Expression of OATP2B1 as determinant of drug effects in the microcompartment of the coronary artery

ID 3289949
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Year 2015
Title Expression of OATP2B1 as determinant of drug effects in the microcompartment of the coronary artery
Journal Vascular Pharmacology
Volume 72
Pages / **Article-Number** 25-34
Mesh terms Atorvastatin, pharmacology; Cell Proliferation, drug effects; Cells, Cultured; Coronary Vessels, metabolism; Endothelial Cells, metabolism; Humans; Hydroxymethylglutaryl-CoA Reductase Inhibitors, pharmacology; Muscle, Smooth, Vascular, metabolism; Myocytes, Smooth Muscle, metabolism; Organic Anion Transporters, metabolism
Clinical success of coronary drug-eluting stents (DES) is hampered by simultaneous reduction of smooth muscle cell (HCASMC) and endothelial cell proliferation due to unspecific cytotoxicity of currently used compounds. Previous in vitro data showing SMC-specific inhibition of proliferation suggested that statins may be suitable candidates for DES. It was aim of this study to further investigate statins as DES drug candidates to identify mechanisms contributing to their cell-selectivity. In vitro proliferation assays comparing the influence of various statins on HCASMC and endothelial cells confirmed that atorvastatin exhibits HCASMC-specificity. Due to similar expression levels of the drug target HMG-CoA reductase in both cell types, cellular accumulation of atorvastatin was assessed, revealing enhanced uptake in HCASMC most likely driven by significant expression of OATP2B1, a known uptake transporter for atorvastatin. In accordance with the finding that endogenous OATP2B1 influenced cellular accumulation in HCASMC we used this transporter as a tool to identify teniposide as new DES candidate drug with HCASMC-specific effects. We describe OATP2B1 as a determinant of pharmacokinetics in the coronary artery. Indeed, endogenously expressed OATP2B1 significantly influences the uptake of substrate drugs, thereby governing cell specificity. Screening of candidate drugs for interaction with OATP2B1 may be used to promote SMC-specificity.
Publisher Elsevier
ISSN/ISBN 1537-1891 ; 1879-3649
edoc-URL http://edoc.unibas.ch/39670/
Full Text on edoc No;
Digital Object Identifier DOI 10.1016/j.vph.2015.06.006
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/26091578
ISI-Number WOS:000360322700004
Document type (ISI) Journal Article