A New Insight Into the Pathogenesis of Coronary Vasospasm

Hiroshi Hibino, Yoshihisa Kurachi

To elucidate the control mechanisms of coronary vascular tone is one of the central interests in cardiac pathophysiology, because ischemic heart disease is one of the major causes of death in many countries. Although the coronary vascular tone is finally determined by the contractile state of smooth muscle, exo-smooth muscle mechanisms including autonomic nerves, endothelial cells, and blood cells have been shown indispensable for the control. Particular types of receptors, ion channels, and intracellular signal-cascades exist in coronary smooth muscle cells and mediate the controls by exo-smooth muscle elements (Figure). For example, stimulation of \( \alpha_1 \)-adrenergic receptor, which is physiologically achieved by noradrenaline (NA) released from sympathetic presynapses, increases the intracellular \( \text{Ca}^{2+} \) (\( \text{Ca}^{2+} \)) via phosphatidylinositol (PI)-turnover and also probably via opening of receptor-activated \( \text{Ca}^{2+} \)-permeable TRP channel. Membrane depolarization does so via opening voltage-dependent \( \text{Ca}^{2+} \) channels. The augmentation of \( \text{Ca}^{2+} \) results in contraction of the smooth muscle cells and thus constriction of the coronary artery.1 Activation of \( \beta_2 \)-adrenergic receptor, in turn, inhibits the coronary smooth muscle contraction through protein-kinase A pathway.2 The contraction is also suppressed by protein-kinase G activated by a dilating factor, nitric oxide (NO), which is produced in the endothelial cells.

In addition to these elements, it has been recently revealed that various types of ATP-sensitive \( \text{K}^+ \) (\( \text{K}_{\text{ATP}} \)) channels distribute not only in smooth muscle cells but also in nerve termini and endothelial cells of the coronary artery3–10 (Figure). At present, it has not been fully elucidated how these \( \text{K}_{\text{ATP}} \) channels play respective roles in the control of coronary artery tone. Yet without direct evidence, it has been widely considered that \( \text{K}_{\text{ATP}} \) channel in coronary smooth muscle cells is the key player. Two lines of experiments using gene-targeting mice for either Kir6.1 or SUR2 have been thought to provide the somehow final evidence for this notion.11,12 In this issue of Circulation Research, Kakkar et al has reported the observations to question the current consensus.13

The \( \text{K}_{\text{ATP}} \) channels distribute in a variety of cells and associate with diverse cellular functions such as insulin secretion from pancreatic ß-cells, shortening of cardiac action potential and cellular loss of \( \text{K}^+ \) during metabolic inhibition in the heart, regulation of skeletal muscle excitability, control of vasculature tone, and neuronal function.14–16 \( \text{K}_{\text{ATP}} \) channels are hetero-octamers comprising a pore-forming inwardly rectifying \( \text{K}^+ \) (Kir) channel subunit, Kir6.x, and a regulatory subunit, sulfonylurea receptor (SURx).17–22 Whereas SURs contribute to the regulation of \( \text{K}_{\text{ATP}} \) channels by various pharmacological agents and intracellular nucleotides, Kir6.xs determine the single-channel properties and the sensitivity to intracellular ATP (ATP), Kir6.2/SUR1 and Kir6.2/SUR2A represent the pancreatic ß-cell and cardiac and skeletal-myocyte \( \text{K}_{\text{ATP}} \) channels, respectively.17,19 These channels are inhibited by ATP, in micromolar range and shows a single-channel conductance of \( \approx 80 \, \text{pS} \) with 150 mmol/L extracellular \( \text{K}^+ \) (\( [\text{K}^+]_o \)). On the other hand, the channel comprising Kir6.1 and SUR2B, an alternatively spliced form of SUR2A, reconstituted the vascular \( \text{K}_{\text{ATP}} \) channel (or alternatively called \( \text{K}_{\text{NADP}} \) channel),20,21 which does not open spontaneously in the absence of ATP, and requires intracellular nucleoside diphosphates, such as ADP, GDP, and UDP, for activation.23,24 The single-channel conductance of the \( \text{K}_{\text{NADP}} \) channel is \( \approx 40 \, \text{pS} \) with 150 mmol/L [\( \text{K}^+]_o \]. Physiologically, this \( \text{K}_{\text{NADP}} \) channel appears to be involved in regulation of resting coronary tone, coronary vasodilatory response to exercise and hypoxia, and endotopic vasodilatation.25–27

The mutant mice lacking either Kir6.1- or SUR2-gene lost the \( \text{K}_{\text{NADP}} \)-conductance from their coronary smooth muscle cells, ensuring that the vascular \( \text{K}_{\text{ATP}} \) channel (ie, \( \text{K}_{\text{NADP}} \) channel) is of an assembly of Kir6.1 and SUR2B.11,12 Both Kir6.1- and SUR2-null mice showed an identical phenotype of spontaneous coronary artery spasm and resultant sudden death, resembling Prinzmetal (or variant) angina in humans.11,12 Because of abundant expression of Kir6.1- and SUR2B-proteins in the vascular smooth muscle cells,3 dysfunction of the smooth muscle induced by loss of the \( \text{K}_{\text{NADP}} \) channel was thought to be the main cause of the phenotypes in the mice.

