

11 TRP Channels

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11.1 Introduction

The TRP superfamily represents a highly diverse group of cation-permeable ion channels related to the product of the *Drosophila trp* (transient receptor potential) gene. The cloning and characterization of members of this cation channel family has experienced a remarkable growth during the last decade, uncovering a wealth of information concerning the role of TRP channels in a variety of cell types, tissues, and species. Initially, TRP channels were mainly considered as phospholipase C (PLC)-dependent and/or store-operated Ca^{2+} -permeable cation channels. More recent research has highlighted the sensitivity of TRP channels to a broad array of chemical and physical stimuli, allowing them to function as dedicated biological sensors involved in processes ranging from vision to taste, tactile sensation, and hearing. Moreover, the tailored selectivity of certain TRP channels enables them to play key roles in the cellular uptake and/or transepithelial transport of Ca^{2+} , Mg^{2+} , and trace metal ions. In this chapter we give a brief overview of the TRP channel superfamily followed by a survey of current knowledge concerning their structure and activation mechanisms.

11.2 TRP Channel History

TRP history started in 1969, when Cosens and Manning performed a screening for *Drosophila* mutants with impaired vision. They identified a mutant that exhibited a transient instead of sustained response to bright light (Cosens and Manning, 1969). Analysis of the photoreceptor cells of the mutant fly strain revealed that sustained light induced a transient rather than the normal sustained, plateau-like receptor potential. The mutant was baptized *trp*, for transient receptor potential. Two decades later, the *trp* gene was cloned (Montell and Rubin, 1989) and subsequently its product, TRP, was characterized as a Ca^{2+} -permeable cation channel, the founding member of the TRP superfamily (Hardie and Minke, 1992). Additional close homologues of TRP, named TRPL (or TRP-like) (Phillips et al., 1992) and TRP γ (Xu et al., 2000) were identified in *Drosophila* photoreceptor cells, and all three proteins were found to contribute to the light-induced currents (Phillips et al., 1992; Reuss et al., 1997; Xu et al., 2000). It is now well established that *Drosophila* TRP is not directly involved in the detection of light, but rather functions as a receptor-operated

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11. TRP Channels

Table 11.1 Permeability properties of members of the TRP superfamily.

Permeability properties	TRP channel
Highly Ca ²⁺ -selective ($P_{Ca}/P_{Na} > 100$)	TRPV5, TRPV6
Relatively nonselective for mono- and divalent cations	TRPCs, TRPV1-4, TRPM2, TRPM3, TRPM8, TRPAs, TRPPs, TRPMLs
Nonselective for monovalent cations, impermeable to divalent cations	TRPM4, TRPM5
Selective for divalent cations including Mg ²⁺ , Ca ²⁺ , and trace metal ions	TRPM6, TRPM7

families of ion channels, where the differences in permeation properties within one family are generally small. It is therefore not too surprising that a consensus pore sequence, such as the well-described "signature" sequence that delineates the selectivity filter of K⁺ channels (TXXTXGYGD) (Yellen, 2002), cannot be defined in TRP channels. At present, data concerning the localization and structure of the pore region and selectivity filter are scarce and limited to the TRPV, TRPC, and TRPM subfamilies (Owsianik et al., 2006b).

11.4.2.1 TRPV

Structure–function analysis of the pore region is most advanced for the TRPV subfamily. Here, sequence comparison revealed that the loop between S5 and S6 of the different TRPVs shows significant sequence homology with the outer pore (P-loop) of potassium channels including KcsA (Voets et al., 2004b), for which a detailed crystal structure has been provided thanks to the pioneering work of the MacKinnon lab (Doyle et al., 1998). Neutralization of negatively charged aspartate residues in the corresponding region in TRPV1, TRPV4, TRPV5, and TRPV6 resulted in altered permeability properties and lowered sensitivity to voltage-dependent block by ruthenium red, Mg²⁺ or Cd²⁺ (Garcia-Martinez et al., 2000; Nilius et al., 2001b; Voets et al., 2002, 2003; Hoenderop et al., 2003), establishing the contribution of this region to the TRPV pore. Most strikingly, neutralization of Asp⁵⁴² in TRPV5 and Asp⁵⁴¹ in TRPV6 converted these channels from highly Ca²⁺-selective to nonselective for monovalent cations (Nilius et al., 2001b; Voets et al., 2003).

