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TRANSIENT RECEPTOR POTENTIAL (TRP) CHANNELS, VASCULAR TONE AND AUTOREGULATION OF CEREBRAL BLOOD FLOW

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SUMMARY

1. Members of the transient receptor potential (TRP) channel superfamily are present in vascular smooth muscle cells and play important roles in the regulation of vascular contractility.
2. The TRPC3 and TRPC6 channels are activated by stimulation of several excitatory receptors in vascular smooth muscle cells. Activation of these channels leads to myocyte depolarization, which stimulates Ca^{2+} entry via voltage-dependent Ca^{2+} channels (VDCC), leading to vasoconstriction. The TRPV4 channels in arterial myocytes are activated by epoxyeicosatrienoic acids, and activation of the channels enhances Ca^{2+} spark and transient Ca^{2+} -sensitive K^{+} channel activity, thereby hyperpolarizing and relaxing vascular smooth muscle cells.
3. The TRPC6 and TRPM4 channels are activated by mechanical stimulation of cerebral artery myocytes. Subsequent depolarization and activation of VDCC Ca^{2+} entry is directly linked to the development of myogenic tone *in vitro* and to autoregulation of cerebral blood flow *in vivo*.
4. These findings imply a fundamental importance of TRP channels in the regulation of vascular smooth muscle tone and suggest that TRP channels could be important targets for drug therapy under conditions in which vascular contractility is disturbed (e.g. hypertension, stroke, vasospasm).

Keywords

autoregulation; cation channels; myogenic tone; transient receptor potential (TRP) channels; vascular Ca^{2+} regulation

INTRODUCTION

Blood flow and pressure in the resistance vasculature are regulated by multiple mechanisms, involving both extrinsic (neuronal, hormonal) and intrinsic (myogenic, metabolic) systems. Myogenic mechanisms have been of considerable and sustained interest since the early observations of Baylis in 1902.¹ Myogenic tone is commonly observed in small arteries and arterioles and is thought to contribute to blood flow autoregulation, whereby blood flow changes only modestly over a substantial range of intravascular pressures.² The myogenic contractile response to increased intravascular pressure or tissue stretch is associated with increased cell Ca^{2+} , most often resulting from depolarization of the vascular smooth muscle cell and Ca^{2+} entry via voltage-dependent Ca^{2+} channels.³ Physiological, negative feedback mechanisms involving localized Ca^{2+} release events (Ca^{2+} sparks) and activation of large conductance Ca^{2+} -sensitive K^+ (BK) channels also contribute to the intrinsic regulatory processes associated with myogenic tone.⁴ Although many of the details of this system have been described, until recently the nature of the ion channels involved in myogenic depolarization has been unclear. Evidence that members of the TRP superfamily of ion channels play a central role in the regulation of vascular smooth muscle contractility, including regulation of myogenic tone, is presented below.

TRP CHANNELS: AN OVERVIEW

There are many recent and excellent reviews of TRP channel biology, to which the reader is referred for a thorough discourse on these interesting ion channels.^{5–7} The mammalian TRP superfamily of cation channels contains over 20 genes, which, based on sequence homology, are grouped into three major subfamilies: (i) TRPV (vanilloid); (ii) TRPC (canonical); and (iii) TRPM (melastatin). Three additional subfamilies, namely TRPP (polycystin), TRPML (mucolipin) and TRPA (ankyrin), have been categorized, bringing the total number of TRP-related proteins to nearly 30. Most cell types express several TRP genes. The TRP proteins are expressed as six transmembrane domain polypeptide subunits and four subunits assemble in the plasma membrane to form functional channels. The TRP channels are frequently described as non-selective cation channels and, with the exception of TRPM4 and TRPM5, are generally permeant to both monovalent and divalent ions.⁸ The TRP channels are activated by various stimuli, such as changes in pressure, temperature, osmolarity, intracellular Ca^{2+} and fatty acids, as well as by receptor–ligand interactions, suggesting that TRP channels may be involved in the regulation of a variety of physiological systems.⁵

Elucidation of functional roles for TRP channels has been hindered by a rather complex molecular biology. The biophysical properties of TRP channels have been investigated primarily in patch-clamp experiments used cultured cells expressing cloned TRP subunit genes. Under these conditions, most functional TRP channels assemble as homotetramers.^{5,9} However, when multiple TRP subunits are coexpressed, the assembly of heterotetrameric channels composed of two or more TRP subunit proteins occurs,⁹ resulting in channels with unique properties (kinetics, permeation, regulation) compared with homomeric channels.^{10,11} Because most cells express multiple TRP subunits, it is likely that heteromeric channels exist *in vivo*. Furthermore, splice variants of TRP mRNAs in smooth muscle have been reported,¹² potentially increasing the number of individual subunits available for

coassembly and further complicating attempts to determine the physiological roles of these channels. Nevertheless, recent evidence, reviewed below, points towards important contributions of TRP channels from each of the major subfamilies (TRPC, TRPV and TRPM) in the control of vasomotor activity.

