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Review

Muscling in on TRP channels in vascular smooth muscle cells and cardiomyocytes

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ABSTRACT

The human TRP protein family comprises a family of 27 cation channels with diverse permeation and gating properties. The common theme is that they are very important regulators of intracellular Ca^{2+} signaling in diverse cell types, either by providing a Ca^{2+} influx pathway, or by depolarising the membrane potential, which on one hand triggers the activation of voltage-gated Ca^{2+} channels, and on the other limits the driving force for Ca^{2+} entry. Here we focus on the role of these TRP channels in vascular smooth muscle and cardiac striated muscle. We give an overview of highlights from the recent literature, and highlight the important and diverse roles of TRP channels in the pathophysiology of the cardiovascular system.

The discovery of the superfamily of Transient Receptor Potential (TRP) channels has significantly enhanced our knowledge of multiple signal transduction mechanisms in cardiac muscle and vascular smooth muscle cells (VSMC). In recent years, multiple studies have provided evidence for the involvement of these channels, not only in the regulation of contraction, but also in cell proliferation and remodeling in pathological conditions.

The mammalian family of TRP cation channels is composed by 28 genes which can be divided into 6 subfamilies groups based on sequence similarity: TRPC (Canonical), TRPM (Melastatin), TRPML (Mucolipins), TRPV (Vanilloid), TRPP (Policystin) and TRPA (Ankyrin-rich protein). Functional TRP channels are believed to form four-unit complexes in the plasma, each of them expressed with six transmembrane domain and intracellular *N* and *C* termini.

Here we review the current knowledge on the expression of TRP channels in both muscle types, and discuss their functional properties and role in physiological and pathophysiological processes.

Contents

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1. TRPs in vascular smooth muscle

1.1. TRPC1

TRPC1 has been one of the most studied TRP channels in VSMC, and its expression has been found at the level of mRNA and protein all across cell types of vascular smooth muscle from arterial to venous, with evidence of differential expression between species, and different vascular beds [1,2]. Studies of native TRPC1 have resulted in an increasing list of diverse physiological roles [3] and in vascular tissue this channel has been implicated in physiological pulmonary vasoconstrictor effects, induced by capacitative Ca^{2+} influx [4]. In pathophysiological conditions, reducing TRPC1 in a murine model through lipofectamine siRNA delivery effectively supressed hypoxia-induced pulmonary arterial hypertension [5,6]. TRPC1 has been proposed to contribute to ROCs (receptor-operated channels) in VSMC, and effect that requires activation of the inositol (1,4,5) triphosphate (IP_3) receptor. However, this channel has been also suggested as one of the essential elements of SOCE pathway, with different pharmacological properties, although there is still controversy about whether it is a regulator of SOCE or pore forming subunit [7–9]. In rabbit mesenteric artery smooth muscle cells, high concentrations of angiotensin II (Ang II) preferentially stimulate TRPC1, causing depolarization and Ca^{2+} influx, vasoconstriction and increase of blood pressure [10]. Enhancement of TRPC1 expression by Ang II and subsequent NF-kB activation in human coronary artery smooth muscle cells (hCASMC) led to hypertrophy, suggesting TRPC1 as a target for pharmacological and genetic modification of the atherosclerotic process [11].

In contrast to these studies, there is evidence that TRPC1 is not a relevant component of store-operated ion channel complexes in VSMC as there is an essential contribution of STIM1 to store-dependent cation influx when TRPC1 is silenced [12,13]. A novel activation mechanism has been described in VSMC, whereby store-operated STIM1-TRPC1 complexes interact and stimulate the phospholipase C (PLC) pathway and therefore protein kinase C (PKC) phosphorylation, leading to channel activation. However, how store depletion stimulates this mechanism is still unclear [14,15]. On the other hand, it has been proposed that TRPC1 phosphorylation via the NO-cGMP-PKG pathway inhibits smooth muscle hyperpolarization and relaxation induced by 11,12-EET [16].

Several lines of evidence indicate that TRPC1 forms heteromultimeric complexes with other members of the TRPC family, leading to different functions. For example, it has been found that NOX4 facilitates TRPC1 and TRPC6 expression induced by bone morphogenetic protein 4, promoting cell proliferation and vascular remodeling [17]. In contrast, TRPC1/TRPC3 complexes mediate lysophosphatidylcholine-induced apoptosis in hCASMC [18]. TRPC1 also forms native heteromeric with TRPC5 in VSMCs with a contractile phenotype, and the resulting complexes are activated by agents that deplete Ca^{2+} stores [19]. In contrast, inhibition of TRPC1/TRPC3 by PKG contributes to NO-mediated vasorelaxation [20]. Interestingly it has been proposed that TRPC1/TRPC5 activity inhibits TRPC6 via a Ca^{2+}- and PKC- dependent mechanism, promoting excitation of mesenteric arteries [21].

Furthermore, several studies show functional interactions between TRPC1 with voltage-gated channels. For instance, in mammary arteries, TRPC1 seems to serve as a linker through which TRPV4 and KCa1.1(α) can interact and induce vascular relaxation [22,23]. In mouse vascular smooth muscle, several lines of evidence indicate that Orai1 and TRPC1 form a macromolecular complex with $Ca_V1.2$ [24].

1.2. TRPC3

Expression of TRPC3 mRNA and protein has been demonstrated in vascular smooth muscle cells from different vascular beds, such as cerebral [25], coronary [26], renal [27], aorta [28] and pulmonary arteries [29]. Contractile responses mediated by TRPC3 channels have been described in cerebral and mesenteric artery VSMC. A range of G-protein coupled receptors such as endothelin-1 [30] and Ang II [31] receptors mediate the activation of TRPC3 channels in VSMC. In airway smooth muscle cells, TRPC3 channel gene knockdown was shown to reduce inward currents, blocking the stimulatory effect of IP_3 and OAG on the channel leading to reduced vasoconstriction [32]. This concept is supported by the studies of other laboratory that showed mesenteric artery vasoconstriction induced by phenylephrine, membrane depolarization and mechanical pressure was considerably decreased in TRPC3 WT compared to KO mice [33].

At first, the mechanism of TRPC3 activation was thought to occur through direct bind of DAG to the channel. However, it was shown that in VSMC, the IP_3 receptor antagonist heparin prevents Ca^{2+} influx, suggesting that IP_3 is a critical element in the activation of TRPC3 channels [32]. A direct coupling between IP_3 receptors and TRPC3 channels has also been proposed [34]. In cerebral arteries, TRPC3 channels were required for IP_3-induced intracellular Ca^{2+} elevation leading to vasoconstriction [35]. Moreover, it was shown that IP_3 receptor and TRPC3 channels could be co-immunoprecipitated in VSMC [36,37]. Other modulators of TRPC3 have been described in VSMC. For instance, protein kinase G was reported to inhibit TRPC3, promoting vasodilation of isolated cerebral arteries [20]. This is supported by another study proposing a mechanism whereby WNK4 associates with TRPC3, causing an inhibitory effect on the channel, followed by decrease in the myogenic tone [38].

Several lines of evidence support the argument that TRPC3 channels in VSMC regulate the vascular tone. The activation of these channels by multiple agonists contributes to increase Ca^{2+} influx in addition to opening IP_3 receptors leading to intracellular Ca^{2+} release from stores causing further membrane depolarization through the opening of voltage-gated Ca^{2+} channels. These studies indicate a potential involvement of TRPC3 channels in the myogenic tone response and vasoconstriction.