TRPV5 and TRPV6 share many permeation properties with voltage-gated Ca²⁺ channels (Tsien et al., 1987; McDonald et al., 1994; Varadi et al., 1999; Hille, 2001; Sather and McCleskey, 2003). A characteristic feature of these highly Ca²⁺-selective channels is the anomalous mole fraction effect. At sub-micromolar Ca²⁺ concentrations, these channels are highly permeable to monovalent cations. With increasing Ca²⁺ concentrations, the channels first become blocked and then start to conduct Ca²⁺. The high ion transfer rate of the Ca²⁺ channel pore in the case of L-type voltage-gated Ca²⁺ channels has been explained by two models: the "repulsion model" (Almers and McCleskey, 1984; Hess and Tsien, 1984; Hess et al., 1986) and the "step model" (Dang and McCleskey, 1998). With moderate changes in

Thomas Voets et al.

11.4.3 Transmembrane Segments S1-S4

In other 6TM channels such as the voltage-gated K^+ and HCN channels, the first four transmembrane segments (S1-S4) form a sensor that detects changes in transmembrane voltage (Swartz, 2004; Bezanilla, 2005). In particular, a cluster of positively charged residues in S4 is known to sense changes in the transmembrane electrical field and to move relative to it (Bezanilla, 2005). Notably, TRP channels lack the clustering of basic residues in S4. According to the latest structural information obtained for voltage-gated K^+ channels, the S1-S4 region acts as an independent domain inside the membrane and its movement is translated into opening of the pore region via an interaction between the S4-S5 linker and the C-terminal part of S6 (Long et al., 2005a,b).

Only few reports describe the functional impact of the S1-S4 segments in regulation of the TRP channel function. Yet, it is conceivable that the S1-S4 domain of TRP channels is similarly involved in channel gating. Indeed, a growing number of studies indicate that the S2-S4 region of TRP channels plays a key role in ligand-dependent channel gating. Jordt and Julius first identified a YS motif in the S2-S3 linker of TRPV1 (Tyr⁵¹¹Ser⁵¹²) that is crucial for binding of the activating ligand capsaicin (Jordt and Julius, 2002). A further study revealed additional residues in S2 and S4 involved in vanilloid sensitivity of TRPV1 (Gavva et al., 2004). Following up on these results, Vriens et al. identified Tyr⁵⁵⁵ in S3 of TRPV4 as a determinant of the sensitivity to the synthetic phorbol ester 4 α -phorbol 12, 13-dideconoate (4 α -PDD) and heat (Vriens et al., 2004b). Finally, Chuang et al. identified residues in S3 and the S2-S3 linker of TRPM8 that are involved in channel activation by the synthetic super-cooling agent icilin (Chuang et al., 2004).

11.4.4 Cytoplasmic Tails

Compared to other 6TM channels, TRP channels can have extremely long cytoplasmic N- and C-terminal tails containing a plethora of potential structural and/or regulatory modules (Clapham, 2003; Montell, 2005). In at least three instances, the C-terminal tails encompass entire functional enzymes: TRPM2 contains a Nudix hydrolase domain in its C terminus, which functions as an ADP-ribose (ADPR) pyrophosphatase (Perraud et al., 2001). TRPM6 and TRPM7 contain a C-terminal atypical α -kinase domain (Nadler et al., 2001; Runnels et al., 2001). Other notable domains are ankyrin repeats, 33-residue motifs consisting of pairs of antiparallel α -helices connected by β -hairpin motifs, which can be identified in the N terminus of most subfamilies of TRP channels. The number of ankyrin repeats is highly variable, ranging from 3-4 in TRPCs and TRPVs, to 14-15 in TRPAs and approximately 29 (!) in TRPNs. The so-called TRP box in TRPCs, a stretch of six amino acids in the proximal part of the C terminus, has initially been proposed as a signature sequence for all TRP channels. However, the TRP box consensus sequence (EWKFAR) is only poorly conserved in TRPVs and TRPMs, and fully absent in the TRPP, TRPML, TRPA, and TRPN subfamilies. The role of these different intracellular domains in

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Thomas Voets et al.

