MECHANISMS OF TUBULAR SECRETION OF DRUGS IN THE KIDNEY, AND DRUG INTERACTIONS INVOLVING DRUG TRANSPORTERS

Hiroyuki Kusuhara
Department of Molecular Pharmacokinetics, Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan

The kidney eliminates endo- and xenobiotic compounds from the circulating blood into the urine. Urinary excretion is determined by glomerular filtration, tubular secretion, and reabsorption from the urine. Particularly, the epithelial cells lining the proximal tubules express various drug transporters with broad substrate specificity in both the basolateral and brush border membranes, thereby forming efficient directional transport of organic compounds across the epithelial cells. These transporters can be inhibited by some drugs at clinically relevant doses, and concomitant use of such drugs causes a drug–drug interaction (DDI). For instance, probenecid, an antihyperuricemia agent, is a well-known inhibitor of organic anion transporters in the kidney. Indeed, probenecid is a very potent inhibitor of the renal organic anion transporters, OAT1 and OAT3, and can inhibit both transporters almost completely at clinical doses. We have used human kidney slices in a transport study to investigate the renal drug uptake process, which also allows drug–drug interaction involving inhibition of the uptake process.

Simultaneous use of nonsteroidal anti-inflammatory drugs (NSAIDs), probenecid, and other drugs has been reported to delay the plasma elimination of methotrexate in patients. The uptake of methotrexate by human kidney slices was saturable with a \( K_m \) of 45–49 \( \mu \)M. Saturable uptake of methotrexate by human kidney slices was markedly inhibited by \( p \)-aminohippurate and benzylpenicillin. These transport characteristics are similar to those of the basolateral organic anion transporter OAT3/SLC22A8. NSAIDs and probenecid inhibited the uptake of methotrexate by human kidney slices, and, particularly, salicylate, indomethacin, and phenylbutazone were predicted to exhibit significant inhibition at clinically observed plasma concentrations. However, the interaction with other NSAIDs cannot be explained by an inhibition of the uptake process. The inhibitory effect of NSAIDs on ABC transporters, such as BCRP, MRP2, and MRP4, was examined. Salicylate and indomethacin were predicted to inhibit MRP4 at clinical plasma concentrations. Except for these two NSAIDs, the interaction cannot be accounted for by the inhibition of known transporters.

Fexofenadine is an orally active nonsedating histamine (H\(_1\))-receptor antagonist that is prescribed for the treatment of allergic rhinitis and chronic idiopathic urticaria. Simultaneous administration of probenecid and cimetidine decreases the renal clearance of fexofenadine in healthy subjects. Because, among the basolateral uptake transporters, OAT3 alone accepts fexofenadine as substrate, DDI between fexofenadine and probenecid has been suggested to involve inhibition of the OAT3-mediated renal uptake of fexofenadine. However, the unbound concentration of cimetidine at clinical doses is far below the \( K_i \) value of cimetidine for OAT3 to account for the DDI by inhibition of the uptake process. This holds true for the organic cation transport system, where the unbound concentration of cimetidine at clinical doses is far below the \( K_i \) value of cimetidine for OCT2. Indeed, this was confirmed using human kidney slices. Probenecid significantly inhibited the uptake of fexofenadine by human kidney slices at 10 \( \mu \)M, while cimetidine produced no significant inhibition even at 100 \( \mu \)M. Therefore, we hypothesized that the DDI of fexofenadine involves inhibition of luminal efflux. As a candidate transporter, we focused on MATE1. Specific uptake of fexofenadine was observed in human multidrug and toxic compound extrusion 1 (hMATE1) expressing HEK293 cells, but only a slight uptake was observed in hMATE2-K expressing cells. The hMATE1-mediated uptake was saturable, and reduced to 60% of the control by cimetidine (3 \( \mu \)M). In addition, cimetidine is a substrate of OCT2. Because of the negative membrane voltage, the intracellular unbound concentration of cimetidine will be greater than the unbound concentration in the plasma, which provides a stronger inhibition of the luminal efflux process than predicted by plasma concentration. These results suggest that the DDI between fexofenadine and cimetidine involves an inhibition of the renal excretion process of fexofenadine via hMATE1.

For the basolateral uptake process, human kidney slices allow the quantitative prediction of DDIs. However, although drug transporters have been identified in the brush border membrane, their significance to the net luminal efflux remains to be examined. To elucidate their importance is the next challenge for achieving more reliable prediction of DDI in the renal elimination of drugs.