Title

Regulation of microvascular function by voltage-gated potassium channels: New tricks for an “ancient” dog

Journal

Microcirculation, 25(1)

ISSN

1073-9688

Authors

Nystoriak, Matthew A
Navedo, Manuel F

Publication Date

2018

DOI

10.1111/micc.12435

Peer reviewed

HHS Public Access

Author manuscript

Microcirculation. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Microcirculation. 2018 January ; 25(1): . doi:10.1111/micc.12435.

Regulation of microvascular function by voltage-gated potassium channels: new tricks for an “ancient” dog

Matthew A. Nystoriak[1] and **Manuel F. Navedo**[2]

[1]Diabetes and Obesity Center, Institute of Molecular Cardiology, Department of Medicine, University of Louisville, Louisville, KY 40202

[2]Department of Pharmacology, University of California, Davis, Davis, CA, 95616

Abstract

Arterial tone is tightly regulated by a variety of potassium (K^+) permeable ion channels at the sarcolemma of vascular smooth muscle cells. In particular, several types of voltage-gated K^+ (K_V) channels provide a significant hyperpolarizing influence and serve to oppose pressure and agonist-induced membrane depolarization to promote smooth muscle relaxation and augmentation of vascular diameter and blood flow. In recent years, a number of studies have underscored previously unknown roles for particular K_V subunits, new modes of channel regulation, and distinct cellular functions for these channels during physiological and pathological conditions. In this overview, we highlight articles contained in this Special Topics Issue that focus on the latest, most exciting advancements in the field of K_V channels in the microcirculation. The collection of articles aims to highlight important new discoveries and controversies in the field of vascular K_V channels as well as to shed light on key questions that require additional investigation.

Keywords

Arteries; Smooth Muscle Cells; Ion Channels; Membrane Potential

Overview

The movement of blood through the vascular network to deliver oxygen and nutrients to tissues of the body is governed by Poiseuille’s law, which states that flow through a tube is highly dependent upon its diameter. Small arteries and arterioles are highly equipped with numerous cellular processes that tightly regulate their diameter and many of these systems rely on the dynamic modulation of vascular smooth muscle membrane potential. The degree of membrane depolarization determines the open state probability of voltage-dependent calcium channels and the concentration of global intracellular calcium that is directly linked,

Correspondence: Dr. Matthew A. Nystoriak, Diabetes and Obesity Center, Delia Baxter Bldg., 580 S. Preston St., Rm 421B, University of Louisville, Louisville KY 40202. matthew.nystoriak@louisville.edu, Tel. 502-852-6024, Fax. 502-853-3663; Dr. Manuel F. Navedo, Department of Pharmacology, University of California, Davis, One Shields Avenue, Tupper Hall Room 2420, Davis, CA 95616. mfnavedo@ucdavis.edu, Tel. 530-752-6880, Fax. 530-752-7710.

DR. MATTHEW A NYSTORIAK (Orcid ID: 0000-0001-8872-158X)

DR. MANUEL F NAVEDO (Orcid ID: 0000-0001-6864-6594)

via calcium-calmodulin activation of myosin light chain kinase, to the degree of smooth muscle contractility. Among the many processes that control the membrane potential of vascular smooth muscle, voltage-gated potassium (K_V) channels have long been considered key mediators of this process. By opposing pressure and agonist-induced membrane depolarization, K_V channels help fine-tune smooth muscle excitability. Accordingly, activation of these channels helps promote smooth muscle relaxation and augmentation of vascular diameter and blood flow. This is critical to counter the development of excessive vascular tone, which could ultimately lead to ischemic conditions and on a systemic level raise total vascular resistance.

Extensive research efforts have centered on understanding how K_V channels are regulated in the vasculature and how this may modulate vascular reactivity in health and disease. Despite the well-known presence of multiple K_V subunits, so often however, these efforts examine only the function of prototypical K_V subunits (e.g. K_V1) on a specific vessel, perhaps due to complexity in the approach, lack of specific inhibitors and/or inherited difficulties of examining and making sense of potentially divergent mechanisms in multiple vascular beds. Moreover, direct examination of K_V subunits and their function in the microcirculation has been hindered, at least in part, by the challenges of dissecting out healthy small vessels and vascular smooth muscle from often convoluted regions of any given tissue. Yet, our community has forge ahead to uncover new fundamental roles of different K_V subunits as well as mechanisms regulating their expression, trafficking to the surface membrane and function during physiological and pathological conditions and in different species.

In the series of articles contained in this Special Topics Issue (STI), recent advances in several important areas surrounding K_V-mediated regulation of (micro)vascular function are highlighted. The issue begins with a review by Dr. William F. Jackson (UMIC-2017-0087: K_V channels and the regulation of vascular smooth muscle tone) presenting historical context and current knowledge, and also defining key gaps related to the expression, function and regulation of K_V channels in vascular smooth muscle and their contribution to vascular reactivity. The next three articles examine mechanisms underlying the surface abundance and regulation of K_V channels in vascular smooth muscle. Hasan and Jaggar (UMIC-2017-0074; K_V channel trafficking and control of vascular tone) explore the exciting field of how dynamic trafficking of K_V subunits influences surface abundance of particular subunits and channel function to control vascular tone. Rhee and Rusch (UMIC-2017-0081; Voltage-gated K^+ channels in the cerebral circulation) provide a timely discussion on evidence supporting the regulation of K_V channels by β-adrenergic signaling through the formation of a novel macromolecular signaling complex in vascular smooth muscle. Dwenger and colleagues (UMIC-2017-0088; Coronary microvascular K_V channels as regulatory sensors of intracellular pyridine nucleotide redox potential) then examine our current knowledge on how coronary K_V channels are modulated by redox signaling and provide a compelling argument for a role for auxiliary K_V beta subunits in matching blood flow with local oxygen demands. The subsequent four papers suitably dissect new observations on K_V function. Byron and Brueggemann (UMIC-2017-0064; K_V7 potassium channels as signal transduction intermediates in the control of microvascular tone) provides a comprehensive examination of the emerging, yet increasingly controversial role of K_V7 channels in the control of vascular smooth muscle function and vascular excitability. Lopez-

