Journal of Molecular and Cellular Cardiology 48 (2010) 83–89

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Review article

Sensing pressure in the cardiovascular system: Gq-coupled mechanoreceptors and TRP channels

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ARTICLE INFO

Article history:
Received 5 February 2009
Received in revised form 6 March 2009
Accepted 13 March 2009
Available online 1 April 2009

Keywords:
Mechanotransduction
Angiotensin
AT1R
Stretch
TRP
Pressure
Mechanoreceptor
Stretch-activated channel
Diacylglycerol
Cardiovascular

ABSTRACT

Despite the central physiological importance of cardiovascular mechanotransduction, the molecular identities of the sensors and the signaling pathways have long remained elusive. Indeed, how pressure is transduced into cellular excitation has only recently started to emerge. In both arterial and cardiac myocytes, the diacylglycerol-sensitive canonical transient receptor potential (TRPC) subunits are proposed to underlie the stretch-activated depolarizing cation channels. An indirect mechanism of activation through a ligand-independent conformational switch of Gq-coupled receptors by mechanical stress is invoked. Such a mechanism involving the angiotensin type 1 receptor and TRPC6 is proposed to trigger the arterial myogenic response to intraluminal pressure. TRPC6 is also involved in load-induced cardiac hypertrophy. In this review, we will focus on the molecular basis of pressure sensing in the cardiovascular system and associated disease states.

Contents

How cells are able to convert a mechanical force into an electrical response (mechanosensory transduction) remains a major biological question. Cells respond to diverse mechanical stimuli including flow (i.e. shear stress), pressure (i.e. stretch) or osmotic stress (i.e. swelling or shrinking). These responses involve different types of ion channels including non-selective, potassium- and chloride-selective ion channels that can respond to either one or several mechanical stimuli.

The TRPC channels have recently been implicated in pressure sensing [1–7]. TRP channels are made of six transmembrane segments and a single pore (P) domain located between segments 5 and 6. Both the amino and carboxy terminal domains face the cytosol. There are 33 TRP channel genes in mammals subdivided into six subfamilies based on homology: TRPC (seven members), TRPM (eight members), TRPV (six members), and the more distantly related TRPML (three members), TRPP (eight members), and TRPA (one member) (for a review and more details, see [8–10]). These subunits associate as tetramers with possible heteromultimerization.

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doi:10.1016/j.yjmcc.2009.03.020

Most TRP channels are non-selective cation channels permeable to Ca^{2+} and have been implicated in a large variety of sensory functions such as temperature sensing [11]. Several TRP channels including TRPA1, TRPC1, TRPC6, TRPV1, TRPV2, TRPV4, TRPM4, TRPM7 and TRPP2 have also recently been implicated in force sensing (for recent reviews see [7,9,12]). Indeed, TRPC6, TRPM4 and TRPV2 have been implicated in the osmotic and stretch sensitivity of arterial myocytes [3,13,14]. However, a direct role for any of these TRP channels in mechanosensory transduction remains highly controversial and the molecular basis of SACs (i.e. channels which are directly gated by force) still remains obscure (see [4,7,15]).

Nevertheless, the function of TRP subunits in mechanotransduction appears to be conserved during evolution. For instance, in yeast, Yvc1p, a vacuolar membrane protein that shows homology to TRPV channels, was shown to be responsible for hyperosmolarity-induced Ca^{2+} release [16–18]. Yvc1p is mechanosensitive and pressure at tens of millimeters of Hg activate this channel [17,18]. Moreover, a role for TRP channels in touch sensing or hearing has also been established through genetical approaches using model systems such as the nematode *Caenorhabditis elegans* and the fruit fly *Drosophila* (for review see [9,19]).

In the present review, we will summarize the evidence that Gq-coupled receptors are directly activated by mechanical stress without the involvement of their ligands. Activation of these mechanoreceptors by pressure leads to the opening of receptor-operated diacylglycerol (DAG)-sensitive TRPC channels resulting in cell depolarization. We will discuss the possibility that this novel mechanosensitive pathway is implicated in a variety of cardiovascular pathologies including ventricular hypertrophy and atrial fibrillation, focusing on the angiotensin II type 1 receptor and the TRPC6 subunit.

1. The diacylglycerol-sensitive TRPC6 channel

All TRPCs, besides the pseudogene *TRPC2*, have been identified in cardiac myocytes, vascular smooth muscle and endothelial cells (for recent reviews see [20,21]). TRPC3/6/7 form a structural and functional subfamily with 70–80% homology. TRPC6 assembles either into homo or heterotetramers with TRPC3 and TRPC7. Members of the TRPC family contain four N-terminal ankyrin repeats and several protein binding-domains. Indeed, TRPC6 interacts with a number of adaptor proteins including cytoskeletal proteins (for review see [22]).

TRPC6 has a ubiquitous expression with high levels in vascular smooth muscle cells and in cardiomyocytes [3,23]. In lung tissues and pulmonary arterial smooth muscle cells (PASMCs) obtained from patients suffering from primary pulmonary artery hypertension, the mRNA and protein expression of TRPC6 is increased compared to those from normotensive or secondary pulmonary hypertension patients [24]. Moreover, PDGF-mediated proliferation of PASMC is associated with c-Jun/STAT-3-induced upregulation of TRPC6 expression [25]. In the heart, immunolabeling experiments localized TRPC6 in T-tubular membranes of cardiomyocytes [5,6].

