 hinges on suppression of neuroprotection by capsazepine, which, it must be emphasized, is an agent with limited selectivity for TRPV1. Nonetheless, capsazepine has also been shown to exert a neuroprotective action in ouabain-induced neurodegeneration, but in that study CB_1 receptor agonism (mediated by anadamide), rather than antagonism, was found to produce a beneficial outcome (472).

Schizophrenia is accompanied by morphological changes in the brain that include enlarged ventricles, a reduced cortical thickness, but an increased prefrontal neuron density. Patients also exhibit reduced pain sensitivity and a diminished niacin skin flare response. The latter symptoms hint towards a defect in TRPV1-expressing afferent nerve fibers. Capsaicin treatment of neonatal rats, surprisingly, causes brain changes that resemble those found in schizophrenic patients, indicating a possible role of TRPV1 during development in the pathogenesis of this disease (299).

The pathophysiology of bipolar disorder has been connected to a variety of TRP channels. TRPM2 is expressed in several human tissues, and abundantly so in the brain, lymphocytes, and hematopoietic cells (160, 294, 380). A truncated variant of TRPM2 is expressed in the striatum (i.e., caudate nucleus and putamen) (157, 294, 460). TRPM2 might be involved in the bipolar-I,II disorder (also known as bipolar illness, manic-depressive illness). Bipolar-I disorder is considered the most severe form of

this mental illness and is characterized by one, or more, manic, or mixed, episodes usually accompanied by major depressive episodes. In a major manic episode the patient may become delusional and even suffer from hallucinations. Bipolar-I disorder, by definition, includes psychotic features. The key difference between bipolar-I and bipolar-II is that bipolar-II has hypomanic but not manic episodes and does not have psychotic features. It has been recently found that bipolar-I patients, but not bipolar-II patients, have decreased mRNA levels for TRPC7 and show increased basal Ca^{2+} levels in a lymphoblast cell line derived from them (525). A putative susceptibility locus of bipolar-I is within the chromosomal regions 12q23-q24.1 (which encodes the Ca^{2+}-ATPase, SERCA) and 21q22.3 to which the TRPM2 gene has been mapped (9, 247, 417). In addition to these findings, it has been shown that SNPs in the promoter region of TRPM2 are significantly associated with bipolar-II, suggesting that TRPM2 polymorphisms contribute to the risk for bipolar-II (515, 516). It is also worth mentioning in connection with depressive mental disorders that leptin, which is connected to TRPC1 (and probably also TRPC3) via OX_1 (218), has antidepressant effects and that impaired leptin production contributes to depression-like phenotypes in a rat model (252). Recently, Roedding et al. (372) reported that TRPC3, TRPC6, and TRPC7, which can all be activated by OAG and lysophosphatides, are absent in B lymphocytes from patients with bipolar disorder.

An intriguing function for TRPM4 can be anticipated from experiments in which the GABA receptor antagonist bicuculline was employed to initiate spontaneous epileptic activity in neocortical slices. TRPM4-like channels are activated during paroxysmal depolarization shift discharges and appear to play a role in maintaining subsequent sustained afterdepolarization waveforms. The latter effect depends on an increase in $[Ca^{2+}]_i$ and can be blocked by maneuvers that inhibit TRPM4 (385). Neuronal damage evoked by reduced blood supply to the brain ("vascular stroke"), which induces severe hypoxia and hypoglycemia, are very often accompanied by a phenomenon in which susceptible neurons slowly lose their membrane potential and then suddenly enter a transient state of complete depolarization, known as spreading depression-like hypoxic depolarization. Spreading depression is associated with an increase in $[Ca^{2+}]_i$. Intriguingly, TRPM4 (and TRPM5) could be a candidate for triggering this dramatic event, although there is at present no direct experimental evidence in support of this conjecture (20, 407). It is also worthwhile mentioning that activation of a current with features reminiscent of TRPM4 is involved in generation of slow (<1 Hz) sleep oscillations (85).

