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TRPV4 and the regulation of vascular tone

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Abstract

Recent studies have introduced the importance of Transient Receptor Potential Vanilloid Subtype 4 (TRPV4) channels in the regulation of vascular tone. TRPV4 channels are expressed in both endothelium and vascular smooth muscle cells and can be activated by numerous stimuli including mechanical (e.g. shear stress, cell swelling, and heat) and chemical (e.g. epoxyeicosatrienoic acids (EETs), endocanabinoids, 4α-phorbol esters). In the brain, TRPV4 channels are primarily localized to astrocytic endfeet processes which wrap around blood vessels. Thus, TRPV4 channels are strategically localized to sense hemodynamic changes and contribute to the regulation of vascular tone. TRPV4 channel activation leads to smooth muscle cell hyperpolarization and vasodilation. Here we review recent findings on the cellular mechanisms underlying TRPV4-mediated vasodilation, TRPV4 channel interaction with other proteins including Transient Receptor Potential Channel 1 (TRPC1), small conductance ($K_{Ca}2.3$) and large conductance ($K_{Ca}1.1$) calcium-activated, potassium-selective channels and the importance of caveolin-rich domains for these interactions to take place.

Introduction

Transient receptor potential (TRP) channels are non-selective cation channels expressed in almost all cells and permeable to $Ca^{2+}$and Na^{+}ions. The TRP channel superfamily is divided according to DNA and protein sequence homology [1]; while this superfamily encompasses a large number of channels, the purpose of this review is to highlight recent findings on the role of TRPV4 channels in the regulation of vascular tone. TRPV4 channels are members of the vanilloid receptor subfamily and expressed in various tissues including lung, spleen, heart, endothelium, cochlear, liver, testes, fat and brain 2-5. TRPV4 channel currents carry $Ca^{2+}$and $Mg^{2+}$with permeability ratios of 6-10 $P_{Ca}/P_{Na}$and 2-3 P_{Mg}/P_{Na}, respectively [6-9] . The single channel conductance for TRPV4 channels is in the range of 90-100 pS (outward currents) and 50-60 pS (inward currents) [7, 9, 10].

At the structural level, the TRPV4 channel has six transmembrane spanning segments (TM1-6) with the pore region located between TM5 and TM6 [10]. The protein has 871 amino acids with intracellular C- and N-termini [10]. Four TRPV4 subunits are needed to assemble a functional channel [10]with part of its volume (~ 30%) in the plasma membrane and the rest (~70%) exposed intracellularly or extracellularly, allowing interactions with associated

proteins [11]. These include inositol trisphosphate (IP_3) receptors [12], actin filaments [13, 14], microtubule-associated protein (MAP) 7 [15], aquaporin (AQP) 5 [16]and AQP4 [17], human osteosarcoma (OS) 9 [18], transient receptor potential polycystic (TRPP) 2 [19], caveolin 1 [20], Cystic fibrosis transmembrane conductance regulator (CFTR) 21 and large conductance Ca^{2+}activated K^+channels (BK or K 1.1) [22, 23] Ca .

Functionally, TRPV4 channels stand out due to the broad range of stimuli that lead to their activation, including physical (cell swelling [5], heat [9, 24], mechanical [25]) and chemical stimuli (endocannabinoids, arachidonic acid (AA), and 4-α-phorbol esters [26, 9]). Table 1 and 2 provide a pharmacological overview of TRPV4 agonists and antagonists. Activation by swelling and endocanabinoids involves cytochrome P450 epoxygenase-dependent AA metabolism to epoxyeicosatrienoic acids (EETs) [26, 27], potent endogenous agonists for TRPV4 channels [2, 5, 22, 28-30]. EETs cause vascular smooth muscle cell hyperpolarization, leading to vascular relaxation. The effect of EETs on smooth muscle cell hyperpolarization persists when the production of nitric oxide (NO) and prostacyclin are inhibited [31]. Thus, EETs are commonly referred to as one of the endothelium-derived hyperpolarizing factors (EDHFs). The role of EETs is especially important in some key vascular beds, including the coronary circulation [31]. EETs may directly bind to TRPV4 to exert their action. A putative arachidonate recognition site, where EETs could bind, is located at N-terminal cytoplasmic domain of TRPV4 [4]. However, there are some controversies regarding EET regioisomer selectivity for TRPV4. 11,12-EET and 14,15-EET are two predominant endogenous EET isoforms [32]. However, one report showed that 5,6-EET and 8,9-EET but not 11,12-EET and 14,15-EET activate TRPV4 in TRPV4-overexpressing HEK293 cells [27]. In contrast, several other studies demonstrated that 11,12-EET and 14,15-EET are able to activate TRPV4 in native smooth muscles [26, 30].

TRPV4 is unequivocally important for the regulation of vascular tone. However, the underlying molecular mechanisms remain unclear. Here, we describe recent advances on the role of TRPV4 channels in the peripheral circulation as well as the cerebral circulation, where TRPV4 channel expression is prominent in astrocytes.

TRPV4 is expressed in vascular smooth muscle cells

Immunostaining, Western blot and reverse transcription-polymerase chain reaction (RTPCR) showed the expression of TRPV4 in smooth muscle cells of rat cerebral arteries [33], smooth muscle of human and rat lung extraalveolar vessels [26], endothelium-denuded rat intralobar pulmonary arteries [34, 35], rat mesenteric artery smooth muscle cells [36], and rat and mouse aortic smooth muscle cells [37].

Dependent on the vascular bed and animal species, EET may act on TRPV4 channels expressed either in vascular smooth muscle cells, endothelial cells or both [31]. In rat cerebral arteries, the endothelium-derived EETs diffuse to nearby smooth muscle cells, activating TRPV4 in smooth muscle cells [22]. Resultant Ca^{2+}entry stimulates Ca^{2+}release from ryanodine receptors, causing an increased frequency of Ca^{2+}sparks [22]. The Ca^{2+}sparks in turn activate $K_{Ca}1.1$ to hyperpolarize vascular smooth muscle cells, leading to vascular relaxation [22]. A 11,12 EET- and 4α-PDD-activated TRPV4-like current was recorded in smooth muscle cells of mouse small mesenteric arteries. The current was absent in myocytes from TRPV4 knockout mice. EETs, via their action on smooth muscle TRPV4, were also found to induce smooth muscle hyperpolarization and vascular relaxation in mouse mesenteric arteries, the effect of which was absent in TRPV4 knockout mice [30]. Endothelial disruption only caused a moderate reduction in 11,12-EET-induced smooth muscle hyperpolarization and vascular relaxation (by ~50%) in these arteries [30]. Thus, the authors reasoned that the remaining 50% was endothelium-independent and could be attributed to

direct EET action on smooth muscle TRPV4. In agreement, the authors also found that inhibiting $K_{Ca}1.1$ in smooth muscle cells could reduce the EET-induced responses by ~50%, further supporting the notion that the endothelium-independent component was ~50%. These data suggest a link between EET, smooth muscle TRPV4 and $K_{Ca}1.1$ in mouse mesenteric arteries. Because EETs can be produced by endothelial cells in response to physiological stimuli such as bradykinin, acetylcholine, pulsatile stretch and shear stress, the functional coupling of smooth muscle TRPV4 with $K_{Ca}1.1$ may play a major role in vascular tone control under different physiological conditions.

