Small molecule activators of Ca²⁺-activated K⁺ channels can enhance endothelium-dependent responses in isolated resistance arteries

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Endothelial cells play a critical protective role in the cardiovascular system by releasing nitric oxide (NO) which mediates vasodilation, regulates local cell growth and protects blood vessels from the deleterious consequences of platelet aggregation and activation of inflammatory processes. Endothelial damage leading to reduced availability of NO disrupts these processes and is a major contributor to the clinical manifestations of chronic cardiovascular disease such as high blood pressure and thrombosis, as well as to acute events such as strokes. It is well-established that NO release occurs concurrently with hyperpolarization of the membrane potential of endothelial cells, an event mediated by opening of small (SKCa) and intermediate (IKCa) conductance Ca²⁺-activated potassium channels. We have previously provided evidence of a link between NO availability and KCa channel activity, and so have tested the hypothesis that pharmacological activation of endothelial KCa channels will enhance NO-mediated responses in isolated mesenteric resistance arteries.

To do this we have applied a combination of functional (wire and pressure myography, and perfusion of the intact mesenteric med), electrophysiological (intracellular recording of membrane potential) and biochemical (simultaneous measurement of arterial diameter with measurement of ROS with DHE) approaches.

Our data molecule activators of KCa channels can: i) dilate myogenically active arteries, ii) potentiate NO-mediated vasorelaxation in arteries mounted under isometric conditions, iii) enhance shear stress-mediated inhibition of nerve-evoked constriction in the intact mesenteric vascular bed, iii) reduce production of reactive oxygen species (ROS) which scavenge NO, and iv) restore NO-mediated relaxation in isolated arteries from diabetic animals. These findings demonstrate the potential beneficial effects of KCa channel openers on NO-mediated responses in the setting of endothelial dysfunction and support the proposal that KCa channels may provide novel targets for new therapeutic approaches to the treatment of cardiovascular disease.