Another example that hints to a contribution of TRPM4 in the pathogenesis of brain swelling during stroke is the discovery in hypoxic gliotic tissue of a nonselective Ca^{2+}-activated channel ($NC_{Ca\text{-}ATP}$) that also opens under conditions of $[ATP]_i$ depletion (65, 402). This channel, which shares many properties with TRPM4 (i.e., single-channel conductance, concentration range of activation by $[Ca^{2+}]_i$, submicromolar block by ATP, voltage-dependent open probability) is found in astrocytes in the adult brain and is regulated by SUR1, similar to the K_{ATP} channel (64). Activation of $NC_{Ca\text{-}ATP}$ causes complete membrane depolarization and cell swelling in astrocytes from injured brains (65, 402). Many diseases in the brain, including traumatic conditions, edema, ischemia, and stroke are exacerbated by cerebral edemas. Importantly, these events induce an upregulation of $NC_{Ca\text{-}ATP}$ (403). Cerebral edema after occlusion of the middle cerebral artery (MCA) stroke is responsible for a high mortality of ~80% of patients (26). Edemas in MCA stroke are paralled by an increased expression of the sulfonylurea receptor 1 (SUR1), driven by an upregulation of the transcription factor Sp 1. Glibenclamide attenuates the development of cerebral edema by MCA stroke. It would be interesting to determine whether TRPM4 is indeed the channel regulated by SUR1 and involved in the pathogenesis of cerebral edemas. If so, TRPM4 might provide a new and promising therapeutic approach to stroke.

TRPM7 plays a universal role in Mg^{2+} homeostasis associated with basic cellular metabolism and activities such as cell viability and proliferation. Cases of anoxic neuronal death have been described that include the involvement of TRPM7 in cellular damage due to an imbalance of the normal physiological processes (1). In situations of brain ischemia, oxygen-glucose deprivation (OGD) and excitotoxicity mediate neuronal death. The key processes involve high Ca^{2+} influx as a consequence of the excitotoxicity. Subsequent production of reactive oxygen/nitrogen species consecutively activates another Ca^{2+} conductance, named I_{OGD}, which is mediated by TRPM7, and results in cellular Ca^{2+} overload and cell death.

In models of ischemic stroke (oxygen and glucose deprivation, NaCN chemical anoxia), the activation of NMDA receptors (NMDA-R) provides a route for toxic Ca^{2+} influx, and TRPM7 probably provides an additional pathway (257). TRPM7 is activated by products of neuronal NO synthase (free radicals, ROS) and transient depletion of extracellular Ca^{2+} and Mg^{2+} (e.g., by a decrease in $[Mg^{2+}]_i$). In addition, depolarization by TRPM7 activation will relieve voltage-dependent block of NMDA-R by Mg^{2+}, inducing a positive feedback on NMDA-R-mediated Ca^{2+} entry. Furthermore, TRPM2 also seems to be critically involved in central nervous system cell death and stroke. Ca^{2+} influx via NMDA-R induces an activating effect on TRPM2, thereby generating a positive feedback on Ca^{2+} entry. Generation of ROS and nitrogen species further activates TRPM2. Subsequent activation of DNA repair enzymes, such as poly-ADPR polymerase, or poly-ADPR glycohydrolase, produce the TRPM2-activating intracellu-

lar ligand ADPR. Furthermore, the opening of the mitochondrial permeability transition pore (mPTP) followed by NAD^+ release and subsequent conversion to ADPR will also activate TRPM2. These situations will create a vicious circle leading finally to cell death and stroke (for a detailed review, see Ref. 257).

11. Sensory systems

Over 35 genes associated with nonsyndromic deafness have been cloned in human and 18 in mouse (see the websites http://dnalab-www.uia.ac/dnalab/hhh/ and http://www.jax.org/hmr/models.html) (300), none of which corresponds to a TRP channel. TRPA1 has been considered as a likely candidate for the elusive mechanically gated transduction channel necessary for the auditory response in mammals (82, 133). The protein is present in the tips of stereocilia in hair cells (though not exclusively), and experimental maneuvers that decrease TRPA1 expression cause defects in hearing (82). In addition, the location of TRPA1 and the biophysical properties of the channel are similar to those of the native transduction channel (295). However, two recent studies (35, 214) conducted with *trpa1*$^{(-/-)}$ mice revealed no obvious deficits in auditory function as evidenced by a normal Preyer reflex, normal auditory brain stem responses to tone pips, clicks and constant tones and unaltered transduction channel function as evaluated by dye accumulation and whole cell recordings from hair cells. Clearly, TRPA1 can no longer be regarded as an essential component of the transduction channel in hearing, at least in adult animals (35, 81, 214).