PROPOSED VASOMOTOR FUNCTIONS OF TRP CHANNELS IN VASCULAR SMOOTH MUSCLE

The TRP channels are well represented in the vasculature, both in endothelial¹³ and smooth muscle cells.¹² In vascular smooth muscle cells, the most highly expressed TRPs are TRPC1, TRPC3, TRPC4, TRPC6, TRPM4, TRPV2 and TRPV4.⁷ Definition of the functional vasomotor roles for these channels in vascular smooth muscle is still incomplete. However, likely functions relate to either receptor-mediated Ca^{2+} entry supporting vasoconstriction or mechanosensitive responses associated with osmotic stress or altered intravascular pressure and correlated changes in intrinsic vascular (i.e. myogenic) tone. Evidence supporting a role for a TRP channels as smooth muscle cell receptors for an endothelium-derived hyperpolarizing factor (EDHF) is also reviewed.

Receptor-mediated vasoconstriction

The presence and contributions of receptor-activated, non-selective cation channels in peripheral vascular smooth muscle cells are well documented.¹⁴ However, the work of Inoue *et al.*¹⁵ was the first to demonstrate that these channels, at least in portal vein smooth muscle cells, are, in fact, TRPC6 channels. In that study, activation of adrenoceptors by phenylephrine produced a current in isolated smooth muscle cells that displayed dual rectification; the channels involved were permeable to divalent cations and had a unitary conductance of approximately 25 pS. This channel could also be activated by diacylglycerol (DAG) analogues. Interestingly, channel activity was potentiated by flufenamate (a non-specific cation channel inhibitor that 'uniquely' enhances α -adrenoceptor-activated non-selective cation currents in the rabbit portal vein) and by extracellular Ca^{2+} . The channel was inhibited by other non-selective cation channel inhibitors, such as cadmium, lanthanum, gadolinium, SK&F96365 and amiloride. Phenylephrine-induced currents with virtually identical properties to those found in the native vascular smooth muscle cells were recorded from HEK cells overexpressing cloned TRPC6. Downregulation of TRPC6 expression in primary cultured portal vein myocytes using antisense oligodeoxynucleotides resulted in suppression of α_1 -adrenoceptor-activated cation currents. These findings show that TRPC6 channels are critical mediators of phenylephrine-induced responses in portal vein smooth muscle cells. A current with biophysical and pharmacological properties similar to that described by Inoue *et al.*¹⁵ was recorded in the smooth muscle-derived A7r5 cell line exposed to vasopressin or membrane-permeable analogues of DAG.¹⁶ Northern blots for all seven TRPCs revealed that only TRPC1 and TRPC6 were present in these cells. Because the current showed properties characteristic of TRPC6 and because there is no evidence to support the presence of a TRPC1/6 heteromeric channel, it is likely that the agonist-induced current was mediated by TRPC6 channels. Paradoxically, α -adrenoceptor-mediated contractions of aortas from TRPC6-knockout mice are enhanced compared with wild-type

mice.¹⁷ However, this may be explained by the increased expression and possible compensatory role of vascular TRPC3 channels in the TRPC6-knockout mice.

Recently, we have observed that another TRPC family member (i.e. TRPC3) is a key player in receptor-mediated contraction of cerebral artery myocytes.^{18,19} Uridine triphosphate (UTP) depolarizes and contracts cerebral and other arteries.²⁰ We found that antisense oligonucleotide suppression of TRPC3 expression in cerebral artery smooth muscle cells reduced the UTP-induced depolarization and vasoconstriction by approximately 50%.¹⁸ In addition, UTP activated whole-cell cation currents in cerebral artery smooth muscle cells that were substantially reduced by downregulation of TRPC3. Thus, a component of the UTP-induced, TRPC3-mediated constriction seems to be due to membrane depolarization and activation of L-type calcium channels. However, recent continuation studies indicate that direct calcium entry via the TRPC3 channel also contributes to the UTP-induced increase in cytosolic Ca^{2+} and contraction of cerebral artery myocytes.¹⁹ Albert *et al.* recently found a TRPC3-like channel that is constitutively active in rabbit ear artery myocytes.¹⁴ Preliminary evidence from our laboratory²¹ supports this observation and suggests that constitutively active TRPC3 channels in rat mesenteric artery myocytes depolarize the membrane potential and increase myocyte sensitivity to the α -adrenoceptor activator phenylephrine.

