TRPV4 calcium entry channel: a paradigm for gating diversity

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TRPV4 is a member of the transient receptor potential (TRP) family of ion channels that mediate Ca2+ entry. The TRPV4 channel is activated by a variety of stimuli, including heat, mechanical stretch, and a range of substances such as arachidonic acid and its metabolites, prostaglandins, and diacylglycerols. TRPV4 is expressed in a variety of tissues, including the kidney, where it plays a role in the regulation of Ca2+ entry.

The free intracellular Ca2+ concentration ([Ca2+]i) is an important regulator of various cell functions. The most important mechanisms for increasing [Ca2+]i are release of Ca2+ from intracellular stores and entry of extracellular Ca2+ via diverse Ca2+ entry channels. In the last 10 years, several novel Ca2+ entry channels belonging to the still expanding family of TRP cation channels have been discovered. More than 20 mammalian TRP genes have been identified, encoding membrane proteins with six transmembrane segments (TM1–TM6) and a putative pore region formed by a short hydrophobic stretch between TM5 and TM6 (for detailed reviews, see Refs. 11, 48, 49). On the basis of their homology, mammalian TRP proteins are classified into three subfamilies (50): TRPC (canonical), TRPV (vanilloid), and TRPM (melastatin). The core transmembrane channel structure of TRP channels resembles that of the pore-forming subunits of voltage-gated and cyclic nucleotide-gated channels and consists of a coassembly of four subunits (32).

THE TRPV SUBFAMILY

TRPV1 (VR-1), the founding member of the TRPV family, was identified by expression cloning as a capsaicin- and heat-gated channel (9). A similar expression cloning strategy for proteins responsible for reabsorption of Ca2+ in the kidney (31) and the gut (63) led to the discovery of TRPV5 (ECaC1) and TRPV6 (CaT1). The remaining three members (TRPV2–4) were identified by using electronic search strategies designed to recognize proteins related to TRPV1 or the related OSM-9 protein from Caenorhabditis elegans (for a detailed review, see Refs. 4, 27). Functionally, the six mammalian members of the TRPV family have been shown to respond to a variety of stimuli, including physical and chemical stimuli. TRPV4, which displays 45% sequence identity with TRPV1, is characterized by a surprising gating promiscuity: it is activated by hypotonic cell swelling, heat, synthetic 4α-phorbols, and several endogenous substances including arachidonic acid (AA), the endocannabinoids anandamide and 2-AG, and cytochrome P-450 metabolites of AA, such as epoxycosatrienoic acids. This review summarizes data on TRPV4 as a paradigm of gating diversity in this subfamily of Ca2+ entry channels.

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All these properties are linked to a single negatively charged aspartic acid residue in the pore region (D542 in TRPV5, D541 in TRPV6) (56).

**TRPV4: STRUCTURE AND EXPRESSION**

Within the TRPV subfamily, TRPV4 displays significantly stronger homology with TRPV1–TRPV3 than with TRPV5 and TRPV6 (Fig. 1). Species differences for TRPV4 are minimal (human/mouse 95.2/96.9%; human/rat 94.8/97.0%, mouse/rat 98.9/99.2% identity/similarity). TRPV4 consists of 871 amino acids with at least three ankyrin repeats in the NH2 terminus (Fig. 2).

TRPV4 is expressed in a broad range of tissues, including lung, spleen, kidney, testis, fat, brain, cochlea, skin, smooth muscle, liver, and vascular endothelium (10, 18, 37, 42, 74, 99). In situ hybridization in the brain indicates expression, in the lamina terminalis of the mouse brain, in neurons of the arched vascular organ of the lamina terminalis, in the median preoptic area, the optic chiasm, neurons of the subfornical organ, the ventral hippocampal commissure, anterior hypothalamic structures, ependymal cells of the choroid plexus in the lateral ventricles, and dorsal root ganglia (DRG) neurons (14, 42, 74). Interestingly, TRPV4 mRNA but not the protein could be detected in the soma of DRG neurons, suggesting that there might exist a mechanism for the transport of the TRPV4 protein from the neuronal bodies to the sensory terminals (26).