TRPV1 is, like TRPA1, expressed in the organ of Corti, and agonists of TRPV1 can reduce cochlear microphonic potentials and elevate the threshold for the auditory nerve compound action potential in a manner that is sensitive to capsazepine. It is suggested that TRPV1 channels located on outer hair cells play a role in cochlear homeostasis, rather than any function in mechanotransduction (539).

TRPV4 is also expressed in the cochlea within hair cells, the stria vascularis, and the spiral ganglion (236). It might, therefore, be involved in sensorineural hearing impairment. Indeed, Tabuchi et al. (432) measured a hearing impairment in *trpv4*$^{(-/-)}$ mice. Up to the age of 8 wk, hearing was normal, but compared with wild-type control animals, *trpv4*$^{(-/-)}$ mice demonstrated a higher hearing threshold as evaluated by the auditory brain stem response once they were older than 24 wk. TRPV4 might thus be associated with a delayed-onset hearing loss and an increased cochlea vulnerability to acoustic injury (432). More than 50% of the cases of sensorineural hearing impairment in children have a genetic etiology, which in the majority of cases is not associated with other clinical symptoms, i.e., the condition is "nonsyndromic." One of the gene loci for autosomal dominant nonsyndromic hearing loss (ADNSHL) has been mapped to a small region in chromosome 12q21–24 where the *TRPV4* gene is located (142). The TRPV4 gene locus has been discussed as the human ortholog of the region affected in the *bronx waltzer (bv)* mutant mice, which are characterized by waltzing behavior, deafness, and the loss of cochlear inner hair cells during early development (see also Ref. 89 for another *bv* ortholog).

TRPML2 and TRPML3 are both expressed in cochlear hair cells. Gain-of-function mutations in TRPML3 are associated with defects in the structure of the stereocilia hair bundle. Localization of TRPML3 to plasma membrane of stereocilia and the structural defects argue for a role of TRPML3 in stereocilia function. It has recently been speculated that TRPML3 could assemble with TRPA1 within stereocilia, but the functional relevance of this to hearing has become doubtful due to the lack of an obvious impairment in hearing in the *trpa1*$^{(-/-)}$ mice (35, 214).

The role of TRP channels in thermosensation has been the subject of several recent and extensive reviews to which the reader is referred (97, 240, 268, 334, 369). The involvement of TRP channels in the development of thermal hyperalgesia has been reported in the preceding sections.

E. TRPs and Aging

Importantly, several TRPV channels seem to be linked to aging. TRPV5 and TRPV6 expression is decreased with age resulting in decreased Ca^{2+} reabsorption (464). A gene named *klotho* seems to play an important role in aging processes, as its deletion in mice results in a syndrome resembling human aging, including short life span, bone aberrations, infertility, skin atrophy, and hypercalcemia, as well as an increase in serum vitamin D (212, 213, 434). Interestingly, *klotho*, which is a β-glucuronidase, is an important regulator of TRPV5. It hydrolyzes extracellular sugar residues on TRPV5, thereby entrapping the channel in the plasma membrane, resulting in durable calcium channel activity (62).

F. TRPs and Cancer

Altered expression of several types of putative "store-operated" Ca^{2+}-entry channels has been demonstrated in various forms of cancer. TRPC1 is downregulated in androgen-independent cancer in the prostate (469). TRPV5 and TRPV6 are both expressed in the prostate, and the expression of the latter is significantly increased in prostate adenocarcinoma compared with benign prostate hyperplasia. Expression of TRPV6 correlates with tumor grade (342, 510), and its expression is decreased by dihydrotestosterone and conversely increased by an androgen

