ESTIMATION OF THE RELATIVE CONTRIBUTION OF EFFLUX TRANSPORTERS TO OVERALL BILIARY EXCRETION FROM IN VITRO SANDWICH-CULTURED RAT HEPATOCYTES

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Several efflux transporters are expressed on the bile canalicular membrane and their substrate specificities overlap with one another. Elucidation of the molecular mechanisms involved in the hepatobiliary transport of drugs is important for determining the influence of functional changes in specific transporters on hepatic distribution and clearance. Thus, to predict the contribution each efflux transporter has on the overall biliary excretion of drugs, we selected inhibitors for specific transporters (Ko143 for BCRP, verapamil for MDR1, and glycyrrhizin for MRP2) and determined appropriate concentrations at which the inhibitors specifically inhibited target transporters in sandwich-cultured rat hepatocytes. Our results indicated that 1 μM Ko143, 10 μM verapamil, and 30 μM glycyrrhizin specifically inhibited the BCRP, MDR1, and MRP2 transporters, respectively. We also observed that a portion of the efflux transport of three kinds of statins (rosuvastatin, pitavastatin, pravastatin) was inhibited in the presence of transporter-specific inhibitors. Verapamil did not inhibit the efflux transport of the statins we tested to the bile pocket in sandwich-cultured rat hepatocytes. In contrast, Ko143 dramatically inhibited the efflux of pitavastatin and partially inhibited the efflux of rosvastatin, whereas it didn’t inhibit the efflux of pravastatin. These results demonstrate the different contributions efflux transporters make to the biliary excretion of these three statins, which are comparable to previous in vivo results. In this study, we constructed the methodology to evaluate the relative importance of each efflux transporter to the biliary excretion of drugs using sandwich-cultured rat hepatocytes and transporter-specific inhibitors.