Lopez and colleagues (UMIC-2017-0069; K_V channels in vascular smooth muscle cell proliferation) argues that the expression and function of specific K_V subunits contributes, through unique mechanisms, to vascular smooth muscle cell proliferation and migration, as well as the phenotypic switching that may occur during pathological conditions. Nishijima and colleagues (UMIC-2017-0091; K_V1 channel expression and vasomotor function in human coronary resistance arteries) report a distinctive study examining the expression, function and regulation of K_V channels in human coronary vascular smooth muscle that may reveal unique mechanisms modulating these channels in the human vasculature. Dabertrand and colleagues (UMIC-2017-0117; The yin and yang of K_V channels in cerebral small vessel pathologies) then elegantly discuss the involvement of K_V channels in control of cerebral hemodynamics and their implication in cerebrovascular dysfunction. Extending on the pathological theme, the final articles bring this STI full circle by examining current knowledge and areas of new inquiry for pathologies associated with K_V channels in vascular smooth muscle. Accordingly, Nieves-Cintrón and colleagues (UMIC-2017-0071; Regulation of voltage-gated potassium channels in vascular smooth muscle during hypertension and metabolic disorders) comprehensively examine our current knowledge on how K_V channel expression, function and regulation is impaired in several pathological conditions and how this impacts the microcirculation. Gollasch, Welsh and Schubert (UMIC-2017-0083; Perivascular adipose tissue and the dynamic regulation of K_V7 and K_{ir} channels: Implications to resistant hypertension) finally review the regulation of K_V channels by perivascular adipose tissue and how targeting of particular K_V subunits and other K^+ channels may be exploited for the development of novel therapeutic options to treat vascular complications associated with hypertension, metabolic disorder and obesity. All articles in this collection push the boundaries of knowledge, define critical gaps and provide innovative ideas and solutions that can guide the field of vascular ion channel biology forward for the next decade.

Perspectives

A variety of voltage-gated potassium (K_V) channel subtypes expressed in vascular smooth muscle control membrane potential of these cells, and are therefore critical regulators of (micro)vascular diameter. The collection of articles presented in this issue provides in depth discussion of the latest research which advances our knowledge of: 1) how specific K_V channel subtypes contribute to the regulation of vascular tone, 2) novel modes of K_V channel functional regulation, and 3) the role of K_V channel modulation in disease states, and also describes new opportunities for future research that may improve therapeutic strategies towards more effective maintenance of adequate blood flow.

Acknowledgments

This work was supported by NIH grants R01-HL098200 and R01-HL121059 and AHA grant 14GRNT18730054 (to MFN), and NIH grants T32HL086350 and P20GM103492 and AHA 16SDG27260070 (to MAN).

References

William F. Jackson, **UMIC-2017-0087**: KV channels and the regulation of vascular smooth muscle tone.

Raquibil Hasan and Jonathan H. Jaggar, **UMIC-2017-0074**; KV channel trafficking and control of vascular tone.

Sung W. Rhee and Nancy J. Rusch, **UMIC-2017-0081**; Voltage-gated K^+ channels in the cerebral circulation.

Marc M. Dwenger, Vahagn Ohanyan, Manuel F. Navedo and Matthew A. Nystoriak, **UMIC-2017-0088**; Coronary microvascular KV channels as regulatory sensors of intracellular pyridine nucleotide redox potential.

Kenneth L. Byron and Lyubov I. Brueggemann, **UMIC-2017-0064**; KV7 potassium channels as signal transduction intermediates in the control of microvascular tone.

José R. López-López, Pilar Cidad and M. Teresa Pérez-García, **UMIC-2017-0069**; KV channels in vascular smooth muscle cell proliferation.

Yoshinori Nishijima, Ankush Korishettar, Dawid S. Chabowski, Sheng Cao, Xiaodong Zheng, David D. Gutterman and David X. Zhang, **UMIC-2017-0091**; KV1 channel expression and vasomotor function in human coronary resistance arteries.

Masayo Koide, Arash Moshkforoush, Nikolaos M. Tsoukias, David C. Hill-Eubanks, George C. Wellman, Mark T. Nelson and Fabrice Dabertrand, **UMIC-2017-0117**; The yin and yang of KV channels in cerebral small vessel pathologies.

Madeline Nieves-Cintron, Arsalan U. Syed, Matthew A. Nystoriak and Manuel F. Navedo, **UMIC-2017-0071**; Regulation of voltage-gated potassium channels in vascular smooth muscle during hypertension and metabolic disorders.

Maik Gollasch, Donald G. Welsh and Rudolf Schubert, **UMIC-2017-0083**; Perivascular adipose tissue and the dynamic regulation of KV7 and Kir channels: Implications to resistant hypertension.