receptor antagonist (342). Prostate carcinoma is a hormone-sensitive malignancy, and nonsteroidal antiandrogens, such as flutamide, are frequently used in prostate cancer treatment. Furthermore, estrogens, which are also used in the therapy of prostate cancer, positively regulate TRPV5 and TRPV6. Hence, TRPV6 might be a molecular mediator involved in the anticancer effects of these compounds. In addition to being a very promising marker for prostate cancer, TRPV6 could also be a target for novel anticancer strategies. Importantly, the channel is consistently overexpressed not only in prostate cancer but also in breast, thyroid, colon, and ovarian carcinomas (541). Ca^{2+} entry through TRPV6 may increase the rate of Ca^{2+}-dependent cell proliferation and thus be directly linked to tumor growth (393).

TRPM1, the founding member of the TRPM family, has been identified as a melanocyte-specific gene that is exclusively expressed in melanoma cells and is downregulated during the development of metastasis in cutaneous malignant melanoma (107). Malignant melanoma is a tumor of epidermogenic origin that develops from moles, or normal-looking skin, as well as in eyes and the meninges. Malignant melanoma is the most aggressive skin tumor with a statistical survival time after diagnosis of ~6 mo (107). The inverse correlation between TRPM1 transcript expression and metastatic potential represents one of the most reliable differential diagnostic markers to discriminate between nonmetastatic and metastatic melanomas. TRPM1 is possibly a tumor suppressor, acting via a yet unknown mechanism. Unfortunately, a thorough functional characterization of TRPM1 remains to be performed. Interestingly, TRPM1 appears in two splice variants: the full-length transcript TRPM1-L comprising 1,533 amino acids and a short splice variant TRPM1-S of 500 amino acids that lacks the channel-forming transmembrane domains (520). A potential, but disputed, mechanism of the regulation of TRPM1 may involve the short cytosolic variant binding to, or interacting with, the long variant to suppress its translocation to the plasma membrane. Upon a specific, yet unidentified stimulus, TRPM1-S might dissociate from TRPM1-L and enable plasma membrane insertion of the latter where subunit proteins can associate and form functional Ca^{2+}-influx channels (520). This model suggests that retention of TRPM1-L in an intracellular compartment is critical in regulating Ca^{2+} influx.

TRPM8 may also play an important role in the pathophysiology of prostate cancer (454). In the androgen-responsive LNCaP cell line, TRPM8 localizes to the endoplasmic reticulum and plasma membrane and has been reported to form a Ca^{2+}-permeable channel at both locations (531). However, in another study performed on LNCaP cells, TRPM8 was found to be largely restricted to the endoplasmic reticulum and functions as a Ca^{2+} release channel (438). In androgen-sensitive (i.e., LNCaP), but not insensitive (i.e., PC-3), cell lines TRPM8 expression is enhanced by androgens. In addition, TRPM8 regulates Ca^{2+} homeostasis in prostate epithelial cells and importantly is required for cell survival defining a potential target for drug action in the management of prostate cancer (438, 531). Although TRPM8 is normally required for survival of prostate epithelial cells, sustained activation of TRPM8 by menthol induces cell death in the LNCaP cell line (531). Moreover, expression of TRPM8 appears to be lost as prostate tumors progress to androgen independence and more severe disease (161). It has been convincingly shown that significant differences exist in the level of expression of TRPM8 between malignant and nonmalignant prostate cancer. TRPM8 is a much more specific marker for prostate cancer than other markers [prostate specific antigen (PSA), kallikrenin 2 (hK2), or prostate stem cell antigen (PSCA)] (125). The TRPM8 gene might also be a promising candidate for targeting in a gene therapy approach. Importantly, one extracellular region in TRPM8, GLMKYIGEV, has been identified as an activating domain for cytotoxic T lymphocytes (193). Thus TRPM8 may provide an endogenous defense mechanisms against cancer growth (see for a detailed review, see Ref. 532).