**TRPV4: FUNCTIONAL HALLMARKS**

The exogenous agonist 4α-phorbol 12,13-didecanoate (4αPDD) activates a large current in TRPV4-expressing cells (Fig. 3, A–C), which is transient in the presence of Ca2+ (Fig. 3A) and shows a complex time course comprising potentiation, subsequent inhibition by higher [Ca2+]i, and desensitization of the agonist response (see below). In the absence of Ca2+, the current decays more slowly (Fig. 3, D–F). Clearly resolvable inward currents can be measured with Ca2+ or Mg2+ as the only permeating extracellular cation, demonstrating that both divalent cations can permeate TRPV4 channels. Permeability values relative to Na+ are 6–10 for Ca2+ and 2–3 for Mg2+ (42, 55, 74, 75, 91, 94). Current-voltage relationships display
slight outward rectification in the presence of extracellular Ca²⁺ and reverse at a positive potential. Outward rectification is also evident at the single-channel level (Fig. 4). Single-channel conductance is 90–100 pS for outward currents and 50–60 pS for inward currents (74, 75, 96, 97). Ruthenium red (RR) reversibly inhibits inward but not outward currents (Fig. 3, G–I).

THE TRPV4 PORE

The ultimate proof that a membrane protein forms a functional channel is the identification of its pore and experimental evidence about mutations in the putative pore region that alter permeation properties. Significant progress in the identification of the molecular determinants of TRP channel pores has been achieved for TRPV1, TRPV4, TRPV5, and TRPV6 channels (23, 32, 56, 89–91). For these channels, point mutations have been described in the linker between TM5 and TM6 that affect Ca²⁺ selectivity, relative monovalent permeability, and blocker sensitivity, providing convincing evidence that, as in the other six TM channels, this linker forms the pore loop containing the selectivity filter.

Figure 5 shows an amino acid sequence alignment of the putative pore regions of the six mammalian TRPV channels, illustrating the high sequence conservation for TRPV1–4. Interestingly, there is also significant homology with the residues in and surrounding the selectivity filter of the KcsA potassium channel, the so-called K⁺ channel “signature sequence” (TXTXGYGD) (17, 103). The GYG motif in the pore of the K⁺-selective channel is changed into a GMG motif for TRPV1, -2, and -4 and a GLG motif for TRPV3. This difference between TRPV1, -2, and -4 on one hand and TRPV3 on the other hand might explain the remarkably higher single-channel conductance of TRPV3 (172 pS at +60 mV vs. ~100 pS for TRPV1, -2 and -4) (101).

The aspartate residue D682 is an important determinant of the Ca²⁺ sensitivity of the TRPV4 pore (Fig. 6). Neutralizing this aspartate to alanine causes a moderate reduction of the relative permeability for divalent cations and of the degree of outward rectification, without significantly altering monovalent permeability. Neutralizing D672 has only minor effects, whereas neutralization of both aspartates causes a much stronger reduction of Ca²⁺ permeability and channel rectification than D682 alone and shifts the permeability sequence for monovalent cations from Eisenman IV to I. Moreover, neutralizing D682 but not D672 strongly reduces the channel’s sensitivity for RR (Fig. 7). In contrast, neutralization of the only positively charged residue in the putative pore region, K675, has no obvious effects on the properties of the TRPV4 channel pore. Interestingly, a mutation to M680 in the region of the K⁺ channel signature sequence, which is likely an equivalent of the GYG motif in K⁺ channels, strongly reduces whole cell current amplitude and impairs Ca²⁺ permeation. Therefore, it is reasonable to speculate that these mutated residues form part of the TRPV4 selectivity filter and that the architecture of the TRPV4 pore is comparable to that of K⁺ channels.

