Cell specific expression of uptake transporters - a potential approach for cardiovascular drug delivery devices

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Enhanced proliferation of human coronary artery smooth muscle cells (HCASMCs) and thereby formation of neointima is one of the factors contributing to failure of coronary stents. Even if the use of drug eluting stents and thereby the local delivery of cytotoxic compounds has significantly improved clinical outcome, unselective cytotoxicity is assumed to hamper clinical success. Novel pharmacological approaches are required to enhance cellular selectivity of locally delivered drugs. Cell specific overexpression of a drug transporter could be used to enhance cellular accumulation and therefore cell specificity. In the herein reported study we tested the possibility of cell specific transporter expression to enhance drug effects in HCASMCs. We generated adenoviral constructs to overexpress the organic cation transporter 1 (OCT1) under control of the promoter of SM22α, which had been previously reported as muscle cell-specific gene. First the activity of the SM22α-promoter was assessed in various cell types supporting the notion of muscle cell-specificity. Subsequently, the activity of the transporter was compared in infected human coronary artery endothelial cells (HCAECs) and HCASMCs revealing enhanced accumulation of substrate drugs in HCASMCs in presence of the SM22α-promoter. Testing the hypothesis that this kind of targeting might serve as a mechanism for cell-specific drug effects we investigated the impact on paclitaxel treatment in HCASMC and HCAECs, showing significantly increased anti-proliferative activity of this substrate drug on muscle cells. Taken together, our findings suggest that cell-specific expression of transport proteins serves as mechanism governing the uptake of cytotoxic compounds for a selective impact on targeted cells.

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