G. Candidate Genes

A role for several TRP channels in the ontogeny of diseases can be suspected based on the chromosomal localization of the encoding genes. The chromosomal localization of all TRP genes and some relevant diseases linked to these loci are summarized in Table 5 (see also Ref. 320). However, it must be emphasized that in most cases causal, pathogenic, mechanisms have not yet been established (see also OMIM data basehttp://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

The so far best-studied connection of a candidate gene connected to a disease syndrome concerns TRPM5. The *TRPM5* gene maps to the chromosomal area 11p15.5 (357). This gene region is involved in maternally induced genetic imprinting. A genetic disorder involving a loss of imprinting in this region is the Beckwith-Wiedemann syndrome (BWS), a disease that is mainly characterized by exomphalus, macroglossia, gigantism, and taste abnormalities. Moreover, BWS patients also demonstrate a strong predisposition for neoplasias, especially for Wilms tumor and the aggressive rhabdomyosarcomas. Therefore, it seems likely that this area contains at least one gene with oncogenic potential and/or a tumor suppressor gene, and impairment in their function, or regulation, will potentially result in disease development. A possible connection between functional TRPM5 and BWS has not yet been discovered. So far, no mutations in the TRPM5 gene that relate to BWS are known. Interestingly, possibly af-

fected genes are *igf2* (insulin-like growth factor II), *cdkn1c* (cyclin-dependent kinase inhibitor 1C), *p21cip1* (cyclin-dependent kinase inhibitor p21), *kcnq1ot1* (potassium channel KCNQ1), and *znf215* (putative transcription factor), which are located in the same chromosomal region. Such a complex situation might be expected with other TRPs, which are involved in syndromic diseases. Interestingly, BWS patients have persistent hypoglycemia and hyperinsulinism, features which are similar to diseases caused by mutations in the SUR1 subunits of the K_{ATP} channel, which is crucial in glucose-regulated insulin release (88, 119, 291, 479). Because TRPM5 is highly expressed in pancreatic β-cells (358), it is tempting to hypothesize that the TRPM5 channel plays a unique regulatory role in islet β-cell function. It can be assumed that the upregulation of insulin secretion has an oncogenic potential, indicating a possible connection between functional TRPM5 and BWS that has not yet been discovered.

H. Lessons From Knockout and Transgenic Mice

In the above, we have already referred several times to results from knockout mice when discussing the possible involvement of TRP channels in several (patho)-physiological processes. Below, we provide a more exhaustive overview of all currently published phenotypes of TRP channel knockout mice (also for reviews, see Ref. 96) (122, 123).

One of the most striking phenotypes was observed in the *trpc2*$^{(-/-)}$ mouse. Note that *trpc2* is a pseudogene in humans! The *trpc2*$^{(-/-)}$ mice exhibit a greatly reduced responsiveness to pheromonal cues in the vomeronasal organ. This deficit correlates with a marked reduction in the functional expression of a nonselective cation channel in the dendrites of vomeronasal neurons that is activated by DAG (253) and is downstream from the receptors that detect pheromones. Behavioral analysis of male *trpc2*$^{(-/-)}$ mice revealed that they no longer exhibit the normal male-male aggression and, in fact, engage in "homosexual" behavior (227, 416, 543).

TRPC4 was the first TRPC channel gene to be deleted in mice (121). The high level of expression of TRPC4 in vascular endothelium together with TRPC1, TRPC2, TRPC3, TRPC6, TRPV4, TRPM4, and TRPM7 mandated a careful examination of vascular phenotypes in the *trpc4*$^{(-/-)}$ mouse. Indeed, analysis of the latter indicates that TRPC4 is an essential component of endothelium-dependent vasorelaxation and regulation of transcellular permeation of the endothelial layer in vivo (121, 439). TRPC4-deficient mouse blood vessels showed an impaired endothelium-derived vasorelaxation due to decreased agonist-induced Ca^{2+} entry. In addition, thrombin-induced Ca^{2+} entry, which occurs subsequent to the activation of G protein-coupled proteinase-activated receptor-1 (PAR_1) in endothelial cells and plays an important role in the pathogenesis of vascular injury and tissue inflammation was markedly reduced in *trpc4*$^{(-/-)}$ mice. Clearly, TRPC4 is important in both endothelium-dependent vasorelaxation and in the control of paracellular endothelial permeability (i.e., the barrier function of endothelial cells) (120, 121, 439). TRPC4 is also present in F2-synaptic terminals of the thalamic network. These terminals provide a GABAergic input into the dorsal lateral geniculate nucleus. GABA release from such F2 terminals depends on Ca^{2+} influx initiated by metabotropic receptors. In *trpc4*$^{(-/-)}$ mice, the 5-hydroxytryptamine (5-HT)-induced release of GABA from the thalamic interneurons is dramatically reduced (292). This GABAergic component is critical for the control of the sleep/wake cycle and processing of visual information and might also be important for the control of retinogeniculate transmission (122). It is not clear yet whether these findings reported for *trpc4*$^{(-/-)}$ mice can be related to human diseases.