Up to the present, the function of smooth muscle TRPV4 has only been reported in rat cerebral arteries and mouse mesenteric arteries [22, 30]. However, it is likely that a similar mechanism exists in other vascular beds. It is well documented that, in a great variety of artery types, EETs stimulate the activity of $K_{Ca}1.1$ channels in smooth muscle cells causing smooth muscle hyperpolarization and vascular relaxation [31]. This mechanism has been documented in mouse skeletal arteries, human internal mammary arteries and coronary arteries from many species [31, 32]. However, EETs do not directly act on $K_{Ca}1.1$ channels. Thus, the well-characterized EET-TRPV4-$K_{Ca}1.1$ axis may provide an attractive mechanistic explanation for smooth muscle relaxation in these arteries.

Recent studies found that TRPV4 may heteromerize with TRPC1 or TRPP2 to form heteromeric channels in vascular endothelial cells and renal cortical collecting duct cells [38, 39]. TRPC1 is ubiquitously expressed in many cell types including vascular smooth muscle cells from many arteries [37]. TRPP2 expression has also been identified in some artery types [37]. In the future, it will be important to determine whether heteromeric TRPV4-C1 and/or TRPV4-P2 exist in vascular smooth muscle cells and whether EETs act on homomeric or heteromeric TRPV4 to initiate hyperpolarizing responses in vascular smooth muscle cells. Interestingly, studies have shown that TRPC1 and $K_{Ca}1.1$ can form a physical complex in vascular smooth muscle cells [40]and that the complex plays an important role in smooth muscle hyperpolarization and the control of vascular tone [40]. Based on this evidence, it is reasonable to propose the existence of a TRPV4-TRPC1-$K_{Ca}1.1$ complex in vascular smooth muscle cells. EETs may act on this complex to induce smooth muscle hyperpolarization and vascular relaxation.

TRPV4 is expressed in endothelial cells

In the endothelium, TRPV4 was first identified in mouse aorta by Bernd Nilius's group, [7]and since then, it has been shown to be ubiquitously expressed in endothelial cells of both large conductance vessels and small resistance vessels. Indeed, RT-PCR, western blot analysis and intracellular calcium measurements demonstrate that TRPV4 is functionally expressed in mouse aortic endothelial cells [29]. Köhler's group investigated the expression and function of TRPV4 in rat carotid artery and arteria gracilis endothelial cells by using in situ patch-clamp techniques, single-cell RT-PCR and pressure myography, [41]whereas Alvarez and coworkers studied TRPV4 in rat pulmonary artery and microvascular endothelium [26]. More recently, TRPV4 localization was examined by Willette et al.[42]in a variety of rat tissues, and a generalized pattern of immunoreactive TRPV4 staining was identified in the endothelium and epithelium [42].

From a functional perspective, as shown by Zhang et al. [43], acetylcholine-induced nitric oxide (NO) production was significantly reduced in vascular endothelial cells and EDHF-mediated relaxation was also attenuated in small mesenteric arteries of TRPV4 knockout mice. These results are in agreement with previous data from Köhler et al.[44], showing that in large vessels, like carotid arteries, the inhibition of nitric oxide synthase almost completely abolished 4α-PDD induced vasodilation whereas in small vessels selective inhibition of

calcium activated potassium channels (SKCa/K_{Ca}2.3 and IKCa/K_{Ca}3.1) inhibited the TRPV4-induced vasodilation. Very recently, Sonkusare et al. [45] demonstrated that even a small number of active TRPV4 channels were able to mediate local calcium signals that activated IK and SK channels and induced maximal dilation of resistance arteries, thereby contributing to the regulation of vascular function [45]. Thus intracellular calcium increases mediated by TRPV4 channels trigger both NO-and/or EDHF-dependent vasodilatation, an effect that appears to be dependent on the vascular bed. Interestingly, in several cell types including endothelial and smooth muscle cells, calcium handling proteins are located in caveolae. K_{Ca}2.3 [46]and K 1.1 [47] Ca channels have been shown to reside in caveolin-rich lipid domains. Direct measurement of calcium waves in endothelial cells have suggested that caveolae could be the sites that initiate calcium entry and calcium dependent signal transduction [48]. Recent data demonstrate that, similar to TRPC1 [49], TRPV4 may interact physically with the structural caveolar protein caveolin-1 and that the interaction is functionally important for 4α-PDD-evoked calcium increase [20]. The fact that TRPV4 may heteromerize with TRPC1 [39], as well as the work of Graziani and coworkers showing that caveolar integrity is essential for AA recruitment and EDHF signaling in porcine arteries [50], provides additional evidence in favor of a potential involvement of caveolar microdomains in TRP-mediated calcium signaling and subsequent vasodilation.

TRPV4 expression in astrocytes

In the brain, TRPV4 mRNA is expressed in both neuronal and non-neuronal cell types including astrocytes and microglia [51-54], endothelial cells and vascular smooth muscle cells [33]. Importantly, and relevant to the control of vascular tone, Marrelli et al [33]showed TRPV4 channel expression in endothelial cells of middle cerebral arteries and demonstrated its regulation by PLA_2activation. Similar to the potential polarized expression of TRPV4 channels in the abluminal face of the endothelium 33, Benfenati et al. [55]reported that expression of TRPV4 channels is localized mostly to astrocytic membranes at the interface between brain parenchyma and extracerebral liquid spaces and on astrocytic endfeet abutting pial and parenchymal blood vessels [55]. The unique arrangement of TRPV4 channels on perivascular astrocyte processes was also reported by Butenko et al. [56] in the rat hippocampal CA1 region. Given that cell-cell communication by astrocytes is primarily mediated through dynamic intracellular Ca^{2+}changes, information regarding the activity of TRPV4 channels in astrocytes is important to further our understanding of the physiological function of these cells in the CNS.

Moreover, the important observation that astrocytic endfeet processes possess parallel vasoactive mechanisms to those described in vascular cells, particularly endothelial cells, supports the notion that cerebral vascular smooth muscle cells are modulated from their luminal and abluminal sides by both endothelial cell and astrocyte signaling pathways, respectively. As with endothelial cells, astrocytes modulate vascular tone through K^+signaling [57]and via the release of AA metabolites such as EETs [58-60], 20-HETEs [61] and prostacyclin [62, 63]. The resemblance of these vasoactive pathways to those described in vascular cells, in addition to the expression of TRPV4 channels in astrocytic endfeet processes at the gliovascular interface, points to the possibility that astrocytic TRPV4 channels are also involved in the regulation of vascular tone. In response to neuronal activity, glutamate released at the synapse activates metabotropic glutamate receptors (mGluR) in astrocytes leading to an increase in intracellular Ca^{2+}which in turn activates PLA_2[64]. The resulting production of AA and its metabolism follows similar pathways to those described in endothelial cells (e.g. conversion to metabolites such EETs). As described above, EETs are endogenous activators of TRPV4 channels. Blanco et al. [65] showed that 11, 12 EET increased Ca^{2+}oscillations in cortical astrocytes. The study, however, did not evaluate whether these Ca^{2+}responses in astrocytes were indeed mediated via TRPV4

channel activation. mGluR-induced increases in Ca^{2+}also has been shown to increase the single channel open probability of BK channels expressed in astrocytic endfeet processes [65, 57]. Depending on the K^+concentration released, efflux of $K^+$from astrocytes results in vasodilation [57, 66] or vasoconstriction [66].

