PATHOPHYSIOLOGICAL ROLES OF RENAL TUBULAR DRUG TRANSPORTERS
Satohiro Masuda & Ken-ichi Inui
Department of Pharmacy, Kyoto University Hospital, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

In human genome, 350 and 48 genes encode SLC and ABC transporters have been identified and functionally characterized, respectively. In the kidney, tubular organic ion transporters belonging SLC22A, SLC47A and ABCB/C families were considered to play pivotal roles for preventing and/or inducing nephrotoxicity by drugs. Classically, renal dysfunction leads to decrease the tubular secretion of drugs is considered to be associated with the expression level of tubular transporters. However, the transcellular transport of ionic drugs depends on the sum of both basolateral and luminal transporters. Therefore, molecular variations of drug transporters in the disease states should be clarified to predict the variation of renal handling of drugs, and prevent further drug-induced renal impairment. Although Ccr is practically used as a marker of the general renal function, especially glomerular filtration rate (GFR), some situations show discrepancy between tubular detoxification and GFR. Because tubular secretion of drug depends on the function of tubular drug transporters, their regulatory mechanisms are basically different from GFR. Using subtotal nephrectomized rats, we have studied the expressional and functional variations of tubular drug transporters associated with progressive renal failure. Although the decreased expression of basolateral rOct2 was recovered by administration of testosterone, that of luminal rMate1 was not changed. The tubular secretory clearance of cimetidine was closely associated with the expression of rOct2. In addition, the expression level of the luminal Mate1 was also found to be associated with that pharmacokinetic parameter. These results suggested that both basolateral rOct2 and luminal rMate1 cooperatively play important role in the tubular secretion of cationic drugs even in chronic renal failure. An anticancer agent cisplatin is commonly used in the many kinds of chemotherapy regimens, but its renal toxicity has been serious problem in patients receiving the drug with hydration more than 3,500 mL/day preventing renal impairment. We clarified that the renal distribution of cisplatin was mainly mediated by hOCT2/SLC22A2, but the luminal hMATE transporters can not transport it, and therefore, accumulated cisplatin cause subsequent renal impairment. However, its derivative oxaliplatin does not affect renal function, because its tubular accumulation is considered to be decreased mainly MATE2-K-mediated tubular secretion. We will discuss the physiological and pathophysiological roles of renal tubular drug transporters.

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