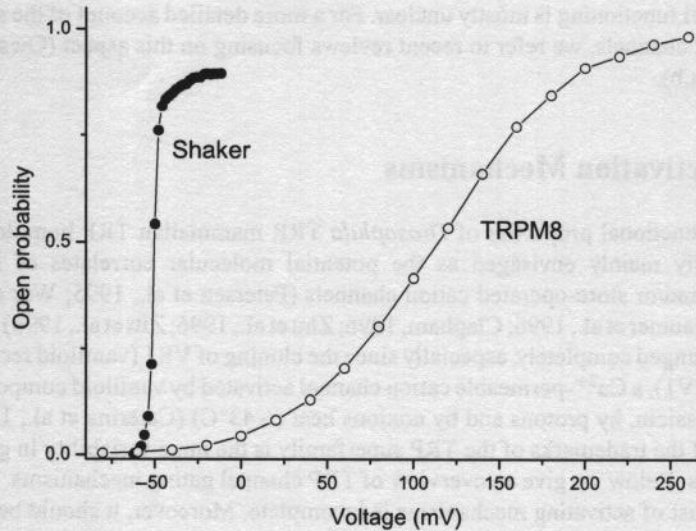


Fig. 11.3 Comparison of the voltage dependence of TRPM8 with that of the archetypical voltage-gated K^+ channel Shaker. Note that the activation curve for TRPM8 mainly extends into the nonphysiological voltage range (>50 mV) and has a much shallower voltage dependence.

For a detailed account of the knowledge and controversies concerning PLC- and/or store-dependent TRPC activation we refer to recent reviews (Putney, 2004, 2005).

11.5.2 Voltage-Gated TRP Channels

For a long time, TRP channels were considered to be channels with little or no voltage dependence (Clapham, 2003). This view was mainly founded on the absence of the cluster of positively charged residues in S4, which was known to constitute the voltage sensor of other 6TM channels. Moreover, the first observations of voltage dependence in members of the TRP superfamily revealed voltage-dependent activation curves that extended mainly into the nonphysiological positive voltage range and were characterized by very low gating valences (Fig. 11.3), suggesting that voltage dependence was an epiphenomenon of little physiological relevance (Gunthorpe et al., 2000; Nilius et al., 2003, 2005b). However, recent studies have demonstrated that factors such as temperature or chemical ligands can drastically shift the voltage-dependent activation curves toward the physiological voltage range, and that this constitutes an important mechanism for TRP channel gating (see below).

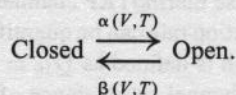
11.5.3 Temperature-Sensitive TRP Channels

Since the discovery of the TRPV1 as a heat-activated channel, seven additional mammalian temperature-sensitive TRP channels [also called thermoTRPs (Patapoutian

Thomas Voets et al.

membrane depolarization. Thermal activation reflects a robust but graded shift of the voltage dependence of activation from strongly depolarized potentials toward the physiological potential range. This finding implies that the thermal sensitivity of these channels depends on voltage, and that temperature-dependent activation represents a gradual increase in the open probability of the channel rather than a threshold phenomenon. Moreover, it strongly argues against temperature-dependent phase transition of the lipid membrane or conformational transitions of the channel protein as a mechanism for thermal activation, as such processes would predict a single sharp thermal threshold (Voets et al., 2004a).