To date, TRPV4 channel function in astrocytes is associated with osmosensation, thus playing an important role in the maintenance of brain volume [67]17 as achieved through the activity of AQP4 channels expressed in endfeet processes [17, 68, 69]. It has been demonstrated that AQP4 channels colocalize with TRPV4 channels in astrocytic endfeet, providing evidence for their co-participation in regulatory volume decrease [17].

Although a role for astrocytic TRPV4 channels has yet to be demonstrated in the control of vascular tone, given their association with K^+channels (also preferentially expressed in astrocytic endfeet processes [65, 70]), it is tempting to speculate that the activation of TRPV4 channels in astrocytes contributes to K^+channel signaling and neurovascular coupling. Along these lines, Higashimori et al.[71]showed that the synthetic EET analog 11-nonyloxy-undec-8(Z)-enoic acid or the mGluR agonist,*t*-ACPD significantly increased $K_{Ca}1.1$ channel currents in perivascular astrocytes. EETs-induced outward currents were also associated with an increase in the frequency of Ca^{2+}oscillations in astrocytes, supporting the idea that EETs-induced intracellular Ca^{2+}changes contribute to K^+signaling in astrocytes [71]and likely the control of vascular tone [57].

In addition to EETs, glutamate-mediated activation of mGluR in astrocytes results in the release a number of vasoactive signals (i.e. NO, ATP, adenosine), which could also contribute to astrocyte TRPV4 channel regulation. Among them, NO is of particular interest. TRPV4 channel activation is linked to NO production [43, 72], which in turn can lead to sustained increases in astrocyte Ca^{2+}levels [73]. A recent study showed that TRVP4 channel activation resulted in endothelial Ca^{2+}increase and NO-mediated vasodilation [41]. In addition, NO has been shown to induce sustained increases in astrocytic Ca^{2+}in cultured astrocytes [73]. Based on these studies and the fact that NO can readily cross the blood brain barrier and alter astrocyte [73]and neuronal activity [74], another unresolved role for TRPV4 channels in the control of vascular tone may be linked to NO signaling. Thus, given their distinctive molecular and biophysical properties, their strategic expression within the neurovascular unit and their ability to respond to a variety of vascular- and glial-derived signals in the brain, TRPV4 channels expressed in astrocytes may be regarded as ideal candidates to sense and/or transduce hemodynamic information into a glial response (changes in intracellular calcium). Comparable to our current knowledge on TRPV4-channel induced activation in the endothelium and vascular smooth muscle cells, additional work is needed to determine whether astrocytic TRPV4 channels contribute to the regulation of vascular tone via similar mechanisms.

TRPV4 expression in perivascular nerves

TRPV4 channels have shown to be expressed in sensory nerves and to co-localize with calcitonin gene-related peptide (CGRP) as well as substance P [75, 76]. Gao and Wang showed that the depressor effect of the TRPV4 channel, 4αPDD was attenuated following degeneration of capsaicin-sensitive sensory nerves or in the presence of $CGRP_{8-37}$(an antagonist of CGRP). Moreover, they showed that intravenous administration of 4αPDD increased plasma CGRP; the hypotensive effect of TRPV4 channel activation was, at least in part, mediated by the activation of Ca^{2+}-activated K^+channels [36]. Using a model of baroreflex impairment, McHugh et al. showed a role for TRPV4 channels as osmosensors in the portal region and their potential participation in the afferent input of the pressor response [77]. The authors suggested that spinal afferents may relay information from the

hepatic/portal environment to dorsal root ganglion neurons which express TRPV4 channels [78, 79]resulting blood pressure regulation through sympathetic output[77].

TRPV4 in disease

Although TRPV4 channels appear to have an important role in the regulation of vascular tone, TRPV4$^{-/-}$ mice do not show altered blood pressure at rest [30]. Earley et al., suggested the participation of TRPV4 channels in a negative feedback mechanism which opposes hypertension in the presence of a hypertensive challenge [30, 43, 80]. Using the synthetic TRPV4 activator, GSK1016790A, Willette et al provided evidence that circulatory collapse induced by exogenous TRPV4 activation is mediated by a NO-independent failure of the endothelial-epithelial permeability barrier in the lung and other tissues [42]. Impaired pressure and stretch sensing has been reported in C-fibers of the dorsal root ganglia [15]and retinal ganglion cells [81], respectively, in TRPV4$^{-/-}$ mice. Several reports suggest that TRPV4 channels are likely involved in hypoxia-induced pathogenesis. Following cerebral hypoxia/ischemia, TRPV4 channel expression is increased in hippocampal astrocytes resulting in augmented astrocytic Ca^{2+}oscillatory frequency and possibly astroglial reactivity in the brain [56]. In chronic hypoxic pulmonary hypertension, Yang and coworkers identified TRPV4 channels as an obligatory calcium entry pathway that is upregulated [35]. In mouse mesenteric arteries, TRPV4 activity is favored by hypoxic insult that is associated with an increased Ca^{2+}response in endothelial cells upon agonist stimulation, contributing to a potentiated EDH-mediated dilation.

As flow-activated channels in vascular endothelial cells, TRPV4 are good candidates for shear stress activation and, consequently, have been investigated in different models of arteriogenesis. In rats, after femoral artery ligation, TRPV4 participates in collateral remodeling and growth [82]. The same group also provided evidence that pharmacological TRPV4 activation enhanced cerebral arteriogenesis[83]. TRPV4 channel activation has been associated with pulmonary hypertension [84], bone disorders [85], neurodegenerative skeletal muscle dysplasias [86] and hyponatremia [87, 88]to name a few.

Summary and Perspectives

In summary, current studies suggest that activity of TRPV4 channels in endothelial and vascular smooth muscle cells contribute to the regulation of vascular tone. Importantly, TRPV4-induced Ca^{2+}increases in endothelial and vascular smooth muscle cells contribute to vasodilation. The broad range of stimuli activating TRPV4 channels, along with their strategic location in the endothelium, favors flow and shear-stress mediated release of EDHF and vasodilation. Moreover, recent studies have shed light on the interaction between TRPV4 channels and $SK_{Ca}$and IK_{Ca}, suggesting a key cellular mechanism by which TRPV4-mediated Ca^{2+}increases in endothelial cells induce vasodilatory responses [45]. The structural arrangement of TRPV4 channels allows for interaction with a number of proteins including K^+channels and other members of the TRP channel family (e.g TRPC1). Particular interest has also been placed on caveolin, as several calcium handling proteins from endothelial and smooth muscle cells reside in caveolae (e.g. K_{Ca}2.3 [46]and K_{Ca}1.1 [47]channels); the interaction between TRPV4 and caveolin-1 appear to be an important component of 4α-PDD-evoked calcium increase [20].