In this issue of Circulation Research, Kakkar et al attempted to test this hypothesis by generating and analyzing the transgenic mice that harbored the \( \text{K}_{\text{NADP}} \) channel only in vascular smooth muscle cells but not in any other cells.13 The authors engineered the SUR2-null mice to express SUR2B-protein specifically in vascular smooth muscle by using its specific promoter, SM22a. Kakkar et al observed not only protein expression but also restoration of the functional \( \text{K}_{\text{NADP}} \) channel in the smooth muscle cells. Unexpectedly, this selective expression of the \( \text{K}_{\text{NADP}} \) channel could not rescue the
The mechanism for control of vascular tone. Activation of voltage-gated Ca$^{2+}$ channel at the presynapse of sympathetic nerve increases intracellular Ca$^{2+}$, which triggers a release of norepinephrine (NE). NE stimulates adrenergic $\alpha_1$ receptor ($\alpha_1R$) in the smooth muscle cells and drives PI-turnover as described in this scheme. The intracellular Ca$^{2+}$, which flows into the cells via smooth-muscle’s Ca$^{2+}$ channel or moves from endoplasmic reticulum (ER), contracts the cells. The construction of smooth muscle cells is prevented by activation of adrenergic $\beta_2$ receptor ($\beta_2R$), or by a vasodilator NO that is produced by stimulation of receptors such as acetylcholine M1 receptor (M1R), adenosine type 2 receptor (A2R), and adrenergic $\alpha_2$ receptor ($\alpha_2R$). Functional K$_{ATP}$ channels are expressed in the presynapse, the smooth muscle cells, and endothelial cells. These K$_{ATP}$ channels are considered to be involved in vasodilatation process. Opening of presynaptic K$_{ATP}$ channel may hyperpolarize the membrane potential, which would close the Ca$^{2+}$ channel and attenuate NA release. Endothelial K$_{ATP}$ channel enhances A$_2$R- and $\alpha_2$R-induced dilatation by increasing NO-production. Activation of the K$_{ATP}$ channel in smooth muscle cells, which is also called K$_{dep}$ channel, has been believed to contribute to an inhibition of the constriction. However, the present study in this issue questions this hypothesis.

For example, application of the drugs that open K$_{ATP}$ channels (K$^+$ channel opening drugs [KCOs]) such as cromakalim and nicorandil dilates coronary artery.1,6,28,29 It has been believed that the action of KCOs on coronary artery can be attributed mainly to direct effect of these agents on vascular smooth muscle K$_{dep}$ channel containing SUR2B and Kir6.1. Based on this concept, a number of KCOs have been developed in the last several decades targeting ischemic heart diseases as well as hypertension.13 Among them only nicorandil is clinically proven to be effective in anti-anginal therapy, and many others cannot be adopted for clinical usage because of their significant side effects including lower-extremity edema.30 The study of Kakkar et al indicates the possibility that exo-smooth muscle mechanism might be involved in the action of some KCOs, which might result in clinically different effectiveness.13

The possible exo-smooth muscle mechanisms associated with K$_{ATP}$ channels in the coronary artery are: In the endothelial cells the K$_{ATP}$ channels are activated by adenosine and $\alpha_2$-AR stimulation and contribute to generation of NO.31,32 In the sympathetic neurons opening of presynaptic K$_{ATP}$ channels attenuates NA-release (Figure). KCOs would enhance these exo-smooth muscle actions of the K$_{ATP}$ channels and dilate the coronary artery. Thus, in Kir6.1- or SUR2-null mice, loss of the endothelial K$_{ATP}$ channels may attenuate NO production and provide vascular hypercontractility, resulting in coronary vasospasm. And lack of the K$_{ATP}$ channels in sympathetic neurons would decrease the threshold for NA release, which could associate with vasospasm. Indeed, the hyperactivity of sympathetic nerve is reported to cause coronary spasm in animals.33 To identify the mechanisms of the coronary vasospasm and sudden death in the SUR2- or Kir6.1-null mice, it is necessary to conduct further extensive studies, such as generation and analyses of transgenic mice that restore the K$_{ATP}$ channels in other specific regions. It should be also kept in mind that the mechanisms for the coronary vasospasm in humans and those in null-mice might not be the same. Nevertheless, it is certain that the present work by Kakkar et al has pointed out an important possibility that exo-smooth muscle K$_{ATP}$ channels may play critical roles in the pathogenesis of the coronary vasospasm and thus should be considered for development of new therapies.

Acknowledgments

Dr Kurachi’s laboratory is supported by following research grants and funds: Leading Project for Biosimulation “Development of models for disease and drug action” (to Y.K.), Grant in Aid for Scientific Research on Priority Areas 17079005 (to Y.K.), Grant in Aid for Scientific Research on Priority Areas 17081012 (to H.H.), Grant in Aid for Scientific Research A 15209008 (to Y.K.), Grant in Aid for Young Scientists (A) 17689012 (to H.H.), and Japan France Integrated Action Program (SAKURA) (to Y.K.), from the Ministry of Education, Science, Sports and Culture of Japan; and Uehara Memorial Foundation (to Y.K.).

References


**Key Words:** ATP-sensitive K+ (K_ATP) channels | coronary spasm | vascular constriction | K+ channel opening drugs (KCO)
A New Insight Into the Pathogenesis of Coronary Vasospasm
Hiroshi Hibino and Yoshihisa Kurachi

doi: 10.1161/01.RES.0000215571.12500.ab

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/98/5/579

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/