Smooth muscle preparations isolated from TRPC6-deficient mice exhibited an exaggerated contractile response to agonists as exemplified by the actions of methacholine and phenylephrine on tracheal and aortic rings, respectively. As noted previously, the Bayliss effect in isolated cerebral arteries is also enhanced in *trpc6*$^{(-/-)}$ animals as is agonist-induced contractions of resistance vessels in the mesenteric bed. Not surprisingly in view of the foregoing, the knockout mouse has a modestly elevated mean arterial blood pressure and a decreased expiration rate in response to methacholine challenge. Smooth muscle cells isolated from the thoracic aorta, or cerebral arteries, of *trpc6*$^{(-/-)}$ mice demonstrate higher basal cation entry, increased TRPC-mediated cation currents, and more depolarized membrane potentials in comparision with cells obtained from wild-type animals. These effects are most likely the result of the upregulation of TRPC3 in the TRPC6-deficient smooth muscle cells (101, 103, 104, 274). To which degree (mal)function of TRPC6 and other TRPC channels is involved in human blood pressure regulation and hypertension remains to be elucidated.

trpv1$^{(-/-)}$ mice have normal responses to noxious mechanical stimuli but exhibit no vanilloid-evoked pain behavior, are impaired in the detection of painful heat, and showed little thermal hypersensitivity in the setting of inflammation. More details on the different aspects of this extensively studied knockout can be found in the preceding sections.

TRPV3 plays a specific role in thermosensation because responses to innocuous and noxious heat, but not to other sensory modalities, are dramatically diminished in *trpv3*$^{(-/-)}$ mice (285). TRPV3 is highly expressed in keratinocytes, and it is likely that heat-activated receptors in keratinocytes are important for thermosensation (285). Several mutant rodent strains are spontaneously hairless.

Two of them, the autosomal dominant DS-Nh (no-hair) mouse and the WBN/Kob-Ht rats, in addition develop under normal conditions atopic dermatitis (AD) that closely resembles the human version of this disease (24). Intriguingly, these two mutant strains possess a point mutation in the S4-S5 linker of the TRPV3 channel (G573S in DS-Nh and G573C in WBN/Kob-Ht mice), which is highly expressed in the skin, in keratinocytes, and in cells surrounding hair follicles (24, 71, 72, 140, 285). Moreover, hair abnormalities have also been reported in the TRPV3 knockout mouse (285), strongly suggesting that TRPV3 might be causally involved in hairlessness combined with dermatitis, an increase of the number of mast cells, and hyperkeratinosis in skin lesions. Functionally, residues in S4 and in the S4-S5 linker are supposed to be involved in voltage-dependent gating of TRP channels such as TRPV3. Therefore, mutations in this region may modify Ca^{2+} influx via TRPV3, which might be causally involved in this disease. Interestingly, defects in Ca^{2+} sequestering endo-(sarco)plasmic reticulum (SERCA2) and Golgi (SPCA1) Ca^{2+} pumps in keratinocytes are related to skin diseases such as the focal dermatitis, Darier's disease (98), and Haley-Haley disease (for a review, see Ref. 465), respectively.

