Abstract

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Liver is the main biotransformation organ of human organism. Not every substance can cross the cell membrane of hepatocytes by simple diffusion. Transport of such substances across the membrane is mediated by specialized transport proteins. Uptake transporters localized on the basolateral membrane of hepatocytes play a crucial role in uptake of compounds from blood into hepatocytes, where the biotransformation takes place. OCT1 transporter belongs between important members of this group, it transports organic cations. Efflux transporters localized on the apical membrane are responsible for transport of substances from hepatocytes to bile canalicular and these transporters mediate their elimination in this way. BCRP is an example of this group of transporters. Drug transporters represent one of the most important mechanisms of drug-drug interactions due to their wide range of substrates. The aim of this study was to evaluate the function of novel cell models using substrate and inhibitors of these transporters. Stably transfected MDCK II cells expressing human OCT1 and/or BCRP transporters were used for this purpose. Lamivudine was used as substrate of studied transporters; it is a nucleoside reverse transcriptase inhibitor used in combination antiretroviral therapy of HIV. Antibacterial chemotherapeutic trimethoprim (an inhibitor of OCT1) and protease inhibitor ritonavir (an inhibitor of BCRP and OCT1) were used for inhibition studies. Significantly higher intracellular accumulation of lamivudine was observed in the monolayer of MDCK-OCT1 compared to control cell line MDCK II using accumulation assays. Decreased temperature (4 °C) significantly reduced intracellular accumulation of lamivudine, confirming the involvement of active transport mechanism. Co-administration of ritonavir or trimethoprim decreased intracellular accumulation of lamivudine. This model can be used for further studies and detection of transporter-mediated drug-drug interactions.