Transmembrane Transporters in Myocytes: Relevance for Statin-induced Myopathy

Annika Hafkemeyer[1], Vincent Rönnpagel[1], Felix Morof[1], Jörn Lange[2], Lyubomir Haralambiev[2], Heinrich Brinkmeier[3], Mladen V. Tzvetkov[1] Gabriele Jedlitschky[1]

Introduction: Statins prevent cardiovascular events by lowering cholesterol levels. Many patients treated with statins experience myalgia or myopathies. Variations in transporter-mediated uptake of statins into hepatocytes are known to affect the frequency of these side effects by influencing the plasma levels of the drugs. However, little is known about the uptake and efflux of statins in skeletal muscle cells.

Objectives: This study aims to characterize the accumulation of various statins in myocytes and identify the transporters that might be involved.

Materials & methods: Transporter expression in the human rhabdomyosarcoma cell line TE671 and in human skeletal muscle tissue was detected by Western blotting and qPCR. Immunofluorescence microscopy was performed to confirm transporter localization. We further characterized the cellular uptake of atorvastatin, simvastatin acid, fluvastatin, pravastatin, and rosuvastatin into the TE671 cells in a time- and concentration-dependent manner. Statin transport was also studied in the presence of potentially interfering compounds such as 4,5-dibromofluorescein, prostaglandin E_2 and lactate, that are known substrates of OATP2B1, OATP2A1 and MCT4, respectively. The cellular drug accumulation was determined by HPLC-MS/MS. Cell viability in the presence of statins was measured in resazurin assays.

Results: We could detect OATP2B1, OATP2A1, MCT4, MRP1, and MRP3-5 on transcript and protein level in TE671 cells and in muscle tissue. Immunofluorescence microscopy revealed localization in the cell membrane and in t-tubules. Saturable uptake of statins was detected with K_m values ranging from 142 µM (simvastatin acid) to 202 µM (atorvastatin). Remarkably, pravastatin was only transported to a minor extent into the cells. Furthermore, studies with the transporter inhibitors suggested that OATP2B1, OATP2A1, and MCT4 may be involved in the statin uptake to varying degrees. The statin accumulation was partially counteracted by an MRP-mediated efflux. In addition, lipophilic statins reduced the cell viability in a concentration-dependent manner, while only weak effects were observed for hydrophilic statins.

Conclusion: Our findings imply that several transporters are involved to a variable extent in the transmembrane transport of statins in myocytes, including OATP2B1, as well as probably OATP2A1 and MCT4. Furthermore, the efficiency of drug accumulation correlates with the ability of the statins to reduce myocyte viability.

1. Department of General Pharmacology, Center of Drug Absorption and Transport (C_DAT), University Medicine Greifswald, Germany

2. Center for Orthopaedics, Trauma Surgery and Rehabilitation Medicine, University Medicine Greifswald, Germany.

3. Department of Pathophysiology, University Medicine Greifswald, Germany.