The *trpv4*$^{(-/-)}$ mouse shows a relatively mild phenotype, including abnormalities in the response to systemic osmotic and somatosensory mechanical stimuli. Possibly, compensatory genes, or pathways, might be upregulated in the TRPV4-deficient animal (237, 279, 426). Nonetheless, *trpv4*$^{(-/-)}$ mice have a modestly increased blood osmolarity and drink significantly less than the wild-type littermates, provided that social (i.e., contact with other animals) and physical (i.e., food) drives to drink are removed (237). If deprived of water, the *trpv4*$^{(-/-)}$ mice show a lower fluid intake, an increased latency to drink, a decreased antidiuretic hormone (ADH) secretion but an undisturbed renal ADH response. Such animals also display an impaired defense against a systemic hyperosmotic challenge and a blunted response to hyposmolar stimulation (237). Although TRPV4 is a channel activated by warm stimuli, behavioral analysis of *trpv4*$^{(-/-)}$ mice indicates that it does not influence the threshold for the detection of painful heat. Rather, TRPV4 is involved in the development of thermal hyperalgesia in response to subcutaneous injection of carrageenan, a seaweed extract that is also used in the food industry (440). TRPV4 is also involved in hypotonicity-induced nociception, that is hyposmotic hyperalgesia (14). It is notable that the temperature-sensitive channels TRPV3 and TRPV4 have been detected in nigral dopaminergic neurons, where changes in temperature up to several degrees have been reported, and are possibly involved in the control of behavioral reaction (147).

In *trpv5*$^{(-/-)}$ mice, osteoclast number and area are increased. However, such cells display a large deficit in bone reabsorption, indicating that TRPV5 is an essential Ca^{2+} transporter in this tissue (469). Interestingly, *trpv5*$^{(-/-)}$-deficient mice did not develop an osteopetrosis (abnormally dense bone), but an osteoporosis (decreased bone mass and density) phenotype indicated by a reduced bone thickness (166). Possible explanations for this apparent paradox are an overexpression of TRPV6 and an increased 1,25-dihydroxyvitamin D_3 level in the *trpv5*$^{(-/-)}$ mice (469). Both TRPV5 and TRPV6 (re)absorb Ca^{2+} in the kidney and the intestine (167, 168).

Although *trpv6*$^{(-/-)}$ mice exist in several laboratories, relatively few data have been disclosed to date. In common with TRPV5, TRPV6 is a main player in calcium absorption and homeostasis. TRPV6 knockout mice suffer from reduced fertility, and some develop alopecia and a form of dermatitis. They also display a deficit in intestinal Ca^{2+} absorption and renal reabsorption, resulting in urinary Ca^{2+} wasting and a decreased bone mineral density (for a reference, see http://ntbiomol.unibe.ch/hediger.html).

The *trpm5*$^{(-/-)}$ mice appear normal but exhibit severe deficits in the perception of sweet, bitter, and umami taste (538). Moreover, they completely lack the temperature sensitivity of sweet taste (316, 437). Whether TRPM5 is involved in taste dysfunctions in humans remains to be explored.

An interesting example of the involvement of TRPML3 in a systemic disease arises from two mutations that have been analyzed in mice. Functional development of hair cells, which express TRPML3, requires a maturation process that organizes the stereocilia in these cells in a correct staircase-like V-shaped pattern. Mutations of TRPML3 (the knockout is lethal) interfere with this maturation. Two mutations of TRPML3 have been detected. One mutation associated with a severe phenotype occurs within the TM1-TM2 linker and involves an isoleucine-to-threonine mutation (the *Va* allele). A second, additional mutation in fifth TM, in which alanine is replaced by proline (the *Va*^{J} allele) partially partially rescues the *Va* allele and is associated with a less severe phenotype (106a). Such mutations induce the very striking phenotype of the varitint waddler mouse (106a, 195). These animals are deaf because two different functions in the cochlea, maintenance of hair bundles and generation of endocochlear potential, are compromised. In the varitint waddler mouse, the V-shaped arrangement of the stereocilia is not maintained during development, but instead becomes progressively disorganized with clumps of stereocilia that appear to drift apart. Beyond deafness, the varitint waddler mouse is characterized by balance defects, head-bobbing, circling behavior, and waddling (all of which are indicative of a vestibular defect). The animal also exhibits a distinctive coat pigmentation, specifically gray, white, and chestnut brown colors arranged in variable patches. This striking pigmentation probably results from a defective trafficking of melanosomes and indicates

that TRPML3 is involved in the formation of such vesicles. These defects are not confined to the skin; melanocytes are extensively found in the stria vascularis where they are essential to the maintenance of the endocochlear potential that provides a part of the driving force for cation entry into hair cells via the mechanotransduction channel. In the mutant animal, the number of melanocytes within the stria vascularis is greatly reduced, and the ensuing secretion defect causes a reduced, or absent, endocochlear potential (54, 106a, 411).