ACTIVATION MECHANISMS

Synthetic TRPV4 agonists. Although TRPV4 was originally considered to be a channel activated upon hypotonic cell swelling, functional characterization of the channel was greatly advanced by the discovery that the synthetic 4αPDD acts as a robust and direct channel activator. This phorbol ester, which has only weak PKC-activating potency (ED₅₀ > 25 μM) and does not activate TRPV1 or other TRPV channels, is the most potent known activator of TRPV4 with an ED₅₀ of 200–400 nM (94). The phorbol 12,13-didecanoate 20-homovanillate phorbol-vanillate (PDDHV), a potent activator of TRPV1 (78), fails to activate TRPV4 channels in inside-out patches. However, PDDHV activates TRPV4 currents in whole cell record-
ings and also increases $[\text{Ca}^{2+}]_{o}$, suggesting that its vanillyl moiety has to be cleaved by intracellular esterases (Watanabe H, Vriens J, and Nilius B, unpublished observations). The TRPV4 current activated by 4αPDD is transient, and repetitive applications result in decreased responses, indicative of desensitization. The classic PKC activator phorbol 12-myristate 13-acetate (PMA), which is structurally similar to 4αPDD, displays a 10- to 50-fold lower potency than 4αPDD in activating TRPV4 channels (94). These data strongly suggest that 4αPDD acts via a mechanism distinct from the classic interaction of a phorbol 12,13-diester with a phorbol ester/phorbol-binding site, homologous to the C1 domains described for PKC and “nonkinase” phorbol ester receptors (40), and it is therefore unlikely that activation results from binding of 4αPDD to such a site. In addition, the region of best alignment with several PKCs, chimerins, and MUNC13 has very low homology and is located in the pore region (650H-699C), which makes it unlikely that phorbols are bound via a known motif to TRPV4.

**Endogenous TRPV4 agonists.** The potent activation of TRPV4 by 4αPDD fueled the search for possible endogenous TRPV4 agonists. Endocannabinoids are a class of endogenous lipids, including amides and esters of long-chain polyunsaturated fatty acids (15, 16, 45) that activate metabotropic cannabinoid receptors. The endocannabinoid anandamide (AEA) and the metabolite 12-hydroxyeicosatetraenoic acid are potent activators of TRPV1 (27, 72, 82, 104, 105). Recently, AEA and its metabolite arachidonic acid (AA) were found to cause a robust increase in intracellular Ca$^{2+}$ and activate typical whole cell currents in TRPV4-expressing cells (96). AEA and the related endocannabinoid 2-arachydonyl glycerol (2-AG) (45) are transported into the cell through the action of a membrane transporter and degraded via a lipoxygenase. AEA is hydrolyzed to AA exclusively by fatty acid amidohydrolase (FAAH) (13, 15), whereas 2-AG can also be hydrolyzed through monacylglycerol lipase and other esterases (84). Methanandamide, a nonmetabolizable analog of AEA, is not able to activate TRPV4, and phenylmethylsulfonyl fluoride, a selective FAAH inhibitor, inhibits the effects of AEA but not of AA, indicating that FAAH-dependent hydrolysis of AEA to AA is required for TRPV4 activation (96). Surprisingly, AA is not able to activate TRPV4 in cell free patches, indicating that cellular metabolism of AA is required for channel activation. ETYA, a nonspecific

