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In vivo TRPC functions in the cardiopulmonary vasculature

Alexander Dietrich [a,*], Hermann Kalwa [a], Beate Fuchs [b], Friedrich Grimminger [b], Norbert Weissmann [b], Thomas Gudermann [a]

[a] *Institute for Pharmacology and Toxicology, School of Medicine, University of Marburg, 35043 Marburg, Germany*
[b] *University of Giessen Lung Center (UGLC), Department of Internal Medicine II/V, 35392 Giessen, Germany*

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Abstract

Cardiovascular diseases are the leading cause of death in the industrialized countries. The cardiovascular system includes the systemic blood circulation, the heart and the pulmonary circulation providing sufficient blood flow and oxygen to peripheral tissues and organs according to their metabolic demand. This review focuses on three major cell types of the cardiovascular system: myocytes of the heart as well as smooth muscle cells and endothelial cells from the systemic and pulmonary circulation. Ion channels initiate and regulate contraction in all three cell types, and the identification of their genes has significantly improved our knowledge of signal transduction pathways in these cells. Among the ion channels expressed in smooth muscle cells, cation channels of the TRPC family allow for the entry of Na^+ and Ca^{2+}. Physiological functions of TRPC1, TRPC3, TRPC4, TRPC5, TRPC6 and TRPC7 in the cardiovascular system, dissected by down-regulating channel activity in isolated tissues or by the analysis of gene-deficient mouse models, are reviewed. Possible functional roles and physiological regulation of TRPCs as homomeric or heteromeric channels in these cell types are discussed. Moreover, TRP channels may also be responsible for pathophysiological processes of the cardiovascular system like hypertension as well as cardiac hypertrophy and increased endothelial permeability.

Keywords: TRPC; Heart; Systemic circulation; Pulmonary circulation; Smooth muscle cells; Endothelial cells; Cardiomyocytes

1. Introduction

Cardiovascular disease is the leading cause of death for both men and women in the industrialized countries and accounts for nearly 40% of all deaths. The cardiovascular system includes the systemic blood circulation and the heart providing a sufficient blood flow to peripheral tissues and organs based on their metabolic demand. It also includes the pulmonary circulation which supplies the systemic blood circulation with oxygen and removes carbon dioxide from it. This review will focus on three major cell types of the cardiovascular system: myocytes of the heart, as well as smooth muscle cells and endothelial cells from the systemic and pulmonary circulation (Fig. 1A). Ion channels initiate and regulate contraction, and the identification of their genes has significantly improved our knowledge of signal transduction pathways in these cells. Evidence is also being accumulated for the role of cation influx in slowly progressing remodelling processes of the cardiovascular system manifested as cardiac hypertrophy, cardiomyopathy, arteriosclerosis, pulmonary hypertension, and other proliferative/degenerative disorders. Apart from voltage-gated calcium channels, non-selective cation channels have also been identified as important players in the regulation of vascular tone and cell proliferation by mediating the entry of cations like $Ca^{2+}$and Na^+.

The family of classical or canonical TRP cation channels (TRPC) is composed of proteins that are highly related to *Drosophila* TRP, the founding member of the TRP superfamily which are involved in the photoreceptor signal transduction pathway (see Refs. [1,2] for a recent review).

* Corresponding author at: Institut für Pharmakologie und Toxikologie, Philipps-Universität Marburg, Karl-von-Frisch Strasse 1, 35043 Marburg, Germany. Tel.: +49 6421 28 65105; fax: +49 6421 28 65600.
E-mail address: dietrica@staff.uni-marburg.de (A. Dietrich).