Studies have demonstrated the importance of TRPV4 channels expressed in vascular smooth muscle cells as mediators of vasodilation via EET. TRPV4-induced Ca^{2+}increases lead to Ca^{2+}sparks and subsequent activation of K_{Ca}1.1 channels, causing, in turn, smooth muscle hyperpolarization and vasodilation [22]. In addition, TRPV4 channel interaction with other proteins such as the TRPV4-TRPC1-K_{Ca}1.1 complex in vascular smooth muscle cells may

prove to be yet another mechanism for smooth muscle hyperpolarization and vascular relaxation.

Clearly, the wide expression of TRPV4 channels in various tissues along with the broad range of stimuli which can activate them, give rise to a multiplicity of mechanisms and pathologies associated with TRPV4 channel dysregulation. TRPV4 channels, thus, may represent a novel pharmacotherapeutic target in a wide range of diseases.

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References

1. Ramsey IS, Delling M, Clapham DE. An introduction to TRP channels. Annu Rev Physiol. 2006; 68:619–647. [PubMed: 16460286]
2. Plant TD, Strotmann R. Trpv4. Handb Exp Pharmacol. 2007; (179):189–205. [PubMed: 17217058]
3. Kunert-Keil C, Bisping F, Kruger J, Brinkmeier H. Tissue-specific expression of TRP channel genes in the mouse and its variation in three different mouse strains. BMC Genomics. 2006; 7:159. [PubMed: 16787531]
4. Nilius B, Vriens J, Prenen J, Droogmans G, Voets T. TRPV4 calcium entry channel: a paradigm for gating diversity. Am J Physiol Cell Physiol. 2004; 286(2):C195–205. [PubMed: 14707014]
5. Vriens J, Watanabe H, Janssens A, Droogmans G, Voets T, Nilius B. Cell swelling, heat, and chemical agonists use distinct pathways for the activation of the cation channel TRPV4. Proc Natl Acad Sci U S A. 2004; 101(1):396–401. [PubMed: 14691263]
6. Voets T, Prenen J, Vriens J, Watanabe H, Janssens A, Wissenbach U, Bodding M, Droogmans G, Nilius B. Molecular determinants of permeation through the cation channel TRPV4. J Biol Chem. 2002; 277(37):33704–33710. [PubMed: 12093812]
7. Watanabe H, Davis JB, Smart D, Jerman JC, Smith GD, Hayes P, Vriens J, Cairns W, Wissenbach U, Prenen J, Flockerzi V, Droogmans G, Benham CD, Nilius B. Activation of TRPV4 channels (hVRL-2/mTRP12) by phorbol derivatives. J Biol Chem. 2002; 277(16):13569–13577. [PubMed: 11827975]
8. Watanabe H, Vriens J, Janssens A, Wondergem R, Droogmans G, Nilius B. Modulation of TRPV4 gating by intra- and extracellular Ca2+ Cell Calcium. 2003; 33(5-6):489–495. [PubMed: 12765694]
9. Watanabe H, Vriens J, Suh SH, Benham CD, Droogmans G, Nilius B. Heat-evoked activation of TRPV4 channels in a HEK293 cell expression system and in native mouse aorta endothelial cells. J Biol Chem. 2002; 277(49):47044–47051. [PubMed: 12354759]
10. Everaerts W, Nilius B, Owsianik G. The vanilloid transient receptor potential channel TRPV4: from structure to disease. Prog Biophys Mol Biol. 2010; 103(1):2–17. [PubMed: 19835908]
11. Verma P, Kumar A, Goswami C. TRPV4-mediated channelopathies. Channels (Austin). 2010; 4(4):319–328. [PubMed: 20676052]
12. Garcia-Elias A, Lorenzo IM, Vicente R, Valverde MA. IP3 receptor binds to and sensitizes TRPV4 channel to osmotic stimuli via a calmodulin-binding site. J Biol Chem. 2008; 283(46):31284–31288. [PubMed: 18826956]
13. Becker D, Muller M, Leuner K, Jendrach M. The C-terminal domain of TRPV4 is essential for plasma membrane localization. Mol Membr Biol. 2008; 25(2):139–151. [PubMed: 18307101]
14. Ramadass R, Becker D, Jendrach M, Bereiter-Hahn J. Spectrally and spatially resolved fluorescence lifetime imaging in living cells: TRPV4-microfilament interactions. Arch Biochem Biophys. 2007; 463(1):27–36. [PubMed: 17374521]
15. Suzuki M, Mizuno A, Kodaira K, Imai M. Impaired pressure sensation in mice lacking TRPV4. J Biol Chem. 2003; 278(25):22664–22668. [PubMed: 12692122]

16. Liu X, Bandyopadhyay BC, Nakamoto T, Singh B, Liedtke W, Melvin JE, Ambudkar I. A role for AQP5 in activation of TRPV4 by hypotonicity: concerted involvement of AQP5 and TRPV4 in regulation of cell volume recovery. J Biol Chem. 2006; 281(22):15485–15495. [PubMed: 16571723]

17. Benfenati V, Caprini M, Dovizio M, Mylonakou MN, Ferroni S, Ottersen OP, Amiry-Moghaddam M. An aquaporin-4/transient receptor potential vanilloid 4 (AQP4/TRPV4) complex is essential for cell-volume control in astrocytes. Proc Natl Acad Sci U S A. 2011; 108(6):2563–2568. [PubMed: 21262839]

18. Wang Y, Fu X, Gaiser S, Kottgen M, Kramer-Zucker A, Walz G, Wegierski T. OS-9 regulates the transit and polyubiquitination of TRPV4 in the endoplasmic reticulum. J Biol Chem. 2007; 282(50):36561–36570. [PubMed: 17932042]

19. Kottgen M, Buchholz B, Garcia-Gonzalez MA, Kotsis F, Fu X, Doerken M, Boehlke C, Steffl D, Tauber R, Wegierski T, Nitschke R, Suzuki M, Kramer-Zucker A, Germino GG, Watnick T, Prenen J, Nilius B, Kuehn EW, Walz G. TRPP2 and TRPV4 form a polymodal sensory channel complex. J Cell Biol. 2008; 182(3):437–447. [PubMed: 18695040]

20. Saliez J, Bouzin C, Rath G, Ghisdal P, Desjardins F, Rezzani R, Rodella LF, Vriens J, Nilius B, Feron O, Balligand JL, Dessy C. Role of caveolar compartmentation in endothelium-derived hyperpolarizing factor-mediated relaxation: Ca2+ signals and gap junction function are regulated by caveolin in endothelial cells. Circulation. 2008; 117(8):1065–1074. [PubMed: 18268148]

