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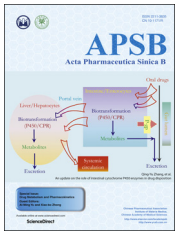

REVIEW

Renal drug transporters and their significance in drug–drug interactions

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KEY WORDS

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Abstract The kidney is a vital organ for the elimination of therapeutic drugs and their metabolites. Renal drug transporters, which are primarily located in the renal proximal tubules, play an important role in tubular secretion and reabsorption of drug molecules in the kidney. Tubular secretion is characterized by high clearance capacities, broad substrate specificities, and distinct charge selectivity for organic cations and anions. In the past two decades, substantial progress has been made in understanding the roles of transporters in drug disposition, efficacy, toxicity and drug–drug interactions (DDIs). In the kidney, several transporters are involved in renal handling of organic cation (OC) and organic anion (OA) drugs. These transporters are increasingly recognized as the target for clinically significant DDIs. This review focuses on the functional characteristics of major human renal drug transporters and their involvement in clinically significant DDIs.

Abbreviations: ABC, ATP-binding cassette; ATP, adenosine triphosphate; AUC, area under the plasma concentration curve; BBB, blood–brain barrier; C_{max}, maximum plasma concentration; CHO, Chinese hamster ovary; CL, plasma clearance; CL_R, renal clearance; DDIs, drug–drug interactions; f_e, fraction of the absorbed dose excreted unchanged in urine; FDA, U.S. Food and Drug Administration; GSH, glutathione; HEK, human embryonic kidney; IC_{50}, half maximal inhibitory concentration; ITC, International Transporter Consortium; K_i, inhibitory constant; MATE, multidrug and toxin extrusion protein; MPP^+, 1-methyl-4-phenylpyridimium; MRP, multidrug resistance-associated protein; MSD, membrane-spanning domain; MW, molecular weight; NBD, nucleotide-binding domain; NME, new molecular entity; NSAID, non-steroidal anti-inflammatory drugs; OA, organic anion; OAT or Oat, organic anion transporters; OATP or Oatp, organic anion-transporting peptide; OC, organic cation; OCT or Oct, organic cation transporter; OCTN, Organic zwitterions/cation transporters; PAH, *p*-aminohippurate; P-gp, P-glycoprotein; SLC, solute carrier; SNP, single-nucleotide polymorphism; TMD, transmembrane domain; TEA, tetraethylammonium; URAT, urate transporter

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1. Introduction

Renal clearance is a major pathway of drug elimination. About 32% of the top 200 prescribed drugs in the U.S. in 2010 are renally eliminated with more than 25% of the absorbed dose excreted unchanged in urine[1]. Renal elimination is the result of three concurrent processes occurring in the nephron, which include glomerular filtration, tubular secretion, and tubular reabsorption. Glomerular filtration is a passive process while tubular secretion, and sometimes reabsorption, involves a variety of transporters located on the basolateral and luminal membranes of the tubular epithelium. These transporters are predominantly expressed in the proximal tubule and they work in tandem to eliminate drugs from the blood circulation to the urine[1-3]. Both basolateral and apical transporters tend to be charge selective for anionic and cationic drugs, although recent study suggests that there is some degree of overlap[3,4]. In humans, major transporters involved in tubular secretion of cationic drugs include organic cation transporter 2 (hOCT2) on the basolateral membrane and the multidrug and toxin extrusion proteins 1 and 2-K (hMATE1 and hMATE2-K) on the apical membrane[1,3]. P-glycoprotein (P-gp) is also expressed in the apical member to facilitate the excretion of larger and more hydrophobic cations. The major transporters engaged in secretion of anionic drugs include organic anion transporters 1 and 3 (hOAT1 and hOAT3) on the basolateral membrane and multidrug resistance-associated proteins 2 and 4 (hMRP2 and hMRP4) on the apical membrane[1,3]. In addition, several closely related transporters are present in the proximal tubules and they may also contribute to renal handling of drugs and metabolic wastes.

