01C10-2

SIGNIFICANCE OF ACTIVE HEPATIC UPTAKE IN SYSTEMIC EXPOSURE OF STATINS
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Cumulative studies have demonstrated that hepatic transporters, such as OATP1B1 and OATP1B3, play important roles in hepatic clearance of anionic drugs. The purpose of this study is to examine the importance of hepatic uptake in the overall hepatic elimination of HMG-CoA reductase inhibitors (so-called, statins), such as pravastatin, pitavastatin, atorvastatin and fluvastatin, in humans. These statins are anions at physiological pH, and are taken up into hepatocytes in a concentration-dependent manner both in rats and humans, suggesting that transporters are involved in their hepatic uptake. \textit{In situ} uptake clearance of four statins was also determined by a multiple indicator dilution technique in rats. The uptake clearance of statins other than pitavastatin was comparable with the \textit{in vivo} overall hepatic intrinsic clearance obtained from the plasma concentration time profiles after intravenous and intraduodenal administration. Therefore, it is likely that hepatic uptake is the rate-determining process for these statins as far as their overall hepatic elimination is concerned. The scaling factor is defined as the ratio of \textit{in situ} to \textit{in vitro} uptake clearance and the \textit{in vivo} uptake clearance in humans was predicted from the \textit{in vitro} value obtained using cryopreserved human hepatocytes and the rat scaling factor. The predicted value was close to the \textit{in vivo} overall hepatic intrinsic clearance in humans, and the intrinsic metabolic clearance of the four statins determined using human liver microsome or S9 was much lower than the \textit{in vivo} overall hepatic intrinsic clearance even in the cases of atorvastatin and fluvastatin that are thought to be eliminated mainly via hepatic metabolism by P450. These results suggest that the hepatic uptake process must be taken into consideration when predicting hepatic clearance, in addition to the metabolic clearance, of these statins.

01C10-3

IDENTIFICATION OF NONSYNONYMOUS SNPS WITH COMPLETE LOSS OF TRANSPORT ACTIVITY FOR $^{\text{H}}$/ORGANIC CATION ANTIPORTERS (MATE1 AND MATE2-K)
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$^{\text{H}}$/organic cation antiporters (multidrug and toxin extrusion: MATE1/SLC47A1 and MATE2-K/SLC47A2) play important roles in the tubular secretion of cationic drugs. We have recently identified a single nucleotide polymorphism (SNP) in the promoter region of MATE1 (-32G>A), which causes a decrease of Sp1-binding and promoter activity of about 50%. However, other genetic information for these transporters, especially the polymorphisms in the coding region, and their effect on functional properties, has not been well evaluated. In the present study, therefore, we screened for polymorphisms in all exons of MATE1 and MATE2-K in 89 Japanese subjects. Transport activities and cell surface expression of each variant were evaluated by a transient expression system. We identified a total of 7 nonsynonymous coding SNPs (cSNPs), which encoded variants for MATE1 (V10L, G64D, A310V, D328A, and N474S) and for MATE2-K (K64N and G211V). Most of the variants showed a significant decrease in the transport activity. Notably, MATE1 G64D and MATE2-K G211V showed a complete loss of transport activity. Membrane expression levels of MATE1 G64D and MATE2-K G211V evaluated by cell surface biotinylation were significantly decreased compared with that of the wild-type MATE1 and MATE2-K, respectively. This is the first demonstration to identify cSNPs to affect the transport activity of MATE1 and MATE2-K in Japanese.