SK Channel Modulation and Coronary Microvascular / Endothelial Dysfunction

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Abstract

Endothelial SK channels play a key role in maintaining coronary microvascular function under physiological and pathophysiological conditions. The objective of our study is to investigate endothelial SK channel modulation of microvascular function in the setting of ischemia/reperfusion, hypoxia/reoxygenation and metabolic stress. Using the cardioplegic arrest/cardiopulmanry bypass (CP/CPB) models of animal and human along with isolated coronary arterioles and endothelial cells, we found that CP/CPB significantly decreased coronary endothelial SK channel activity and SK channel activators-induced coronary microvascular relaxation. However, these effects were more pronounced in the endothelial cells and coronary arterioles harvested from patients with poorly controlled diabetes than that of patients with non-diabetes. Importantly, pretreatment of the endothelial cells and arterioles with SK channel activator NS309 significantly improved the relaxation responses to ADP and substance P following cardioplegic hypoxia and reoxygenation. However, these beneficial effects were diminished in diabetic endothelial cells and microvasculature. Furthermore, inclusion of SK activator NS309 in cardioplegic solution improved the recovery of cardiac dysfunction in the pigs with cardioplegic arrest and cardiopulmonary bypass (CPB). Finally, inhibition of PKCβ remarkably increased endothelial SK channel activity and improved coronary endothelium-dependent relaxation following diabetes and cardioplegic hypoxia/reoxygenation injury. In conclusion, modulation of endothelial SK channel function should /be a potential therapeutic target for preserving coronary microvascular endothelial function, improving myocardial flow and myocardial perfusion, and enhancing the recovery of cardiac function in the setting of diabetes and cardioplegic arrest and CPB.