21. Arniges M, Vazquez E, Fernandez-Fernandez JM, Valverde MA. Swelling-activated Ca2+ entry via TRPV4 channel is defective in cystic fibrosis airway epithelia. J Biol Chem. 2004; 279(52): 54062–54068. [PubMed: 15489228]

22. Earley S, Heppner TJ, Nelson MT, Brayden JE. TRPV4 forms a novel Ca2+ signaling complex with ryanodine receptors and BKCa channels. Circ Res. 2005; 97(12):1270–1279. [PubMed: 16269659]

23. Fernandez-Fernandez JM, Andrade YN, Arniges M, Fernandes J, Plata C, Rubio-Moscardo F, Vazquez E, Valverde MA. Functional coupling of TRPV4 cationic channel and large conductance, calcium-dependent potassium channel in human bronchial epithelial cell lines. Pflugers Arch. 2008; 457(1):149–159. [PubMed: 18458941]

24. Guler AD, Lee H, Iida T, Shimizu I, Tominaga M, Caterina M. Heat-evoked activation of the ion channel, TRPV4. J Neurosci. 2002; 22(15):6408–6414. [PubMed: 12151520]

25. O'Neil RG, Heller S. The mechanosensitive nature of TRPV channels. Pflugers Arch. 2005; 451(1):193–203. [PubMed: 15909178]

26. Alvarez DF, King JA, Weber D, Addison E, Liedtke W, Townsley MI. Transient receptor potential vanilloid 4-mediated disruption of the alveolar septal barrier: a novel mechanism of acute lung injury. Circ Res. 2006; 99(9):988–995. [PubMed: 17008604]

27. Watanabe H, Vriens J, Prenen J, Droogmans G, Voets T, Nilius B. Anandamide and arachidonic acid use epoxyeicosatrienoic acids to activate TRPV4 channels. Nature. 2003; 424(6947):434–438. [PubMed: 12879072]

28. Loot AE, Popp R, Fisslthaler B, Vriens J, Nilius B, Fleming I. Role of cytochrome P450-dependent transient receptor potential V4 activation in flow-induced vasodilatation. Cardiovasc Res. 2008; 80(3):445–452. [PubMed: 18682435]

29. Vriens J, Owsianik G, Fisslthaler B, Suzuki M, Janssens A, Voets T, Morisseau C, Hammock BD, Fleming I, Busse R, Nilius B. Modulation of the Ca2+ permeable cation channel TRPV4 by cytochrome P450 epoxygenases in vascular endothelium. Circ Res. 2005; 97(9):908–915. [PubMed: 16179585]

30. Earley S, Pauyo T, Drapp R, Tavares MJ, Liedtke W, Brayden JE. TRPV4-dependent dilation of peripheral resistance arteries influences arterial pressure. Am J Physiol Heart Circ Physiol. 2009; 297(3):H1096–1102. [PubMed: 19617407]

31. Campbell WB, Fleming I. Epoxyeicosatrienoic acids and endothelium-dependent responses. Pflugers Arch. 2010; 459(6):881–895. [PubMed: 20224870]

32. eletou M, Vanhoutte PM. EDHF: an update. Clin Sci (Lond). 2009; 117(4):139–155. [PubMed: 19601928]

33. Marrelli SP, O'Neil RG, Brown RC, Bryan RM Jr. PLA2 and TRPV4 channels regulate endothelial calcium in cerebral arteries. Am J Physiol Heart Circ Physiol. 2007; 292(3):H1390–1397. [PubMed: 17071727]
34. Martin E, Dahan D, Cardouat G, Gillibert-Duplantier J, Marthan R, Savineau JP, Ducret T. Involvement of TRPV1 and TRPV4 channels in migration of rat pulmonary arterial smooth muscle cells. Pflugers Arch. 2012; 464(3):261–272. [PubMed: 22820913]
35. Yang XR, Lin AH, Hughes JM, Flavahan NA, Cao YN, Liedtke W, Sham JS. Upregulation of osmomechanosensitive TRPV4 channel facilitates chronic hypoxia-induced myogenic tone and pulmonary hypertension. Am J Physiol Lung Cell Mol Physiol. 2012; 302(6):L555–568. [PubMed: 22207590]
36. Gao F, Wang DH. Hypotension induced by activation of the transient receptor potential vanilloid 4 channels: role of Ca2+-activated K+ channels and sensory nerves. J Hypertens. 2010; 28(1):102–110. [PubMed: 19996988]
37. Watanabe H, Murakami M, Ohba T, Takahashi Y, Ito H. TRP channel and cardiovascular disease. Pharmacol Ther. 2008; 118(3):337–351. [PubMed: 18508125]
38. Du J, Wong WY, Sun L, Huang Y, Yao X. Protein Kinase G Inhibits Flow-Induced Ca2+ Entry into Collecting Duct Cells. J Am Soc Nephrol. 2012
39. Ma X, Qiu S, Luo J, Ma Y, Ngai CY, Shen B, Wong CO, Huang Y, Yao X. Functional role of vanilloid transient receptor potential 4-canonical transient receptor potential 1 complex in flow-induced Ca2+ influx. Arterioscler Thromb Vasc Biol. 2010; 30(4):851–858. [PubMed: 20093626]
40. Kwan HY, Shen B, Ma X, Kwok YC, Huang Y, Man YB, Yu S, Yao X. TRPC1 associates with BK(Ca) channel to form a signal complex in vascular smooth muscle cells. Circ Res. 2009; 104(5):670–678. [PubMed: 19168436]
41. Kohler R, Heyken WT, Heinau P, Schubert R, Si H, Kacik M, Busch C, Grgic I, Maier T, Hoyer J. Evidence for a functional role of endothelial transient receptor potential V4 in shear stress-induced vasodilatation. Arterioscler Thromb Vasc Biol. 2006; 26(7):1495–1502. [PubMed: 16675722]
42. Willette RN, Bao W, Nerurkar S, Yue TL, Doe CP, Stankus G, Turner GH, Ju H, Thomas H, Fishman CE, Sulpizio A, Behm DJ, Hoffman S, Lin Z, Lozinskaya I, Casillas LN, Lin M, Trout RE, Votta BJ, Thorneloe K, Lashinger ES, Figueroa DJ, Marquis R, Xu X. Systemic activation of the transient receptor potential vanilloid subtype 4 channel causes endothelial failure and circulatory collapse: Part 2. J Pharmacol Exp Ther. 2008; 326(2):443–452. [PubMed: 18499744]
43. Zhang DX, Mendoza SA, Bubolz AH, Mizuno A, Ge ZD, Li R, Warltier DC, Suzuki M, Gutterman DD. Transient receptor potential vanilloid type 4-deficient mice exhibit impaired endothelium-dependent relaxation induced by acetylcholine in vitro and in vivo. Hypertension. 2009; 53(3):532–538. [PubMed: 19188524]
44. Kohler, R.; Hoyer, J. Role of TRPV4 in the Mechanotransduction of Shear Stress in Endothelial Cells. In: Liedtke, WB.; Heller, S., editors. TRP Ion Channel Function in Sensory Transduction and Cellular Signaling Cascades. 2007. Chap 27
45. Sonkusare SK, Bonev AD, Ledoux J, Liedtke W, Kotlikoff MI, Heppner TJ, Hill-Eubanks DC, Nelson MT. Elementary Ca2+ signals through endothelial TRPV4 channels regulate vascular function. Science. 2012; 336(6081):597–601. [PubMed: 22556255]
46. Absi M, Burnham MP, Weston AH, Harno E, Rogers M, Edwards G. Effects of methyl beta-cyclodextrin on EDHF responses in pig and rat arteries; association between SK(Ca) channels and caveolin-rich domains. Br J Pharmacol. 2007; 151(3):332–340. [PubMed: 17450174]
47. Riddle MA, Hughes JM, Walker BR. Role of caveolin-1 in endothelial BKCa channel regulation of vasoreactivity. Am J Physiol Cell Physiol. 2011; 301(6):C1404–1414. [PubMed: 21900688]
48. Isshiki M, Anderson RG. Function of caveolae in Ca2+ entry and Ca2+-dependent signal transduction. Traffic. 2003; 4(11):717–723. [PubMed: 14617355]
49. Brazer SC, Singh BB, Liu X, Swaim W, Ambudkar IS. Caveolin-1 contributes to assembly of store-operated Ca2+ influx channels by regulating plasma membrane localization of TRPC1. J Biol Chem. 2003; 278(29):27208–27215. [PubMed: 12732636]
50. Graziani A, Bricko V, Carmignani M, Graier WF, Groschner K. Cholesterol- and caveolin-rich membrane domains are essential for phospholipase A2-dependent EDHF formation. Cardiovasc Res. 2004; 64(2):234–242. [PubMed: 15485682]