Vasodilation induced by epoxyeicosatrienoic acids

Members of the TRPV subfamily are also present in vascular smooth muscle cells in the cerebral²² and peripheral⁷ circulations. We have found that epoxyeicosatrienoic acid (EETs) compounds, which are produced by the vascular endothelium and have been proposed to be one form of EDHF,²³ activate TRPV4 channels in cerebral artery myocytes.²² Entry of calcium through the activated TRPV4 channels then induces the localized release of Ca^{2+} from ryanodine-sensitive receptors located on the sarco-endoplasmic reticulum in the form of events termed calcium sparks. The Ca^{2+} spark events then activate nearby sarcolemmal BK channels and increase the frequency of macroscopic outward K^{+} currents. The EET-induced increase in BK currents results in smooth muscle hyperpolarization and vasodilation. These experiments support the hypothesis that TRPV4 forms a Ca^{2+} signalling complex that includes ryanodine receptors and BK channels and that the TRPV4 channel may serve as a receptor molecule for EETs in vascular smooth muscle.

Activation of TRP channels, myogenic tone and autoregulation of blood flow

Several members of the TRP channel superfamily have been reported to be mechanosensitive ion channels. A number of studies suggest that TRP channels present in vascular smooth muscle cells are important mediators of the myogenic vasoconstrictor response to increases in intravascular pressure. For example, Welsh *et al.*²⁴ identified a non-selective cation current in cerebral artery myocytes that was activated by cell swelling. Downregulation of TRPC6 expression using antisense oligodeoxynucleotides attenuated these currents, as well as the smooth muscle membrane depolarization and vasoconstriction induced by elevation of intraluminal pressure.²⁵ These results suggest that membrane stretch activates a TRPC6- dependent depolarizing cation current that contributes to myogenic constriction of cerebral arteries. Indeed, Spassova *et al.*²⁶ have recently observed that

osmotic (hypotonicity) and pressure (negative pipette pressure) stimuli activate TRPC6 channels that have been overexpressed in HEK 293 or Chinese hamster ovary (CHO) cells. Such channel activation is blocked by GsMTx-4, a peptide toxin from the venom of the tarantula *Grammostola spatulata* and a specific inhibitor of mechanosensitive ion channels,²⁷ further supporting the proposal that TRPC6 channels are sensors of mechanical stimuli.

Several recent reports indicate that a member of the melastatin TRP channel family (TRPM4) may also contribute to stretch-induced myogenic depolarization of cerebral artery myocytes.²⁸ TRPM4 and the closely related TRPM5 are unique among TRP channels for their relatively limited permeability to calcium.⁸ This and several other identifying biophysical properties have been well described for the TRPM4 channel.²⁹ We have recently observed that message for TRPM4 (but not TRPM5) channels is present in cerebral artery smooth muscle cells.²⁸ Subsequently, monovalent cation selective channels, activated by intracellular Ca^{2+} ,²⁸ protein kinase C (PKC)³⁰ and membrane stretch,³¹ were identified in isolated cerebral artery myocytes. These currents, as well as the smooth muscle depolarization and constriction of isolated cerebral arteries in response to both elevated intravascular pressure and PKC activation, are greatly attenuated when expression of TRPM4 is suppressed using TRPM4 antisense oligonucleotides *in vitro*.^{28,30} We have recently applied an *in vivo* antisense oligonucleotide approach³² that resulted in the acute suppression of cerebral artery TRPM4 expression in the living animal.³³ These experiments were designed to allow evaluation of the role of cerebral myocyte TRPM4 in the autoregulation of cerebral blood flow. Seven days after *in vivo* exposure to TRPM4 antisense oligodeoxynucleotides, pressure-induced depolarization and vasoconstriction of arteries³³ and stretch-induced cation channel activation in cerebral artery myocytes (Fig. 1; Table 1) isolated from antisense-treated rats were greatly suppressed. Moreover, as shown in Fig. 2, *in vivo* exposure of cerebral arteries to TRPM4 antisense oligodeoxynucleotides significantly compromised autoregulatory function in the intact animal.³³ Viewed together, these studies indicate a prominent role for vascular TRPM4 channels in myogenic tone and autoregulation of cerebral blood flow.

