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P-gp Inhibitory Potential of Phospholipids

S. SIMON, R. SCHUBERT

Department of Pharmaceutical Technology and Biopharmacy, University of Freiburg, Germany

E-mail: silke.simon@pharmazie.uni-freiburg.de (S. Simon)

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Introduction:

Oral drug administration is mainly regulated by the step of intestinal absorption. For various substances uptake is strongly superimposed by an active efflux back into the lumen via ATP-driven pumps like the P-glycoprotein (P-gp), significantly decreasing their bioavailability.

P-gp inhibitory effects can be determined via the calcein accumulation assay (CAA) or transport studies in cellular systems. Hereby it was previously shown that particular phospholipids (PL) reduce the efflux of a common P-gp substrate [2].

The aim of this study is to identify further potent PL derivatives and their molecular mechanism of action and to investigate the influence of different experimental parameters.

Experimental Methods:

Cell culture: CaCo2 and MDCKII-mdr1 cells were routinely maintained in supplemented DMEM. Cells were grown for either 21 days in Transwell® plates in case of transport studies, or for 8, resp. 4 days (MDCKII-mdr1) in 96-well plates in case of CAA.

Lipid formulations: Lipid derivatives were applied as liposomal formulations in HBSS.

Transport studies: CaCo2 cell layers were pre-incubated with lipid and digoxin (³H-labeled) was added apically for absorptive, resp. basolaterally for secretory studies. Monolayer integrity was determined via transepithelial electrical resistance (TEER) measurements and the ratio of the apparent permeability coefficients (P_{app}) of both directions displayed P-gp effects.

CAA: After pre-incubation with lipid or Verapamil as a positive control the intracellular accumulation of the fluorescent dye calcein indicated P-gp inhibition.

Results:

In the transport studies one achieved a concentration-dependent enhancement of netto drug absorption with C12-PG, C6-PS and various unsaturated symmetric and asymmetric PC lipids. CAA confirmed these findings in both celllines for C12-PG and other middle-chained saturated PC derivatives.

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