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Transient receptor potential canonical type 3 channels: Interactions, role and relevance - A vascular focus

T.H. Grayson [a,b,*], Timothy V. Murphy [b], Shaun L. Sandow [a,b,**]

[a] Inflammation and Healing Cluster, Faculty of Science, Health, Education and Engineering, University of the Sunshine Coast, Maroochydore, Qld 4558, Australia
[b] Department of Physiology, School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia

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ABSTRACT

Transient receptor potential canonical type 3 channels (TRPC3) are expressed in neural, cardiac, respiratory and vascular tissues, with both similarities and differences between human and animal models for the same cell types. In common with all members of the six subfamilies of TRP channels, TRPC3 are non-voltage gated, non-selective cation channels that are mainly permeated by Ca^{2+}, and have distinct molecular, biophysical, anatomical and functional properties. TRP channels are present in excitable and non-excitable cells where they sense and respond to a wide variety of physical and chemical stimuli. TRPC3 are expressed in the endothelium and/or smooth muscle of specific intact arteries, such as mesenteric, cerebral and myometrial, where they are critical for the control of vascular tone, and show altered activity in development and disease. In artery endothelium, TRPC3 contributes to endothelium-derived hyperpolarization and nitric oxide-mediated vasodilation. In artery smooth muscle, TRPC3 contributes to constrictor mechanisms. In both endothelium and smooth muscle, TRPC3 contributes to function via caveolae-caveolin dependent and independent mechanisms. In different cell types and states, like other TRP channels, TRPC3 can form complexes with other TRP proteins and associated channels and accessory proteins, including those associated with endo(sarco)plasmic reticulum (ER/SR), thereby facilitating Ca^{2+} channel activation and/or refilling ER/SR Ca^{2+} stores. The diversity of TRPC3 interactions with other vascular signaling components is a potential target for artery specific control mechanisms. This brief perspective highlights recent advances in understanding the functional diversity of TRPC3, with an emphasis on vascular health and disease.

Contents

1. Introduction . . . 0
2. Gene structure and variation . . . 0
3. Transcriptional regulation . . . 0
4. Protein and channel assembly . . . 0
5. Activation and regulation . . . 0
6. Interactions with other Ca^{2+} store receptors . . . 0
7. TRPC3 and store-operated Ca^{2+} entry (SOCE) . . . 0
8. Interactions with other ion channels . . . 0
9. TRPC3 in vascular function and disease . . . 0
10. TRPC3 as a therapeutic target . . . 0
11. Overview, concluding remarks and cautions . . . 0
Disclosures . . . 0
Acknowledgements . . . 0
References . . . 0

* Correspondence to: T.H. Grayson, Department of Physiology, School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia.
** Correspondence to: S.L. Sandow, Inflammation and Healing Cluster, Faculty of Science, Health, Education and Engineering, University of the Sunshine Coast, Maroochydore, Qld 4558, Australia.
E-mail addresses: t.grayson@unsw.edu.au (T.H. Grayson), shaun.sandow@unsw.edu.au (S.L. Sandow).

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Abbreviations

BTP	bis(trifluoromethyl)pyrazole
CaM	calmodulin
CIRB	calmodulin IP_3R binding
DAG	diacylglycerol
EC	endothelial cell
EDH	endothelium-derived hyperpolarization
ER	endoplasmic reticulum
ERK	extracellular signal-related kinase
ET-1	endothelin 1
ET_B	endothelin receptor type B
I_{CRAC}	inward Ca^{2+} release activated current
IL-2	interleukin-2
IP_3	inositol 1,4,5-trisphosphate
IP_3R	receptor
K2P	two pore domain K^+ channels
K_{Ca}	Ca^{2+}-activated K^+ channels (S, small; I, intermediate; B, large)
K_{ir}	inwardly rectifying K^+ channel
K_v	voltage-dependent K^+ channel
MEGJs	myoendothelial gap junctions
NCX	Na^+/Ca^{2+} exchanger
NFAT	nuclear factor of activated T-cells
NF-κB	nuclear factor kappa light chain gene enhancer of activated B cells
NO	nitric oxide
PI3K	phosphatidylinositol 3-kinase
PI3P	phosphatidylinositol 3-phosphate
PIP2	phosphatidylinositol 4,5-bisphosphate
PKG	protein kinase G
PLC/D	phospholipase C/D
RyR	ryanodine receptor
SERCA	Ca^{2+}-ATPase
SMC	smooth muscle cell
SNP	single nucleotide polymorphism
SOCE	store-operated Ca^{2+} entry
SR	sarcoplasmic reticulum
STIM	stromal interaction molecule
TRP	transient receptor potential channel
TRPC	canonical
TRPM	melastatin
TRPP	polycystin
TRPV	vanilloid
VDCC	voltage-dependent Ca^{2+} channels