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**Fig. 3.** Activation of TRPV4 by 4α-phorbol 12,13-didecanoate (4αPDD). A: at a holding current of 0 mV, application of 1 μM 4αPDD induced an inward current (I) that typically appeared with some delay and rapidly inactivated in the presence of extracellular Ca$^{2+}$. B: time course of currents at +80 (•) and −80 mV (○) measured from repetitively applied voltage ramps from −100 to +100 mV (holding potential 0 mV). C: current-voltage (I-V) relationships measured at times indicated by a and b in B. Note the outward rectification in the presence of extracellular Ca$^{2+}$. D: same protocol as in A, at holding current of 0 mV, but in the absence of extracellular Ca$^{2+}$. Note the delayed inactivation. E: time course of currents activated by 4αPDD at +80 and −80 mV. F: I-V curves at times labeled c and d in E. Note the near absence of rectification in Ca$^{2+}$-free solution. G: inhibition of currents through TRPV4 by ruthenium red (RR; 1 μM). Inward currents were completely blocked (holding current 0 mV). After RR was washed out, a large inward current appeared. H: current traces at +80 and −80 mV. Note that in the presence of RR, 4αPDD activated an outward current but no inward current, indicating a voltage-dependent block of TRPV4 by RR. The inward current appeared after RR was washed out. I: I-V curves at times labeled e–g in H. Block by RR is shown by trace f. Note the absence of the inward current (compare with C). However, after RR was washed out, the typical outwardly rectifying I-V curve reappeared [1.5 mM extracellular [Ca$^{2+}$]($\text{Ca}^{2+}$,o) present].
blocker of all AA-metabolizing enzymes (19, 71), prevents activation of TRPV4 currents by AA, which indicates that lipoxygenase (LOX), cyclooxygenase (COX), and cytochrome P450 (CYP) metabolites of AA might act as potential activators of TRPV4 (96). Activation of TRPV4 by AA was insensitive to indomethacin, nordihydroguaiaretic acid, and a combination of these inhibitors, which ruled out an involvement of the COX and LOX pathways. Miconazole, an inhibitor of P-450 epoxygenase, and 17-octadecynoic acid (17-ODYA), an inhibitor of the P-450 epoxygenase and /H9275/H9275-1-hydroxylases (71), both fully abolished the AA activation of TRPV4 (96). Importantly, the CYP inhibitors ETYA, miconazole, and 17-ODYA do not directly inhibit TRPV4 channels, because they can still be activated by 4/H9251PDD in the presence of these blockers. Given that 5',6'-epoxyeicosatrienoic acid (EET) and, to a lesser extent, 8',9'-EET activate TRPV4 in a membrane-delimited fashion, it is most likely that the epoxygenase pathway is involved in TRPV4 activation. Thus AEA and AA apparently act as endogenous chemical agonists of TRPV4, activating the channels through CYP-dependent formation of 5',6'-EET (96). It is unclear whether these endogenous ligands can directly bind to the channel. Activation of TRPM2 by AA depends on an ISXXTE arachidonate recognition sequence (ARS) (28) that was first shown to be important for AA signaling in the two-pore-domain potassium channel TREK-1 (58). Such an ARS-like sequence, LSRKFD, is present at the TRPV4 COOH-terminal end of the NH2 terminus (amino acids 402–408 in mTRPV4). Its role in the activation of TRPV4 is unclear because the corresponding deletion mutant could not be functionally expressed (Vriens J, Prenen J, and Nilius B, unpublished observations).

Fig. 4. Single-channel currents through TRPV4 activated by 4aPDD. A: cell-attached patch (+60 mV, 1.5 mM [Ca2+]), 1 μM 4aPDD). Single-channel activity and amplitude histogram (top) are shown from the sweep labeled with a star (bottom), showing the time course of open probability (averaged current per sweep divided by single-channel current). Single-channel current was 3.7 pA. B: single TRPV4 channels at different potentials activated by 1 μM 4aPDD. C: single-channel current-voltage (i-V) relationship from more than 5 patches per voltage. From linear regressions, an inward conductance of 60 pS and outward conductance of 102 pS were calculated (currents from amplitude histograms).
vascularis of the cochlea, in sweat glands, and in the osmoregulatory cells of the brain’s circumventricular organs (14, 26, 42, 51, 74), is in agreement with such an osmosensor function.

Presently, the mechanism whereby swelling activates TRPV4 is not yet fully solved. The NH2-terminal intracellular domain of TRPV4 contains three or more ankyrin repeat domains that seem to be involved in responses to physical challenges, because TRPV4 activation is delayed if these ankyrin repeats are lacking (42) (Vriens J and Nilius B, unpublished observations). These repeats may anchor the channel to the cytoskeleton and form a mechanical link for gating. A different mechanism of hypotonicity-induced activation of TRPV4 proceeding via the phosphorylation of TRPV4 has been proposed recently (100). These authors observed in a heterologous expression model that the double aspartate mutations, but not the mutation of D672 alone, decreased the low-affinity block of inward current. TRPV4 acts through the above-described AA-EET-dependent activation of its COOH-terminal Ca2+-binding motif in TRPV6 and with some similarity in Ca2+-dependent block of inward currents through TRPV4 by [Ca2+]i. Note that the pore mutations D682A or D682A in the pore region strongly reduced the Ca2+-dependent block of inward current. C: Ca2+ block represented as ratio of the current at -100 and +100 mV. Concentration for half-maximal block of the wild-type channel was 765 μM [Ca2+]i. Note that the pore mutations D682A or the double aspartate mutations, but not the mutation of D672 alone, decreased the low-affinity block by Ca2+. These results indicate a low-affinity binding of Ca2+ in the TRPV4 pore, which is mainly determined by D682.