51. Everaerts W, Nilius B, Owsianik G. The vallinoid transient receptor potential channel Trpv4: From structure to disease. Prog Biophys Mol Biol. 2009
52. Cohen DM. The transient receptor potential vanilloid-responsive 1 and 4 cation channels: role in neuronal osmosensing and renal physiology. Curr Opin Nephrol Hypertens. 2007; 16(5):451–458. [PubMed: 17693761]
53. Konno M, Shirakawa H, Iida S, Sakimoto S, Matsutani I, Miyake T, Kageyama K, Nakagawa T, Shibasaki K, Kaneko S. Stimulation of transient receptor potential vanilloid 4 channel suppresses abnormal activation of microglia induced by lipopolysaccharide. Glia. 2012; 60(5):761–770. [PubMed: 22331560]
54. Shirakawa H, Nakagawa T, Kaneko S. Pathophysiological roles of transient receptor potential channels in glial cells. Yakugaku Zasshi. 2010; 130(3):281–287. [PubMed: 20190511]
55. Benfenati V, Amiry-Moghaddam M, Caprini M, Mylonakou MN, Rapisarda C, Ottersen OP, Ferroni S. Expression and functional characterization of transient receptor potential vanilloid-related channel 4 (TRPV4) in rat cortical astrocytes. Neuroscience. 2007; 148(4):876–892. [PubMed: 17719182]
56. Butenko O, Dzamba D, Benesova J, Honsa P, Benfenati V, Rusnakova V, Ferroni S, Anderova M. The Increased Activity of TRPV4 Channel in the Astrocytes of the Adult Rat Hippocampus after Cerebral Hypoxia/Ischemia. PLoS One. 2012; 7(6):e39959. [PubMed: 22761937]
57. Filosa JA, Bonev AD, Straub SV, Meredith AL, Wilkerson MK, Aldrich RW, Nelson MT. Local potassium signaling couples neuronal activity to vasodilation in the brain. Nat Neurosci. 2006; 9(11):1397–1403. [PubMed: 17013381]
58. Amruthesh SC, Boerschel MF, McKinney JS, Willoughby KA, Ellis EF. Metabolism of arachidonic acid to epoxyeicosatrienoic acids, hydroxyeicosatetraenoic acids, and prostaglandins in cultured rat hippocampal astrocytes. J Neurochem. 1993; 61(1):150–159. [PubMed: 8515261]
59. Alkayed NJ, Narayanan J, Gebremedhin D, Medhora M, Roman RJ, Harder DR. Molecular characterization of an arachidonic acid epoxygenase in rat brain astrocytes. Stroke. 1996; 27(5): 971–979. [PubMed: 8623121]
60. Metea MR, Newman EA. Glial cells dilate and constrict blood vessels: a mechanism of neurovascular coupling. J Neurosci. 2006; 26(11):2862–2870. [PubMed: 16540563]
61. Mulligan SJ, MacVicar BA. Calcium transients in astrocyte endfeet cause cerebrovascular constrictions. Nature. 2004; 431(7005):195–199. [PubMed: 15356633]
62. Takano T, Tian GF, Peng W, Lou N, Libionka W, Han X, Nedergaard M. Astrocyte-mediated control of cerebral blood flow. Nat Neurosci. 2006; 9(2):260–267. [PubMed: 16388306]
63. Zonta M, Angulo MC, Gobbo S, Rosengarten B, Hossmann KA, Pozzan T, Carmignoto G. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. Nat Neurosci. 2003; 6(1):43–50. [PubMed: 12469126]
64. Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. Glial and neuronal control of brain blood flow. Nature. 2010; 468(7321):232–243. [PubMed: 21068832]
65. Blanco VM, Stern JE, Filosa JA. Tone-dependent vascular responses to astrocyte-derived signals. Am J Physiol Heart Circ Physiol. 2008; 294(6):H2855–2863. [PubMed: 18456724]
66. Girouard H, Bonev AD, Hannah RM, Meredith A, Aldrich RW, Nelson MT. Astrocytic endfoot Ca2+ and BK channels determine both arteriolar dilation and constriction. Proc Natl Acad Sci U S A. 2010; 107(8):3811–6. [PubMed: 20133576]
67. Simard M, Nedergaard M. The neurobiology of glia in the context of water and ion homeostasis. Neuroscience. 2004; 129(4):877–896. [PubMed: 15561405]
68. Amiry-Moghaddam M, Frydenlund DS, Ottersen OP. Anchoring of aquaporin-4 in brain: molecular mechanisms and implications for the physiology and pathophysiology of water transport. Neuroscience. 2004; 129(4):999–1010. [PubMed: 15561415]
69. Amiry-Moghaddam M, Xue R, Haug FM, Neely JD, Bhardwaj A, Agre P, Adams ME, Froehner SC, Mori S, Ottersen OP. Alpha-syntrophin deletion removes the perivascular but not endothelial pool of aquaporin-4 at the blood-brain barrier and delays the development of brain edema in an experimental model of acute hyponatremia. FASEB J. 2004; 18(3):542–544. [PubMed: 14734638]

