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Ion channels and transporters as therapeutic targets in the pulmonary circulation

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ABSTRACT

Pulmonary circulation is a low pressure, low resistance, high flow system. The low resting vascular tone is maintained by the concerted action of ion channels, exchangers and pumps. Under physiological as well as pathophysiological conditions, they are targets of locally secreted or circulating vasodilators and/or vasoconstrictors, leading to changes in expression or to posttranslational modifications. Both structural changes in the pulmonary arteries and a sustained increase in pulmonary vascular tone result in pulmonary vascular remodeling contributing to morbidity and mortality in pediatric and adult patients. There is increasing evidence demonstrating the pivotal role of ion channels such as K^+ and Cl^- or transient receptor potential channels in different cell types which are thought to play a key role in vasoconstrictive remodeling. This review focuses on ion channels, exchangers and pumps in the pulmonary circulation and summarizes their putative pathophysiological as well as therapeutic role in pulmonary vascular remodeling. A better understanding of the mechanisms of their actions may allow for the development of new options for attenuating acute and chronic pulmonary vasoconstriction and remodeling treating the devastating disease pulmonary hypertension.

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Abbreviations: 5-HT, 5-hydroxytryptamine, i.e. serotonin; ADM, adrenomedullin; ASIC, acid-sensing ion channel; BK_{Ca}, large conductance Ca^{2+}-activated K^+ channel; CFTR, cystic fibrosis transmembrane regulator; CGRP, calcitonin gene-related peptide; CIC, voltage-gated Cl^- channel; ENaC, epithelial Na^+ channel; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; GPCR, G protein coupled receptor; HPV, hypoxic pulmonary vasoconstriction; IK_{Ca}, intermediate conductance Ca^{2+}-activated K^+ channel; IK_v, voltage-gated K^+ current; iNOS, inducible nitric oxide synthase; IP3, inositol triphosphate; IP3R, inositol triphosphate receptor; IPAH, idiopathic pulmonary arterial hypertension; K_{ATP}, ATP-sensitive K^+ channel; K_{Ca}, Ca^{2+}-activated K^+ channel; K_{ir}, inward rectifier K^+ channel; K_v, voltage-gated K^+ channel; NCX, Na^+/Ca^{2+} exchanger; NHE, Na^+/H^+ exchanger; NKA, Na^+/K^+ ATPase; PA, pulmonary artery; PAEC, pulmonary arterial endothelial cells; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PASMC, pulmonary arterial smooth muscle cell; PDE, phosphodiesterase; PDGF, platelet-derived growth factor; PGI_2, prostacyclin; PH, pulmonary hypertension; PKA, cAMP-dependent protein kinase; PKC, protein kinase C; PKG, cGMP-dependent protein kinase; PLC, phospholipase C; PMCA, plasma membrane Ca^{2+} ATPase; PM-SR, plasma membrane-sarcoplasmic reticulum; PVR, pulmonary vascular resistance; ROCE, receptor-operated Ca^{2+} entry; RyR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum Ca^{2+} ATPase; SERT, serotonin transporter; sGC, soluble guanylate cyclase; SK_{Ca}, small conductance Ca^{2+}-activated K^+ channel; SMC, smooth muscle cell; SOCE, store-operated Ca^{2+} entry; SR, sarcoplasmic reticulum; STIM, stromal interaction molecule; TASK, TWIK-related acid-sensitive K^+ channel; TK, tyrosine kinase; TMD, transmembrane domain; TMEM16A, Ca^{2+}-activated Cl^- channel; TRPC, transient receptor potential canonical; TRPV, transient receptor potential vanilloid; VGCC, voltage-gated Ca^{2+} channel; VIP, vasoactive intestinal peptide.

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1. Introduction

For there are indeed many who openly confess that the greatest part of those things which we do know is the least of the things which we know not.

[(William Harvey, 1628)]

The pulmonary circulation is unique compared with systemic vascular beds. During normoxic conditions, the pulmonary circulation is at low pressure and vasodilated — compared with the high-pressure systemic circulation. The high flow favors pulmonary gas exchange and the low pressure allows the right ventricle to operate at low energy cost. The most significant difference in the regulation between all systemic organs and the lung is that hypoxia elicits vasoconstriction of small resistance vessels in the pulmonary circulation (Bradford & Dean, 1894). This physiological response that diverts mixed desaturated venous blood away from hypoxic alveoli to better ventilated lung segments, thus optimizing the matching of perfusion and ventilation and preventing arterial hypoxemia, is called hypoxic pulmonary vasoconstriction (HPV) (von Euler & Liljestrand, 1946). In contrast, in the systemic circulation, low oxygen tension leads to vasodilatation that increases oxygen delivery to the tissue. There is also a significant anatomical difference between the pulmonary and the systemic circulation. In the systemic circulation, the arterioles have a thick layer of smooth muscle cells (SMC), whereas no such layer exists in the pulmonary arterioles after fetal life. Instead, the larger, muscular arteries merge into small, partially muscularized vessels that have a very low perfusion resistance and directly feed the pulmonary capillaries. The other significant difference concerns blood pressure regulation. In the systemic circulation, arterial pressure is the variable with the most extensive regulation system. The systemic feedback control center for the so-called arterial and low-pressure baroreflexes is located in the brain stem, and the various associated changes in the heart, vessel tone and endocrine secretion are quite well understood. In contrast, the pressure in the pulmonary circulation is not regulated by the central nervous system. During normoxia both at supine rest and during exercise the vessels are very much in a relaxed state with low pulmonary vascular resistance (PVR) (Kovacs et al., 2012). In resting healthy subjects in normoxia the pulmonary arterial pressure (PAP) is within a narrow range, nearly independent of sex, age, race, and posture (Kovacs et al., 2009). On the other hand, during exercise, this pressure, at least in relative terms, increases much more than the systemic pressure and this response depends very much on age (Kovacs et al., 2009). It is well established that an elevated pulmonary pressure is associated with increased mortality. This is true not only for pulmonary arterial hypertension (PAH) (Galie et al., 2009b) but also for patients with chronic obstructive pulmonary disease (COPD) (Weitzenblum et al., 1981; Oswald-Mammosser et al., 1995; Antonelli Incalzi et al., 1997; Andersen et al., 2012; Hurdman et al., 2013), idiopathic lung fibrosis (IPF) (Hamada et al., 2007; Glaser et al., 2013), cardiomyopathy (Lewis et al., 2011) and isolated diastolic dysfunction of the left ventricle (Lam et al., 2009; Burke et al., 2014). However, there are multiple mechanisms that can lead to increased PAP, which may be located not only in the pulmonary vessels but also in the heart, systemic circulation (high cardiac output), and lung mechanics.