The *trpp2*$^{(-/-)}$ mice die in utero between embryonic day 13.5 and parturition. They exhibit structural defects in the cardiac septum as well as cyst formation in maturing nephrons and pancreatic ducts and show embryonic whole body edemas, renal failure, and bone deformation. As observed for patients with ADPKD, the massive formation of renal cysts results from thousands of large spherical cysts of different diameter derived from every nephron segment. The *trpp2*$^{(+/-)}$ mice exhibit an intermediate survival but lack cystic disease or renal failure (512, 513). TRPP2 is active in node monocilia during embryogenesis and plays a role in the establishment of left-right asymmetry. TRPP2 mutations result in abnormalities of the left-right axis determination during body development in mice. Laterality depends on a pathway that involves the asymmetrically expressed genes *nodal*, *Ebaf*, *Leftb*, and *Pitx2*. A knockout allele of TRPP2 that resulted in addition to malformations described above in embryos showed right pulmonary isomerism, randomization of embryonic turning, heart looping, and abdominal situs. The laterality genes *Leftb*, *nodal*, *Ebaf*, and *Pitx2* showed a defective expression pattern (343).

I. PIP_2-TRP Connection and Its Impact on Disease

Emerging evidence indicates that the acid membrane phospholipid PIP_2 plays an important role in the regulation of many TRP channels. TRPV1 is tonically inhibited by PIP_2 (68, 359), whereas TRPM4 (310a), TRPM5 (244), TRPM7 (378), TRPM8 (243, 373), and TRPV5 (223, 373) are all activated in the presence of PIP_2. Rohacs et al. (373) proposed a general role for the proximal COOH-terminal TRP domain in PIP_2 regulation of TRPM8 and other PIP_2-activated TRP channels, whereas Prescott and Julius (359) identified a more distal COOH-terminal region as a crucial determinant of PIP_2 inhibition (359, 373). It is intriguing to speculate that some of the diseases that are linked to a defective PIP_2-mediated signaling are also connected to TRP channel functioning (155). For example, bipolar disorder is linked to PIP_2. The transition from cardiac hypertrophy to heart failure is linked to an increased apopotosis, which in turn is correlated with a decreased level of PIP_2. Lowe syndrome (mental retardation, lens cataract, glaucoma, growth defects, and renal dysfunction) is linked to a decreased phosphatidylinositol 5-phosphatase function, causing elevated PIP_2 levels. In view of the frequently dramatic effects of PIP_2 on TRP channels (e.g. Ref. 310a) it must be considered that alterations in the availability of PIP_2 could translate into dysregulation of channel activity and potentially contribute to pathology.

IV. CONCLUSION

TRP channels play an important role as multifunctional cellular sensors. They are involved in so many fundamental cell functions that the investigation of their role in human pathophysiology and disease will become an urgent priority in biomedical sciences. This review has been written with the intention of being as comprehensive as possible. Therefore, diseases have been included for which a TRP connection is indisputably tentative. Diseases that directly involve perturbations in signaling mediated by TRP channels will be identified without ambiguity as soon as more molecular biological and functional information becomes available. Although many TRP channels are well studied in heterologous overexpression systems, functional work in native cells and isolated organs is still rather limited. Moreover, conditional and organ-specific transgenic models should also be used more extensively. Another limitation that hampers our understanding of TRP function is the lack of selective pharmacology as well as specific antibodies for detection of TRP channels in the native cells. Nevertheless, anticipating the burgeoning literature in this field, we believe that the progress will be rapid.

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Address for reprint requests and other correspondence: B. Nilius, Laboratorium voor Fysiologie, KU Leuven, Campus Gasthuisberg, B-3000 Leuven, Belgium (e-mail: Bernd.Nilius@med.kuleuven.be).

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