A New Insight Into the Pathogenesis of Coronary Vasospasm

Hiroshi Hibino, Yoshihisa Kurachi

The K<sub>ATP</sub> channels distribute in a variety of cells and associate with diverse cellular functions such as insulin secretion from pancreatic β-cells, shortening of cardiac action potential and cellular loss of K<sup>+</sup> during metabolic inhibition in the heart, regulation of skeletal muscle excitability, control of vasculature tone, and neuronal function. K<sub>ATP</sub> channels are hetero-octamers comprising a pore-forming inwardly rectifying K<sup>+</sup> (Kir) channel subunit, Kir6.x, and a regulatory subunit, sulfonylurea receptor (SURx). Whereas SURs contribute to the regulation of K<sub>ATP</sub> 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 β-cell and cardiac and skeletal- myocyte K<sub>ATP</sub> channels, respectively. These channels are inhibited by ATP, in micromolar range and shows a single-channel conductance of ~80 pS with 150 mmol/L extracellular K<sup>+</sup> ([K<sup>+</sup>]<sub>i</sub>). On the other hand, the channel comprising Kir6.1 and SUR2B, an alternatively spliced form of SUR2A, reconstituted the vascular K<sub>ATP</sub> channel (or alternatively called K<sub>NDP</sub> channel), which does not open spontaneously in the absence of ATP, and requires intracellular nucleoside diphosphates, such as ADP, GDP, and UDP, for activation. The single-channel conductance of the K<sub>NDP</sub> channel is ~40 pS with 150 mmol/L [K<sup>+</sup>]<sub>i</sub>. Physiologically, this K<sub>NDP</sub> channel appears to be involved in regulation of resting coronary tone, coronary vasodilatory response to exercise and hypoxia, and endotoxic vasodilatation.

The mutant mice lacking either Kir6.1- or SUR2-gene lost the K<sub>NDP</sub>-conductance from their coronary smooth muscle cells, ensuring that the vascular K<sub>ATP</sub> channel (ie, K<sub>NDP</sub> channel) is of an assembly of Kir6.1 and SUR2B. 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. Because of abundant expression of Kir6.1- and SUR2B-proteins in the vascular smooth muscle cells, dysfunction of the smooth muscle induced by loss of the K<sub>NDP</sub> 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 K<sub>NDP</sub> channel only in vascular smooth muscle cells but not in any other cells. The authors engineered the SUR2-null mice to express SUR2B-protein specifically in vascular smooth muscle by using its specific promoter, SM22α. Kakkar et al observed not only protein expression but also restoration of the functional K<sub>NDP</sub> channel in the smooth muscle cells. Unexpectedly, this selective expression of the K<sub>NDP</sub> channel could not rescue the

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From the Division of Molecular and Cellular Pharmacology, Department of Pharmacology, Graduate School of Medicine, Osaka University, Japan.

Correspondence to Dr Yoshihisa Kurachi, Division of Molecular and Cellular Pharmacology, Department of Pharmacology, Graduate School of Medicine, Osaka University, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan. E-mail ykurachi@pharma2.med.osaka-u.ac.jp

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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 α-receptor (α2R) 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 constriction of smooth muscle cells is prevented by activation of adrenergic β-receptor (β2R), or by a vasodilator NO that is produced by stimulation of agents such as acetylcholine M1 receptor (M1R), adenosine type 2 receptor (A2R), and adrenergic α-receptor (α2R). Functional KATP channels are expressed in the presynapse, the smooth muscle cells, and endothelial cells. These KATP channels are considered to be involved in vasodilatation process. Opening of presynaptic KATP channel may hyperpolarize the membrane potential, which would close the Ca\(^{2+}\) channel and attenuate NA release. Endothelial KATP channel enhances A2R- and α2AR-induced dilatation by increasing NO-production. Activation of the KATP channel in smooth muscle cells, which is also called K\(_{\text{ATP}}\) 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\(_{\text{ATP}}\) channels (K\(^{+}\) channel opening drugs [KCOs]) such as cromakalim and nicorandil dilates coronary artery.\(^{16,28,29}\) 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\(_{\text{ATP}}\) 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.\(^{15}\) 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\(_{\text{ATP}}\) channels in the coronary artery are: In the endothelial cells the K\(_{\text{ATP}}\) channels are activated by adenosine and α2-AR stimulation and contribute to generation of NO,\(^{31,32}\) in the sympathetic neurons opening of presynaptic K\(_{\text{ATP}}\) channels attenuates NA-release\(^{8}\) (Figure). KCOs would enhance these exo-smooth muscle actions of the K\(_{\text{ATP}}\) channels and dilate the coronary artery. Thus, in Kir6.1- or SUR2-null mice, loss of the endothelial K\(_{\text{ATP}}\) channels may attenuate NO production and provide vascular hypercontractility, resulting in coronary vasospasm. And lack of the K\(_{\text{ATP}}\) 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\(_{\text{ATP}}\) 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\(_{\text{ATP}}\) channels may play critical roles in the pathogenesis of the coronary vasospasm and thus should be considered for development of new therapies.

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