Protecting endothelial function: A novel therapeutic target of ATP-sensitive potassium channel openers

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See article by Wang et al. [7] (pages 497–503) in this issue.

Endothelial dysfunction is commonly observed in patients with hypertension, type II diabetes mellitus, and hypercholesteremia and is considered to be an early event in the changes accompanying atherosclerosis [1,2]. Disruption of normal endothelial function leads to loss of vasomotor control, reduced production of nitric oxide (NO), formation of a procoagulant surface, and promotion of inflammation [1,2]. These events may lead to destabilization of atherosclerotic plaques and could cause acute coronary syndrome. Indeed, recent clinical studies have demonstrated that endothelial dysfunction is a predictor for the development of cardiovascular events [3,4].

Endothelial cells express a diverse array of ion channels which play important roles in modulating cell function [5]. Since Noma first identified ATP-sensitive potassium (KATP) channels in cardiac myocytes, the physiological roles of KATP channels have been extensively studied in cardiac muscle and other tissues [5,6]. Endothelial KATP channels contribute to maintaining the resting membrane potential. In addition, they also regulate intracellular Ca²⁺ levels that affect the production and release of endothelial autacoids, e.g. NO and prostaglandins [5]. However, it has not been well clarified whether the activation of endothelial KATP channels can modulate the process of endothelial dysfunction.

An article by Wang et al. in this issue [7] demonstrates for the first time that a new ATP-sensitive potassium channel opener, iptakalim, enhances NO release associated with increased intracellular Ca²⁺ levels in cultured aortic endothelial cells. In addition, iptakalim inhibited endothelin-1 release and synthesis that correlated with reduced levels of mRNA for endothelin-1 and endothelin-converting enzyme. Interestingly, the authors also demonstrated that iptakalim inhibited the overexpression of adhesion molecules in aortic endothelial cells under metabolic disturbances induced by oxidized low-density lipoprotein, homocysteine, or hyperglycemia. They concluded that iptakalim is a promising drug that could protect against endothelial dysfunction through activating KATP channels in endothelial cells.

Iptakalim has been established as a newly selective KATP channel opener by substantial pharmacological, biochemical, and electrophysiological studies as well as a receptor-binding test [8]. Experimental studies demonstrated that iptakalim selectively relaxes small arteries in vitro and acts more strongly in hypertensive states. In addition, iptakalim can reverse hypertensive vascular and cardiac remodeling. A Phase II clinical study is ongoing for the development of iptakalim as an antihypertensive drug.

Nicorandil, a hybrid of nitrate and a KATP channel opener, is clinically used as a coronary vasodilator. A recent study demonstrated that nicorandil exerts anti-apoptotic effects through the opening of mitochondrial KATP channels in endothelial cells [9]. These experimental studies suggest that endothelial KATP channels play an important role in protecting endothelial function. Recently, the IONA study demonstrated that nicorandil therapy in patients with stable angina decreased the composite endpoint of death from coronary artery disease, non-fatal myocardial infarction, and unstable angina by 21% [10]. Since the benefit of nicorandil was observed even in patients who received nitrates, the IONA study strongly suggests that clinical benefits of nicorandil can
be attributed to the activation of KATP channels rather than the nitrate effects.

One possible mechanism by which the activation of KATP channels reduces cardiac events is through preconditioning effects [11]. KATP channels, located on the sarcolemma and the inner membrane of the mitochondria of cardiomyocytes, play a key role in cardioprotection against ischemia and reperfusion injury [12]. The opening of mitochondrial KATP plays a key role in cardioprotection against ischemia and the inner membrane of the mitochondria of cardiomyocytes, effects [11]. KATP channels, located on the sarcolemma and channels reduces cardiac events is through preconditioning duration, and prevents intracellular Ca2+ overload [5,12]. Based on these experimental results, a clinical trial to test whether a combination of coronary reperfusion therapy and infusion of nicorandil reduces myocardial infarct size and improves left ventricular function in patients with acute myocardial infarction have been conducted in Japan [13]. Unexpectedly, treatment with nicorandil was not associated with differences in infarct size or left ventricular ejection fraction compared with the control [14]. This result suggests that cardioprotective effects of nicorandil are minimal in patients with ST-elevated myocardial infarction treated with percutaneous coronary intervention.

Another potential mechanism by which the activation of endothelial KATP channels reduces cardiovascular events is to improve endothelial function. This is strongly supported by the findings of Wang et al. in this issue that the activation of endothelial KATP channels activates endothelial NO synthase and inhibits the release and synthesis of endothelin-1 [7]. Sanada et al. have demonstrated that the opening of KATP channels attenuates vascular and cardiac remodeling due to chronic inhibition of NO synthesis, suggesting that the improvement in NO synthesis by endothelial KATP channels may play an important role in preventing cardiovascular remodeling [15]. Furthermore, since endothelin-1 is a potent vasoconstrictor and proliferative factor that is implicated in vascular remodeling, the reduction of endothelin-1 synthesis by iptakalim also contributes to protecting endothelial function.

Interestingly, iptakalim could inhibit the overexpression of adhesion molecules in endothelial cells under metabolic disturbances. Because metabolic disorders such as hypercholesterolemia and type II diabetes mellitus are often observed in patients with coronary artery disease, it is possible that iptakalim, a new KATP channel opener, may exhibit additional benefits in these patients. Wang et al. provide the clinically relevant evidence to propose a hypothesis that the improvement in endothelial dysfunction by activation of endothelial KATP channels could be an important strategy to treat patients with high risk for cardiovascular diseases.

References