ROLE OF KV1.3 CHANNEL IN VASCULAR SMOOTH MUSCLE CELLS PROLIFERATION IN A PORCINE MODEL OF RESTENOSIS

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Background: Vascular smooth muscle cells (VSMCs) switch from a contractile to a proliferative phenotype, in response to arterial injury, such as after percutaneous coronary interventions (PCI). This phenotypic switch implies a profound change in the expression of contractile proteins and ion channels. In a previous work, we have demonstrated that Kv1.3 channels functional expression is increased upon arterial injury in different human vascular beds and in a mouse model of restenosis, where specific blockade of Kv1.3 channels with PAP-1, a non-cytotoxic psoralen, inhibits intimal hyperplasia. The present work seeks to reproduce these results in a model of intimal hyperplasia that is clinically more relevant for translational research, a porcine coronary angioplasty model. In addition, preliminary development of a PAP-1 drug-eluting stent is pursued.

Methods: Coronary angioplasty was performed in 3 main coronary arteries. Right coronaries were used as controls. Four weeks after PCI, animals underwent euthanasia, and samples were collected for histology, cell culture and electrophysiology assays. Release of PAP-1 from a PAP-1-coated polymer surface in a cell culture system was estimated by HPLC, and the proliferation of VSMCs assessed by BrdU incorporation analysis.

Results: mRNA expression levels studied by real time PCR showed that Kv1.3 expression were significantly increased in injured compared to uninjured coronaries. Proliferation assays showed that porcine coronary VSMCs proliferation was reduced in the presence of 100 nM PAP-1 (13 ±0,5% versus 18 ±1 % BrdU+ cells, respectively; p<0,01), but not in the presence of another Kv channel blockers, thus demonstrating Kv1.3 modulates coronary VSMC proliferation. The effect of a PAP-1-eluting polymer (concentrations ranging from 100 nM to 1microM) was analyzed on a culture system with human coronary VSMCs, showing an adequate drug release profile, and inhibition of proliferation (p<0,05) versus control-polymer-treated cells.

Conclusion: Kv1.3 channels appear to be a good therapeutical target to treat restenosis. The present study opens the possibility of developing drug-eluting stents with specific Kv1.3 blocking agents, such as PAP-1.