70. Price DL, Ludwig JW, Mi H, Schwarz TL, Ellisman MH. Distribution of rSlo Ca2+-activated K+ channels in rat astrocyte perivascular endfeet. Brain Res. 2002; 956(2):183–193. [PubMed: 12445685]

71. Higashimori H, Blanco VM, Tuniki VR, Falck JR, Filosa JA. Role of epoxyeicosatrienoic acids as autocrine metabolites in glutamate-mediated K+ signaling in perivascular astrocytes. Am J Physiol Cell Physiol. 2010; 299(5):C1068–1078. [PubMed: 20844244]

72. Ding XL, Wang YH, Ning LP, Zhang Y, Ge HY, Jiang H, Wang R, Yue SW. Involvement of TRPV4-NO-cGMP-PKG pathways in the development of thermal hyperalgesia following chronic compression of the dorsal root ganglion in rats. Behav Brain Res. 2010; 208(1):194–201. [PubMed: 19948193]

73. Bal-Price A, Moneer Z, Brown GC. Nitric oxide induces rapid, calcium-dependent release of vesicular glutamate and ATP from cultured rat astrocytes. Glia. 2002; 40(3):312–323. [PubMed: 12420311]

74. Ferraro G, Sardo P. Nitric oxide and brain hyperexcitability. In Vivo. 2004; 18(3):357–366. [PubMed: 15341192]

75. Grant AD, Cottrell GS, Amadesi S, Trevisani M, Nicoletti P, Materazzi S, Altier C, Cenac N, Zamponi GW, Bautista-Cruz F, Lopez CB, Joseph EK, Levine JD, Liedtke W, Vanner S, Vergnolle N, Geppetti P, Bunnett NW. Protease-activated receptor 2 sensitizes the transient receptor potential vanilloid 4 ion channel to cause mechanical hyperalgesia in mice. J Physiol. 2007; 578(Pt 3):715–733. [PubMed: 17124270]

76. Koltzenburg M. The role of TRP channels in sensory neurons. Novartis Found Symp. 2004; 260:206–213. discussion 213-220, 277-209. [PubMed: 15283452]

77. McHugh J, Keller NR, Appalsamy M, Thomas SA, Raj SR, Diedrich A, Biaggioni I, Jordan J, Robertson D. Portal osmopressor mechanism linked to transient receptor potential vanilloid 4 and blood pressure control. Hypertension. 2010; 55(6):1438–1443. [PubMed: 20385965]

78. Liu TT, Bi HS, Lv SY, Wang XR, Yue SW. Neurol Res. 2010; 32(5):466–471. [PubMed: 19278577]

79. Cenac N, Altier C, Chapman K, Liedtke W, Zamponi G, Vergnolle N. Transient receptor potential vanilloid-4 has a major role in visceral hypersensitivity symptoms. Gastroenterology. 2008; 135(3):937–946. 946 e931-932. [PubMed: 18565335]

80. Gao F, Sui D, Garavito RM, Worden RM, Wang DH. Salt intake augments hypotensive effects of transient receptor potential vanilloid 4: functional significance and implication. Hypertension. 2009; 53(2):228–235. [PubMed: 19075100]

81. Ryskamp DA, Witkovsky P, Barabas P, Huang W, Koehler C, Akimov NP, Lee SH, Chauhan S, Xing W, Renteria RC, Liedtke W, Krizaj D. The polymodal ion channel transient receptor potential vanilloid 4 modulates calcium flux, spiking rate, and apoptosis of mouse retinal ganglion cells. J Neurosci. 2011; 31(19):7089–7101. [PubMed: 21562271]

82. Troidl C, Troidl K, Schierling W, Cai WJ, Nef H, Mollmann H, Kostin S, Schimanski S, Hammer L, Elsasser A, Schmitz-Rixen T, Schaper W. Trpv4 induces collateral vessel growth during regeneration of the arterial circulation. J Cell Mol Med. 2009; 13(8B):2613–2621. [PubMed: 19017361]

83. Schierling W, Troidl K, Apfelbeck H, Troidl C, Kasprzak PM, Schaper W, Schmitz-Rixen T. Cerebral arteriogenesis is enhanced by pharmacological as well as fluid-shear-stress activation of the Trpv4 calcium channel. Eur J Vasc Endovasc Surg. 2011; 41(5):589–596. [PubMed: 21316269]

84. Ducret T, Guibert C, Marthan R, Savineau JP. Serotonin-induced activation of TRPV4-like current in rat intrapulmonary arterial smooth muscle cells. Cell Calcium. 2008; 43(4):315–323. [PubMed: 17669489]

85. Mizoguchi F, Mizuno A, Hayata T, Nakashima K, Heller S, Ushida T, Sokabe M, Miyasaka N, Suzuki M, Ezura Y, Noda M. Transient receptor potential vanilloid 4 deficiency suppresses unloading-induced bone loss. J Cell Physiol. 2008; 216(1):47–53. [PubMed: 18264976]

86. Auer-Grumbach M, Olschewski A, Papic L, Kremer H, McEntagart ME, Uhrig S, Fischer C, Frohlich E, Balint Z, Tang B, Strohmaier H, Lochmuller H, Schlotter-Weigel B, Senderek J, Krebs A, Dick KJ, Petty R, Longman C, Anderson NE, Padberg GW, Schelhaas HJ, van Ravenswaaij-

Arts CM, Pieber TR, Crosby AH, Guelly C. Alterations in the ankyrin domain of TRPV4 cause congenital distal SMA, scapuloperoneal SMA and HMSN2C. Nat Genet. 2010; 42(2):160–164. [PubMed: 20037588]

87. Carreno FR, Ji LL, Cunningham JT. Altered central TRPV4 expression and lipid raft association related to inappropriate vasopressin secretion in cirrhotic rats. Am J Physiol Regul Integr Comp Physiol. 2009; 296(2):R454–466. [PubMed: 19091909]
88. Tian W, Fu Y, Garcia-Elias A, Fernandez-Fernandez JM, Vicente R, Kramer PL, Klein RF, Hitzemann R, Orwoll ES, Wilmot B, McWeeney S, Valverde MA, Cohen DM. A loss-of-function nonsynonymous polymorphism in the osmoregulatory TRPV4 gene is associated with human hyponatremia. Proc Natl Acad Sci U S A. 2009; 106(33):14034–14039. [PubMed: 19666518]
89. Vincent F, Duncton MA. TRPV4 agonists and antagonists. Curr Top Med Chem. 2011; 11(17): 2216–2226. [PubMed: 21671873]
90. Alexander SP, Mathie A, Peters JA. Guide to Receptors and Channels (gRAC). Br J Pharmacol (5th edition). 2011; 164(suppl 1):S1–324. [PubMed: 22040146]