The observation (above) that inhibition of either TRPC6 or TRPM4 leads to comparable suppression of pressure-induced depolarization and myogenic tone suggests some cooperative interaction between these two TRP channels.²⁸ We have hypothesized that mechanical stress activates Ca^{2+} entry through TRPC6 channels and this Ca^{2+} activates nearby TRPM4 channels; Na^{+} entry via TRPM4 channels would then depolarize the smooth muscle membrane and thus increase global Ca^{2+} via enhanced activity of VDCC.²⁸ Confirmation of this proposed TRP channel interaction awaits further investigation.

Other TRPs and possible mechanoactivation

TRPC1 is present in vascular smooth muscle cells⁷ and represents another candidate mechanosensitive cation channel. Indeed, stretch activation of TRPC1 channels expressed in oocytes has been demonstrated.³⁴ However, to date, no evidence has been presented to indicate a mechanosensitive role for TRPC1 in vascular smooth muscle.

TRPV2 appears to be a mechanically activated ion channel in mouse aortic smooth muscle cells.³⁵ Specifically, hypotonic swelling of aortic myocytes activates a Ca^{2+} current that is unaffected by inhibitors of L-type VDCC or by pretreatment with caffeine to deplete intracellular Ca^{2+} stores. This swelling-activated current is blocked by ruthenium red, a non-selective inhibitor of TRPV channels, and by antisense-mediated suppression of TRPV2 expression. Whether activation of TRPV4 occurs during physiological activation of arteries that demonstrate myogenic tone remains to be determined.

TRP channels and vascular disease

The broad distribution of TRP channels in the vasculature and the important roles these channels appear to play in vasomotor function suggest the possibility that these channels may also contribute to the mechanisms of vascular disease. Evidence to this effect is beginning to emerge. In particular, TRP channels may play important roles in vascular cell proliferation and remodelling associated with arterial injury, hypoxia and hypertension.^{36,37} The expression and activity of members of the TRPC family, specifically TRPC1 and TRPC6, are upregulated during these pathological states; associated changes in cell Ca^{2+} regulation mediated by TRP channels may be centrally involved in the mechanisms of vascular dysfunction that occur with vascular injury. Potential contributions of other members of the TRP channel superfamily in vascular disease remain to be elucidated.

CONCLUSIONS

It is apparent that multiple TRP channels are present in vascular smooth muscle and that these channels participate in various mechanisms of vasomotor control, including receptor-operated activation of smooth muscle depolarization and vasoconstriction involving TRPC3 and TRPC6 channels, as well as pressure-induced depolarization and myogenic constriction of small arteries, which involves TRPC6 and TRPM4 channels (Fig. 3). *In vivo*, TRPM4, likely due to its important role in the regulation of myogenic tone, is a key contributor to the mechanism of cerebral blood flow autoregulation.

Acknowledgments

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Fig. 1.

Single-channel currents in a cerebral artery myocyte isolated from a TRPM4 sense-treated rat. (a) Small inward currents at steady pipette pressure (-5 mmHg). (b) Larger (approximately 1.5 pA) currents activated by increasing pipette pressure from -5 to -50 mmHg. Cell attached patch, pipette voltage ($-V_p$) = -60 mV. The composition of the bath solution was (in mmol/L): NaCl 145; KCl 3; HEPES 10; CaCl_2 1; MgCl_2 1; glucose 10 (pH 7.4). The composition of the pipette solution was (in mmol/L): NaCl 140; KCl 3; HEPES 10; CaCl_2 1; mannitol 10; iberiotoxin 0.0001 (pH 7.4).

Fig. 2.

Cerebral blood flow (CBF) in male rats 7 days after treatment with either TRPM4 sense (●) or TRPM4 antisense (○) oligodeoxynucleotides via cerebral ventricular infusion. * $P < 0.05$ compared with TRPM4 sense-treated animals. MAP, mean arterial pressure. (Reproduced with permission from Earley *et al.*³⁰)

Fig. 3.

Model cell showing the proposed roles for various transient receptor potential (TRP) channels in cerebral artery vascular smooth muscle cells. EETs, epoxyeicosatrienoic acids; SR, sarcoplasmic reticulum; NA, noradrenaline; PKC, protein kinase C; IP₃, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; PLC, phospholipase C.

Table 1

Frequency of observations of TRPM4-like channels in cells from TRPM4 sense- and antisense-treated rats

<i>In vivo</i> treatment	Cells with stretch-activated channels (cells with channels/cells patched)
TRPM4 sense	69% (9/13)
TRPM4 antisense	21% (3/14)*

* $P < 0.05$ compared with sense-treated ($n = 5$ animals for each treatment group; two to three cells per animal).