Activation by heat. An emerging characteristic of TRPV channels is their distinct response to changes in temperature. TRPV1 is activated at temperatures above 42°C and shows a slight sensitization during repeated stimulations (8, 38). The temperature threshold for TRPV3 activation is about 39°C, but this channel shows strong sensitization during repetitive heat challenges (60, 73, 101). TRPV4 is activated at temperatures above ~27°C. In contrast to TRPV1 and TRPV3, it desensitizes upon repeated heat applications (26, 97). When constantly exposed to 37°C, TRPV4 can still respond to increased temperatures, i.e., its shows incomplete desensitization (26). Likely, TRPV4 is constitutively active at body temperature. Ca2+-dependent inactivation is a possible adaptive mechanism to reduce channel open probability by the resulting increase in [Ca2+]i (94, 95) (see also Modulation by Ca2+). The mechanism of heat activation of TRPV4 is unclear. However, the observation that heat in contrast to, for example, 4aPDD or 5',6'-EET does not activate TRPV4 channels in cell-free inside-out patches (10, 95) argues against direct activation and points to an indirect or messenger-mediated mechanism.

Modulation by Ca2+. Intracellular Ca2+ is an important regulator of TRPV4 channels and, depending on the concentration, either potentiates or inhibits channel activity (75, 94, 95). Stimulation with 4aPDD activates TRPV4 current with a certain latency, followed by inactivation. This decay is accelerated by increasing the extracellular Ca2+ concentration and is delayed in the absence of extracellular Ca2+. The ED50 for intracellular Ca2+-dependent inactivation of TRPV4 is ~400–600 nM (94, 95), but the nature of this Ca2+-dependent negative feedback mechanism has not yet been identified. Inactivation in the presence of extracellular Ca2+ was much slower in a mutant channel with a point mutation in the sixth transmembrane domain (F707A) (95).

An increase in intracellular Ca2+ was shown to first stimulate TRPV4 (75), and TRPV4 currents stimulated by hypotonic solutions or phorbol esters were strongly reduced at all potentials in the absence of extracellular Ca2+. The permeant divalent cations Ba2+ and Sr2+ were less effective than Ca2+ in potentiating TRPV4. This effect depended on an intracellular site in the COOH terminus, to which calmodulin binds in a Ca2+-dependent manner. This site, however, does not affect inactivation. A positively charged α-helical stretch VGRL-RRDRWSSVVPRVV, similar to the COOH-terminal Ca2+/calmodulin-binding motif in TRPV6 and with some similarity...
to the PKC pseudosubstrate site (52), has been identified in the COOH terminal of TRPV4 starting at position 814 (75). By mutagenesis, it has been shown that this motif is the structural determinant of Ca2⁺/H11001-dependent potentiation (75). The same site seems essential for the spontaneous opening of TRPV4 channels in the absence of any agonist (75). This spontaneous activation might be responsible for the observed elevated Ca2⁺/H11001 levels in nonstimulated TRPV4-expressing cells (42, 74, 96, 97, 99). Interestingly, mutant channels with a single mutation in the COOH terminus of TRPV4 (E797) were constitutively open, i.e., spontaneous activation seemed to be increased (95), suggesting that this site may interfere with Ca2⁺/H11001 binding at the neighboring calmodulin-binding motif.