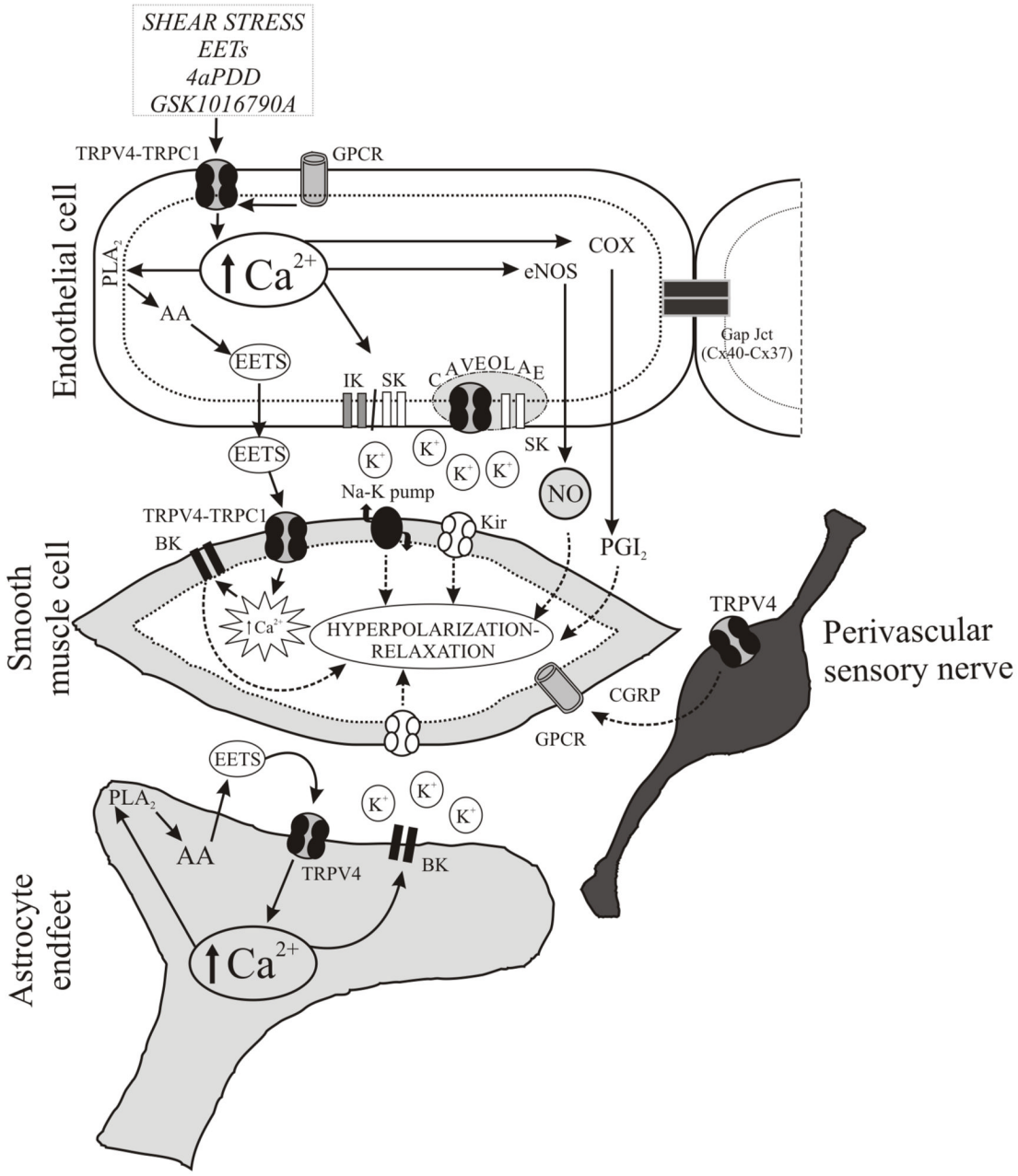

Figure 1. Contribution of TRPV4 channels to the regulation of vascular tone

As shown, heteromeric TRPV4-TRPC1 channels expressed in endothelial cells can be activated by shear stress, agonists (4αPDD, GSK1016790A) and epoxyeicosatrienoic acids (EETs) resulting in an increase in intracellular $Ca^{2+}$and the release of various vasoactive substances such as EETs, nitric oxide (NO) and prostaglandin (PGI_2) leading to vasodilation. In addition, TRPV4 channels in caveolae interact with small conductance potassium channels (SK) contributing to the release of $K^+$from endothelial cells. In smooth muscle cells, K^+-induced hyperpolarization is mediated through the activation of the Na/K pump as well as inwardly rectifying potassium channels (Kir). TRPV4-TRPC1 channels in smooth muscle cells are activated by EETs which trigger Ca^{2+}sparks from ryanodine receptors and the subsequent activation of large conductance calcium-activated potassium-

selective channels (BK) resulting in smooth muscle cell hyperpolarization and vasodilation. In cerebral parenchymal arterioles, the abluminal side of the vessel is surrounded by astrocytic endfeet processes which also modulate vascular tone. Glutamate-mediated rise in intracellular Ca^{2+}leads to vasodilation through activation of KCa1.1 channels, K^+release and activation of Kir channels in smooth muscle cells. The rise in intracellular Ca^{2+}stimulates phospholipase A_2(PLA_2) and mobilizes arachidonic acid (AA) which then is metabolized to form EETs (among other signals); EETs released at the gliovascular interface activates TRPV4 channels in astrocytic endfeet processes further contributing to the rise in intracellular $Ca^{2+}$and K^+channel signaling. In perivascular nerves, TRPV4 channel activation has been associated with the release of calcitonin gene-related peptide (CGRP) activation of G-protein coupled receptors (GPCR) in smooth muscle cells and vasodilation.

Table 1

Data summary for TRPV4 agonists [(a)]

Agonist	*Potency (IC_{50}, μM)*	*Species*	*Cross-reactivity*
4α-PDD	0.16-0.92 0.16-0.93 4.4	human mouse rat	---
5,6-EET, 8,9-EET,11,12-EET	0.15 for 5,6-EET	human mouse Rat	activates G protein coupled receptor
Bisandrographolide	0.79-0.95	mouse	--
RN-1747	0.77 4.0 4.1	human mouse rat	activates TRPV1 at 100 μM, inhibits TRPM8 (IC_{50}=4μM)
GSK-1016790A	0.003-0.005 0.0185 0.010	human mouse rat	activates TRPV1 (EC_{50}=5nM)

[(a)] modified from 8931

Table 2

Data summary for TRPV4 antagonists [(a)]

Antagonist	*Potency (IC_{50}, μM)*	*Species*	*Cross-reactivity*
RN-1734	2.3 5.9 3.2	human mouse rat	---
RN-9893	<0.12 <0.06 <0.12	human mouse rat	---
HC-067047	0.048 0.017 0.133	human mouse rat	inhibits TRPM8, HERG at submicromolar
Ruthenium Red	<0.086-1 <0.21-1 <0.2-0.33	human mouse rat	inhibits all TRPVs, TRPM6, TRPM8, TRPA1, RyR1-3
Capsazepine	18.6 13.5	human rat	Inhibits TRPV1, TRPM8
Citral	32	mouse	Inhibits TRPA1, activates TRPV1, TRPV3, TRPM8

[(a)] modified from 89, 90