ROLE OF KV1.3 CHANNELS IN INTIMAL HYPERPLASIA

ACC Moderated Poster Contributions
McCormick Place South, Hall A
Monday, March 26, 2012, 11:00 a.m.-Noon

Session Title: Biomechanistic Insights in Vascular Disease
Abstract Category: 1. Chronic CAD/Stable Ischemic Heart Disease: Basic
Presentation Number: 1195-121

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Background: Vascular smooth muscle cells (VSMCs) are able to switch from a contractile to a proliferative phenotype, and this process is central to intimal hyperplasia formation. Phenotypic modulation requires a change in gene expression profile, including a switch in ion transport mechanisms. Potassium (K+) channels have been suggested to have a role in the processes of cell proliferation. Changes in K+ channels expression are associated with functional changes in the electrophysiological properties of VSMCs, which are linked to cell growth. We have previously obtained a global portrait of ion channel expression in contractile versus proliferating VSMCs in different vascular beds, in vitro and in vivo, and have identified a marked increase in Kv1.3 mRNA expression during the switch to a proliferative phenotype. The aim of our study is to investigate the effect of the selective blockade of Kv1.3 channels in VSMC proliferation. For this purpose, we have selected PAP-1 (phenoxyalkoxypsoralen-1), a potent suppressor of T cells proliferation in vitro, which inhibits Kv1.3 with a high selectivity over other K+ channels.

Methods: Porcine coronary SMCs were isolated and cell proliferation analysis was measured with a BrdU incorporation assay. Using an arterial injury model previously validated by our group, an endothelial denudation injury was induced to murine femoral arteries. A constant infusion of PAP-1 (50 microg/Kg) was administered after injury, through the subcutaneous implant of Alzet osmotic mini-pumps, during 28 days, time-point at which animals were euthanized and arterial segments collected for morphometric and immunohistochemical analysis.

Results: PAP-1 (10 nM) significantly reduced cell proliferation versus control cells (13.2±1% vs. 18±1%, p<0.05). Intimal proliferation was reduced in PAP-1-treated animals, compared with control, vehicle-treated, mice (Intima-to-media ratios of 0.18±0.11 vs. 1.06±0.40; p=0.01).

Conclusion: The selective blockade of Kv1.3 channels decreases in vitro SMCs proliferation and in vivo intimal hyperplasia formation. Our results point to Kv1.3 channels as a new promising therapeutical target to avoid restenosis.