1. Introduction

Transient receptor potential (TRP) channels are a large and diverse family of mostly nonselective cation channels that are non-voltage gated and mainly permeated by Ca^{2+}, and that sense and respond to a wide variety of physical and chemical stimuli (see Nilius & Szallasi, 2014). TRP channels are composed of TRP protein subunits that share the same basic topology, consisting of 6 transmembrane domains, a pore-forming loop, and intracellular N and C termini, and can assemble as tetramers distributed in the plasma membrane and various organelles of most cell types and tissues. Such overlap in distribution has afforded TRP proteins the potential to function as homo- and hetero-tetrameric channels that can sense, integrate and transduce a wide range of exogenous and endogenous signals into appropriate responses in excitable and non-excitable cells. This diversity of structure and function includes constitutively active channels, as well as channels gated by a wide variety of physical (e.g. light, temperature, pressure, voltage) and chemical (e.g. ligands, lipids, ions) signals. The 28 mammalian TRP channels (27 in humans) can be grouped into 6 subfamilies, one of which is the canonical TRP (TRPC) subfamily of 7 members (6 in humans, where TRPC2 is a non-functional pseudogene). Members of the TRPC subfamily can be further distinguished on the basis of sequence homology and function. Briefly, TRPC1/C4/C5 can be activated by phospholipase C (PLC) but are unresponsive to diacylglycerol (DAG), whereas TRPC3/C6/C7 can be activated by DAG independently of protein kinase C (PKC) (Hofmann et al., 1999: Trebak, Bird, McKay, Birnbaumer, & Putney, 2003; Venkatachalam, Zheng, & Gill, 2003).

Although TRPC3 has been the subject of extensive investigation, a clearly defined role remains to be uncovered. TRPC3 channels are constitutively expressed in excitable and non-excitable cells and TRPC3 is abundant in the brain (Kunert-Keil, Bisping, Krüger, & Brinkmeier, 2006; Riccio et al., 2002), sensory neurons for touch and hearing (Sexton et al., 2016), cardiac muscle, lung, airway smooth muscle (SM), pituitary gland (Kunert-Keil et al., 2006; Riccio et al., 2002), and vascular endothelium and SM (Adebiyi, Narayanan, & Jaggar, 2011; Senadheera et al., 2012; Senadheera, Bertrand, Grayson, Leader, Murphy, et al., 2013), although the pattern and level of expression appears to vary between human and mouse tissues (Kunert-Keil et al., 2006; Riccio et al., 2002). In addition, there is evidence of developmental regulation of expression in some tissues including the embryonic brain (Strübing, Krapivinsky, Krapivinsky, & Clapham, 2003). Nevertheless, mice lacking TRPC3 (*Trpc3* −/−) display surprisingly few obvious phenotypic changes apart from a mildly impaired walking behaviour, but without the expected impact on brain development given its apparent high level CNS expression (Hartmann et al., 2008). In addition, compensatory processes, as observed in studies of other TRPC channels (Dietrich, Mederos y Schnitzler, Kalwa, et al., 2005), and possibly related to the length of time required for the development of a distinguishable phenotype, may obscure a more complete picture of the physiological role of TRPC3. In such cases, the use of multiple specific TRPC subtype knockout mice may assist in identifying loss-of-function phenotypes (Liao, Abramowitz, & Birnbaumer, 2014).

The identification of gain-of-function TRPC3 mutations that make a readily discernible contribution to disease has thus far been restricted to ataxia in the chemically mutagenized moonwalker (*Mwk*) mouse (Becker et al., 2009, 2011), an indirect involvement in Williams-Beuren syndrome, a rare neurodevelopmental disorder associated with hypercalcemia (Letavernier, Rodenas, Guerrot, & Haymann, 2012), and the recent report of a patient with adult-onset cerebellar ataxia (Fogel, Hanson, & Becker, 2015). Despite this, there is accumulating evidence favouring the involvement of TRPC3 in allergic airway disease (Song et al., 2016), malignant hyperthermia (Eltit, Ding, Pessah, Allen, & Lopez, 2013), atherosclerosis (Smedlund, Birnbaumer, & Vazquez, 2015; Tano et al., 2014), cardiac hypertrophy and arrhythmia (Doleschal et al., 2015; Domínguez-Rodríguez et al., 2015; Kiyonaka et al., 2009; Li et al., 2016; Makarewich et al., 2014; Nakayama, Wilkin, Bodi, & Molkentin, 2006; Onohara et al., 2006; Seo et al., 2014; Watanabe, Iino, Ohba, & Ito, 2013), hypertension (Adebiyi et al., 2011; Park et al., 2011; Thilo, Loddenkemper, et al., 2009; Thilo, Baumunk, et al., 2009; Wang, Tang, et al., 2016), renal fibrosis (Saliba et al., 2015), chronic pain (Alkhani et al., 2014), progression of ovarian cancer (Yang, Cao, Zhou, Feng, & Wang, 2009; Zeng, Yuan, Yang, Atkin, & Xu, 2013), melanoma (Oda et al., in press), cerebral ischemia/reperfusion injury (Chen, Liu, et al., in press; Chen, Lu, et al., in press), and ataxia (Becker et al., 2009, 2011; Fogel et al., 2015). There is evidence implicating TRPC3 in glucose sensing by hypothalamic neurons, potentially affecting insulin secretion, food intake and hepatic glucose production (Chrétien et al., 2017), and in defective insulin-mediated glucose uptake by cardiomyocytes and skeletal muscle fibres from insulin-resistant mice (Fauconnier et al., 2007; Lanner et al., 2009), although a potential role for TRPC3 in glucose-stimulated insulin secretion by pancreatic beta cells, a process that may be impaired in type 2 diabetes, remains

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