Modulation by phosphorylation. The mechanism of TRPV1 activation and potentiation by PKC-dependent phosphorylation has been investigated in detail (39, 57, 67, 85). It has recently been shown that PMA, a known activator of PKC, also activates TRPV4 (21). Concentrations of PMA that are subthreshold at room temperature (94) activate TRPV4 at 37°C through a PKC-dependent pathway. The PMA activation of TRPV4 is dramatically reduced in the presence of the PKC inhibitors calphostin C and staurosporine (21), indicating that phorbols activate TRPV4 via PKC-independent and -dependent mechanisms. The potentiating effect of PKC stimulation on TRPV4 activation by other stimuli, such as endogenous agonists, cell swelling, and heat, has not yet been studied in detail. Putative PKC phosphorylation sites are indicated in Fig. 1. Probably, S88, S134, and S528 are the most likely candidates for mediating functional effects.

Remarkably, modulation by lipids, such as phosphatidylinositol 4,5-bisphosphate (PIP2), is still completely unknown for TRPV4. The COOH terminus of TRPV1 contains a modular PIP2 binding site (a cluster of basic residues interspersed by hydrophobic amino acids, e.g., LRSSRVGHRKNFLV-PLLREASARDQSAQPEVYLRFQSS for hTRPV1). Binding of PIP2 to this site causes tonic inhibition of the channels, and PLC-mediated hydrolysis sensitizes the channel for activation by capsaicin, protons, and heat (68). This site, however, is not conserved in TRPV4, but all TRPV4s contain a low-homology site with six basic amino acids between residues 400 and 446 whose possible functional impact is still unknown.

Interference of various stimuli. TRPV4 is coexpressed with TRPV3 in mouse keratinocytes (10). Heat responses were significantly enhanced under hypotonic conditions and inhib-
possesses activation properties distinct from those of TRPV1. Unlike TRPV1, TRPV4 is rapidly activated by a diverse range of stimuli, including mechanical, chemical, and physical signals. It is particularly responsive to extracellular calcium, as well as to changes in cell morphology and heat.

TRPV4 is expressed in a variety of tissues and cell types, including endothelial cells, smooth muscle cells, and neurons. This distribution suggests that TRPV4 may play a role in regulating blood flow and temperature homeostasis. For example, TRPV4 activation in endothelial cells can lead to vasodilation, whereas in smooth muscle cells, it can cause vasoconstriction.

One key question remains: What are TRPV4 channels good for? The ability of this unique channel to respond to a broad variety of signals has evoked hypotheses about its possible involvement in processes ranging from sensory detection and thermoregulation to regulation of vascular tone and signaling in the brain. At present, most of this is still speculative, but the recent creation of TRPV4-deficient mice will allow a direct testing of these hypotheses.

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The TRPV4 activators AEA and 2-AG likely play an important role in the control of the vascular tone and potentially in shock conditions (44, 69, 70, 92, 93, 105). Interestingly, their effects could not be fully explained by an action on CB1 and CB2 receptors or on TRPV1 channels (24, 29, 35, 36, 92). Our data about the activation of TRPV4 by AEA and 2-AG might provide the missing link for the action of these compounds on endothelium.

Endocannabinoids are potent neuromodulators that may mainly act as retrograde messengers (20, 98). The pounds on endothelium.

Our data about the activation of TRPV4 by AEA and 2-AG and CB2 receptors or on TRPV1 channels (24, 29, 35, 36, 92). Their effects could not be fully explained by an action on CB1 receptors or on TRPV1 channels (24, 29, 35, 36, 92). In shock conditions (44, 69, 70, 92, 93, 105). Interestingly, their role in the control of the vascular tone and potentially in hearing (41).

NOTE ADDED IN PROOF

After acceptance of this paper, the W. Liedtke laboratory published impressive data on the involvement of TRPV4 in osmoregulation. TRPV4-deficient mice drink less water, become more hyporesmolar, have a decreased blood level of antidiuretic hormone, and show an impaired response to hyper- and hyposmolar stimuli. Data indicate that TRPV4 is a necessary osmotic sensor in the circumventricular organs in the mammalian CNS (Liedtke W and Friedman JM. Abnormal osmotic regulation in trpv4−/− mice. Proc Natl Acad Sci October 27, 2003; 10.1073/pnas.173541610).

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REFERENCES

TRPV CHANNELS


27.同盟Review