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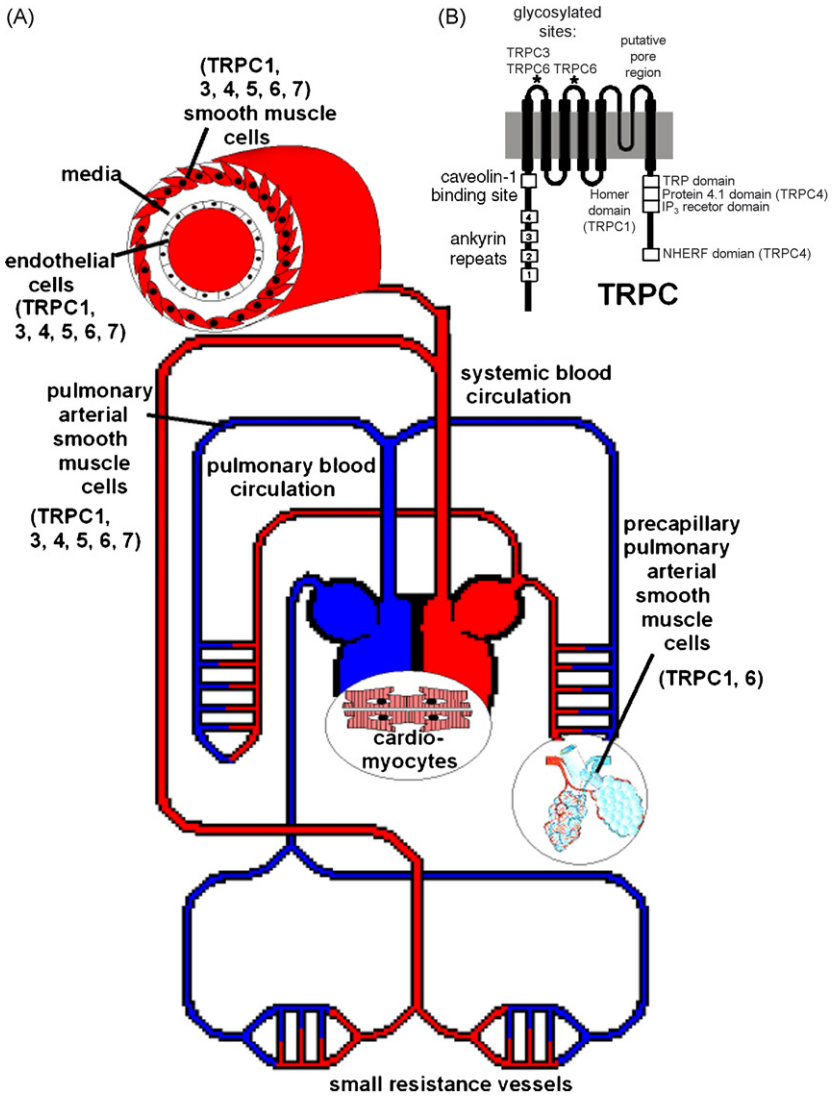

Fig. 1. TRPC expression and functional characterization in the cardiovascular system. (A) Schematic drawing of the cardiovascular system with the localization of the analyzed cell types and their TRPC expression pattern. For TRPC expression in cardiomyocytes see text and Table 1. (B) Plasma membrane topology of and functional domains in TRPC channels. TRPC channels have four ankyrin repeats, glycosylation site 1 in TRPC1, 3, and 6, glycosylation site 2 in TRPC6, a TRP box, an 4.1 protein binding region in TRPC4, an IP_3-receptor binding site and a NHERF binding domain in TRPC4. See text for details.

Its seven family members can be subdivided into subfamilies on the basis of their amino acid homology. While TRPC1 and TRPC2 are almost unique, TRPC4 and TRPC5 share a ~65% homology in their group. TRPC3, 6 and 7 form a structural and functional TRPC3/6/7 subfamily sharing a 70–80% homology and their direct activation by diacylglycerol (DAG) [3]. Thus, TRPC3/6/7 are gated by agonist-induced receptor activation and subsequent phospholipase C activation resulting in DAG production from phosphatidylinositol 4,5-bisphosphate (PIP_2) and mediate receptor operated cation entry (ROC). For the other TRPC channels (TRPC1, 4 and 5) as well as for TRPC3 and TRPC7 store-operated cation entry (SOC) mechanisms are discussed. These types of channels are proposed to be regulated by the filling status of intracellular Ca^{2+} stores. Inositol-1,4,5 trisphosphate (IP_3)-induced store depletion through IP_3 receptors localized at the membrane of the endoplasmatic reticulum is mimicked by application of thapsigargin or cyclopiazonic acid (CPA) which inhibits ATP-driven SERCA (for sarcoplasmic/endoplasmatic reticulum Ca^{2+}) pumps resulting in Ca^{2+} leakage from intracellular stores and subsequent Ca^{2+} entry from extracellular compartments. The underlying mechanisms of this signalling pathway are not known with certainty so far, but there are at least four general theories (reviewed in Refs. [3,4]: (1) a calcium influx factor (CIF), which would activate SOC channels is released from the ER after store depletion, (2) agonist-bound IP_3 receptors in close vicinity to the plasma membrane are able to activate TRPC channels by direct protein-protein interaction, (3) a TRPC channel transported in a cytoplasmic vesicle is thought to fuse with the