A two-state gating model was found to accurately approximate the temperature-dependent activation of TRPV1, TRPM8, TRPM4, and TRPM5 (Voets et al., 2004a; Talavera et al., 2005):



For TRPM8, the temperature dependence of channel opening (α) is much less steep than that of channel closing (β), which leads to channel activation upon cooling. In the case of TRPV1, TRPM4, and TRPM5, α displays a much steeper temperature dependence than β , leading to channel activation upon heating (Voets et al., 2004a; Talavera et al., 2005). According to Eyring rate theory, α and β are related to membrane voltage and temperature according to

$$\alpha = \kappa \frac{kT}{h} \cdot e^{\frac{-\Delta H_{\text{open}} + T \Delta S_{\text{open}} + \delta z F V}{RT}}$$

$$\beta = \kappa \frac{kT}{h} \cdot e^{\frac{-\Delta H_{\text{close}} + T \Delta S_{\text{close}} - (1-\delta) z F V}{RT}},$$

where ΔH_{open} and ΔH_{close} represent the enthalpies and ΔS_{open} and ΔS_{close} the entropies associated with channel opening and closing, respectively. R represents the gas constant ($8.31 \text{ J mol}^{-1} \text{ K}^{-1}$), T the absolute temperature, z the effective charge associated with voltage-dependent gating, δ the fraction of z moved in the outward direction, F the Faraday constant ($9.65 \times 10^4 \text{ C mol}^{-1}$), k Boltzmann's constant ($1.381 \times 10^{23} \text{ J K}^{-1}$), and h Planck's constant ($6.626 \times 10^{-34} \text{ J s}$). κ is the transmission coefficient, which is usually assumed to equal 1. Half-maximal activation occurs when $\alpha = \beta$, which occurs at membrane potential $V_{1/2}$ given by the expression:

$$V_{1/2} = \frac{1}{zF} (\Delta H - T \Delta S),$$

where ΔH and ΔS represent the difference in enthalpy and entropy between the open and closed state, respectively ($\Delta H = \Delta H_{\text{open}} - \Delta H_{\text{close}}$; $\Delta S = \Delta S_{\text{open}} - \Delta S_{\text{close}}$). Note that the shallow voltage dependence of TRP channels ($z < 1$) is highly relevant,

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11. TRP Channels

et al., 2003), and for Nanchung, a TRPV channel required for hearing in *Drosophila* (Kim et al., 2003). Further research is required to establish whether these channels have a physiological role as mechano- or osmosensors.

Recently, Maroto and colleagues observed a high abundance of TRPC1 in the protein fraction that reconstitutes the mechanosensitive cation channel (MscCa) from *Xenopus laevis* oocytes in liposomes (Maroto et al., 2005). Antisense inhibition of TRPC1 expression in *Xenopus* abolished endogenous MscCa, whereas heterologous TRPC1 expression led to a dramatic increase in MscCa activity. They concluded that TRPC1 forms all or part of vertebrate MscCa (Maroto et al., 2005), a hypothesis that strongly challenges the general view of TRPC channels as store- and/or PLC-dependent channels (Clapham, 2003).

Loss-of-function mutations in the *no mechanoreceptor potential C (nompC)* gene, which codes for the founding member of the TRPN subfamily, abolishes mechanotransduction in *Drosophila* (Walker et al., 2000). Similarly, knock-down of the expression of the zebrafish orthologue leads to larval deafness and imbalance (Sidi et al., 2003). Similarly, vertebrate TRPA1 was implicated in mechanosensation, as a molecular candidate for the transduction channel in vertebrate hair cells (Corey et al., 2004). This conclusion was mainly based on three observations: TRPA1 is highly expressed hair bundles of the hair cells, TRPA1 messenger expression coincides with the onset of hair cell mechanosensitivity, and, most importantly, disruption of TRPA1 expression in zebrafish using morpholino oligonucleotides and in mice using small interference RNA strongly inhibited mechanotransduction in the hair cells (Corey et al., 2004). ~~Although these results clearly implicate TRPN and TRPA channels in mechanosensation, it remains to be demonstrated that they act as mechanosensitive channels.~~