Impressive advances in the understanding of the vascular tone have been made. Many molecular mechanisms of hypoxia signaling and how changes in environmental oxygen tension are translated into signals within the vascular cells have been discovered (Tuder et al., 2013), however, there are also many unsolved questions. Ion channels play an important role both in the systemic and the pulmonary vasculature. While they may be involved in hypoxic vasodilatation of systemic vessels, they are instrumental for hypoxic vasoconstriction of the pulmonary arteries (PA) (Weir & Olschewski, 2006). Indeed, the signal transducers and activators of ion channels, exchangers and pumps in the vascular cells control the vascular tone and diverse cellular processes including Ca^{2+} homeostasis, cellular growth and apoptosis. In pulmonary vascular diseases, such as PAH, an important role of K^+ channels has been suggested by Yuan et al. in 1998 (Yuan et al., 1998b) and this view has been further supported by the discovery of two-pore domain K^+ channels, as the TWIK-related acid-sensitive K^+ channel-1 (TASK-1) controls the resting membrane potential of human pulmonary arterial smooth muscle cells (PASMC) (Olschewski et al., 2006). In agreement with this, mutations in the KCNK3 gene, which encodes the TASK-1 K^+ channel, have been shown to cause hereditary PAH (Ma et al., 2013; Olschewski et al., 2013). Changes in the phosphorylation state of this channel by the tyrosine kinase (TK) c-Src mediate the hypoxia sensitivity of the channel (Nagaraj et al., 2013).

In this review, we give an overview on ion channels, exchangers and pumps and discuss their potential implication in pulmonary vascular diseases as well as therapeutic strategies.

2. Ion channels and transporters in the pulmonary artery

The ability to maintain intra- and extracellular ion concentrations at physiological levels is essential for cell homeostasis. Moreover, a controlled ion flux through ion channels and transporters is necessary for many fundamental physiological processes, including generation of heart rhythm and function of muscles, immune cells, and nerve cells. Ion channels and transporters are membrane-bound proteins responsible for ion flow between the two sides of the cell membrane, as well as cell organelle membranes. They are selective for a particular ion and are either constitutively active or modulated by certain stimuli such as signaling molecules or membrane potential changes. Ion channels form a hydrophilic pore allowing ions to pass through directly; some of them favor a certain direction of ion flux (inward or outward rectification, Fig. 1*A and B*) while others allow both influx and efflux equally, characterized by a nearly linear I–V curve (no rectification, Fig. 1*C*). Transporters move ions by changing their protein conformation which requires energy either from ATP hydrolysis or moving another ion down on its concentration gradient. The resulting changes in membrane potential or spatio-temporal changes in the concentration of a certain ion (e.g. Ca^{2+} waves) trigger key events like muscle contraction, cell communication, proliferation and apoptosis.

2.1. Hyperpolarization and resting Ca^{2+} homeostasis in pulmonary artery smooth muscle cells

The membrane potential of PASMC is an important control mechanism of pulmonary arterial tone and hence arterial diameter. These cells have a steady or slowly oscillating resting membrane potential around −65 to −50 mV in vitro (Platoshyn et al., 2004), close to the predicted equilibrium potential for K^+ ions, which is ~−85 mV (at a physiological extracellular K^+ concentration of 5 mM) (Nelson & Quayle, 1995). High intracellular and low extracellular K^+ concentrations are maintained mostly by the Na^+/K^+ pump function, while the opening of K^+ channels hyperpolarizes the membrane and counterbalances depolarizing forces. The following subsections and the left side of Fig. 2 give an overview on channels and transporters with hyperpolarizing and/or Ca^{2+} removing roles.

2.1.1. K^+ channels

Various distinct K^+ channels have been identified in terms of voltage dependence, rate of activation and inactivation, as well as pharmacology and genetics. At least 8 families of K^+ channel α-subunit genes have been cloned and identified, and each of these families contains a large number of individual members, which means in total over 60 different subunits. In the pulmonary vasculature, electrophysiology allows the characterization of numerous voltage-gated K^+ channels (K_v), the Ca^{2+}-activated K^+ channel (K_{Ca}), M-type K^+ channels, the inward rectifier K^+ channel (K_{ir}), the ATP-sensitive K^+ channel (K_{ATP}) and

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