TRPC6 is a 28–37 pS inwardly and outwardly rectifying channel, with a relatively low selectivity for Ca^{2+} over Na^{+} (PCa^{2+}/PNa^{+}: 5). It shows a very low basal activity and is a receptor-operated channel (ROC). Indeed, TRPC6 has been shown to underlie the α1-adrenoceptor-activated non-selective cation channel in vascular smooth muscle cells and the vasopressin-activated cation channel in the aorta [23,26]. TRPC6 is directly activated by DAG, independently of protein kinase C [27] (also a feature of TRPC3, TRPC7, TRPC2 and TRPC5) and is stimulated by intracelluar Ca^{2+} via a calmodulin-dependent mechanism. Its activity is reduced by protein kinase C-mediated serine phosphorylation, but stimulated by Fyn tyrosine kinase. Pharmacologically, TRPC6 is opened by flufenamate, but inhibited by the non-selective SAC blockers La^{3+}, Gd^{3+}, GsTMx4 [28,29].

Surprisingly, TRPC6 knock-out mice show an elevated blood pressure, enhanced agonist-induced contractility of isolated aortic rings, and enhanced myogenic contractility in cerebral arteries [30]. Furthermore, TRPC3 expression is significantly increased in smooth muscle cells from $TRPC6^{-/-}$ mice. These cells have a higher basal cation entry and consequently a more depolarized membrane potential [30]. This depolarizing current is abolished by TRPC3 specific siRNA [30]. These results indicate that constitutively active TRPC3 channels are up-regulated in $TRPC6^{-/-}$ mice. Remarkably, the acute hypoxic vasoconstriction of pulmonary arteries, unlike the sustained contraction, is completely blunted in $TRPC6^{-/-}$ mice [31], indicating a specific involvement of TRPC6.

In humans, gain of function mutations of TRPC6 which increase Ca^{2+} influx lead to focal and segmental glomerulosclerosis (FSGS) in the kidney [32,33]. TRPC6 was identified as an essential component of the glomerular slit diaphragm, where it interacts with podocin [34]. Mutations in podocin similarly cause disruption of the kidney filter and focal segmental glomerulosclerosis. Finally, the OAG-induced currents are significantly augmented in oocytes coexpressing TRPC6 and podocin [34]. These observations indicate that increased activity of TRPC6 is associated with FSGS.

2. TRPC6 and arterial mechanotransduction

TRPC6 has recently been implicated in arterial pressure sensing [3,4]. Antisensense oligonucleotides to TRPC6 decrease TRPC6 protein expression and attenuate arterial smooth muscle depolarization and constriction caused by elevated intraluminal pressure in cerebral arteries [3]. Suppressing the expression of TRPC6 also reduces the amplitude of the current elicited by cell swelling using a hypotonic solution [3].

TRPC6 has thus been proposed to be a direct sensor of both mechanically and osmotically induced membrane stretch [1,3] (Fig. 1). Pressure-induced activation of TRPC6 in transiently transfected HEK 293 or CHO cells was recorded in the presence of the phospholipase C inhibitor U73122 [1]. The stretch and OAG-mediated opening of TRPC6 is inhibited by the tarantula peptide, GsMTx-4, known to specifically inhibit mechanosensitive channels by modifying the external lipid-channel boundary [1] (Fig. 1).

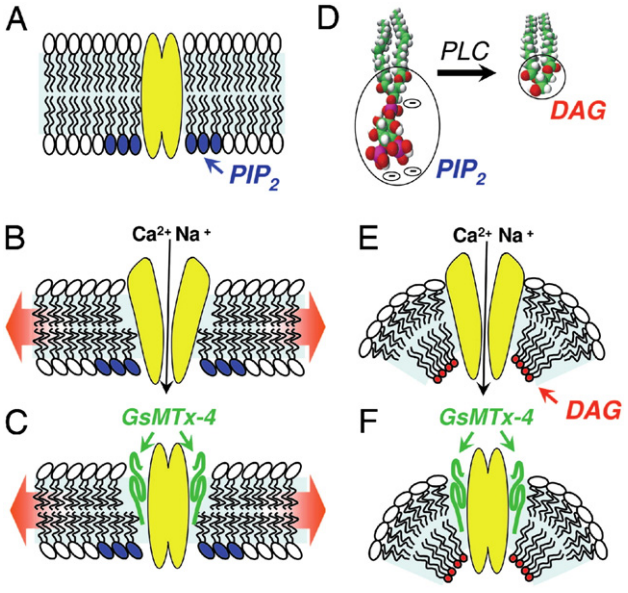

Fig. 1. Model of TRPC6 activation by stretch or diacylglycerol and inhibition by the tarantula peptide, GsMTx-4. (A) The resting closed state of TRPC6. (B) Stretch induces a conformational change in TRPC6, resulting in its transition to the open state. (C) GsMTx-4 peptide inserts in the outer membrane leaflet and inhibits stretch-induced opening of TRPC6. (D) Receptor activation of phospholipase C hydrolyzes PIP_2 and releases DAG. (E) DAG in the inner leaflet induces a convex membrane curvature and opening of TRPC6. (F) GsMTx-4 inhibits channel opening by DAG. Figure from [1].