Three possible mechanisms have been put forward to explain for the transduction of a mechanical signal to the opening of the channel gate. First, mechanical stimuli may lead to changes in the tension in the lipid bilayer, which can then be sensed by the transmembrane segments of the channel resulting in gating of the pore. Such a mechanism is well established for MscL (Perozo et al., 2002), a large conductance mechanosensitive cation channel ubiquitously expressed in bacteria but with no significant homology to TRPs. It was recently shown that the mechanosensitivity of TRPC1 is conserved after incorporation in artificial liposomes, suggesting that it may also directly sense changes in bilayer tension (Maroto et al., 2005). Second, mechanical stress may be directly transduced to the channel, for example, via a connection between cytosolic tails and cytoskeletal elements. Such a mechanism has been proposed to explain the mechanosensitivity of TRPA1 and TRPN1 (Corey et al., 2004; Howard and Bechstedt, 2004; Sotomayor et al., 2005). In particular, it was found

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However, the most recent studies (Bautista et al., 2006; Kwan et al., 2006) conducted with *trpa1*^(-/-) mice revealed no obvious deficits in auditory function. Clearly, TRPA1 can no longer be regarded as an essential component of the transduction channel in hearing, at least in adult animals (Bautista et al., 2006; Kwan et al., 2006). As far as mechano-activation of TRPA1 is concerned, in one study of *trpa1*^(-/-) mice a reduction in sensitivity to mechanical stimulation of the hindpaws was reported (Kwan et al., 2006).

Thomas Voets et al.

activity induces channel gating rather than the channel itself can be mechanosensitive. We have shown that such a mechanism underlies the swelling-dependent activation of TRPV4 (Vriens et al., 2004b). Blockers of phospholipase A2 (PLA₂) and cytochrome P450 epoxygenases inhibit activation of TRPV4 by hypotonic solution but not by the direct ligand 4 α -PDD. Cell swelling is known to directly activate PLA₂. Thus, it was concluded that activation of TRPV4 proceeds via the PLA₂-dependent formation of AA and its subsequent metabolism to 5',6'-EET (Vriens et al., 2004b), which then acts as a channel-activating ligand (Watanabe et al., 2003).

11.5.6 Constitutively Open TRP Channels

Several TRP channels display significant open probability under "control conditions," i.e., in the absence of any of the above-described activatory stimuli. Striking examples are the Ca²⁺-selective TRPV5 and TRPV6, which act as gatekeepers for Ca²⁺ entry in the apical membrane of Ca²⁺-transporting epithelia in kidney and intestine (Hoenderop et al., 2005). Both channels undergo prominent Ca²⁺-dependent inhibition, which acts as a negative feedback brake mechanism to prevent Ca²⁺ overload (Vennekens et al., 2000; Hoenderop et al., 2001; Yue et al., 2001).

An analogous mechanism appears to regulate TRPM6 and TRPM7. These two closely related channels function as influx pathways for Mg²⁺, and are involved in the cellular Mg²⁺ homeostasis and in Mg²⁺ reabsorption in the kidney (Schlingmann et al., 2002; Walder et al., 2002; Schmitz et al., 2003; Voets et al., 2004c). Both channels undergo feedback inhibition by intracellular Mg²⁺, with half-maximal inhibition occurring at a free Mg²⁺ concentration of ~ 0.5 mM (Nadler et al., 2001; Voets et al., 2004c), which is close to the normal resting free Mg²⁺ concentration in mammalian cells.

11.6 Concluding Remarks

The discovery of the TRP superfamily meant a great leap forward in our molecular understanding of the cation channels in nonexcitable and excitable cells. From the above account it is clear that we are only beginning to understand how these fascinating channels work. Given the extremely diverse and complex permeation and gating mechanisms, we foresee that TRP channels will entertain and bother ion channel biophysicists and structural biologists for the coming decades.

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11. TRP Channels

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