Transporter-mediated drug–drug interactions (DDIs) are increasingly recognized as an important modifier of the pharmacokinetics and pharmacodynamics of drugs[2,3,5]. Drugs inhibiting renal drug transporters may cause marked changes in the pharmacokinetics of the affected drug, resulting in clinically significant DDIs[1,2,5]. Furthermore, expression and inhibition of renal drug transporters may result in abnormal drug accumulation in renal tubular cells, leading to drug-induced nephrotoxicity. This review focuses on renal drug transporters and their significance in DDIs and drug-induced nephrotoxicity. We first briefly summarize the current knowledge on major renal drug transporters including their expression, cellular localization, transport mechanisms, and substrate specificities. We then review the basic principles underlying renal DDIs and highlight the importance of renal drug transporters in clinically significant DDIs. The relevant consequences on pharmacokinetics, pharmacodynamics, and drug-induced nephrotoxicity are illustrated using several well-studied clinical DDI examples. Lastly, a brief summary along with current challenges in the field is presented.

2. Major drug transporters in human kidney

More than 400 membrane transporters are encoded by the human genome, and generally fall into the following two superfamilies: the adenosine triphosphate (ATP)-binding cassette (ABC) and the solute carrier (SLC)[1,3]. ABC transporters are primary active transporters that can transport substrates against their electrochemical gradients, utilizing energy generated from ATP hydrolysis. SLC transporters have diverse modes of transport. Facilitative SLC transporters transport substrates down their electrochemical gradients without coupling to an energy input. On the other hand, active SLC transporters can mediate uphill transport of a substrate against its electrochemical gradient by coupling to a co-transported ion (*e.g.*, Na^+ and H^+) or solute[1]. The major drug transporters involved in OC and OA transport in the human kidney are shown in Fig. 1. The molecular and functional characteristics of these transporters are described below.

2.1. *Cationic drug transporters*

2.1.1. *hOCTs (SLC22A)*

hOCTs belong to the SLC22 family[6]. Following the first cloning of rat OCT1 (rOCT1) in 1994[7], 16 additional OCTs were cloned from different species[6]. In human, three OCT isoforms (hOCT1, 2, and 3) have been identified. hOCT2 is about 70% identical to hOCT1[8], and hOCT3 is about 50% identical to hOCT1 and hOCT2[9]. hOCTs are membrane proteins with 553–556 amino acid residues[8,9] and are predicted to have 12 transmembrane domains (TMDs)[6]. In humans, hOCT2 is the major OCT isoform expressed in the kidney[6,8]. hOCT1, on the other hand, is predominantly expressed in the liver; and hOCT3 is broadly expressed in many tissues including the skeletal muscle, heart, placenta, and salivary glands[6,9,10]. hOCT1-3 are polyspecific transporters with a large overlap in substrate specificity[6]. They typically translocate relatively small, hydrophilic, and structurally diverse organic cations[2,6]. In the kidney, hOCT2 is located in the basolateral membrane of renal proximal tubule cells[1]. It mediates the first step in OC secretion in the kidney by translocating drug molecules from systemic circulation into the renal tubule cells[2,6,11]. Transport by hOCT2 is electrogenic and Na^+-independent, and facilitated by the inside-negative membrane potential existing in the kidney tubular cells[8]. Common substrates for hOCT2 include model cations tetraethylammonium (TEA) and 1-methyl-4-phenylpyridimium (MPP^+), endogenous monoamines, the antidiabetic drug metformin, the antihypertensive drug atenolol, the antiviral drug lamivudine, and the cytostatic drug oxaliplatin[1,2,12,13]. Most hOCT2 inhibitors are larger, more hydrophobic cations that may or may not be transported by the transporter[1,2,6]. Several clinically used drugs, including cimetidine, quinidine and dolutegravir, are known hOCT2 inhibitors[2,14]. The mRNA of *hOCT3* is also detectable in the kidney but at a much lower level[15,16]. The membrane localization of hOCT3 in human kidney is unclear. Further investigation is needed to elucidate the role of hOCT3 in renal excretion of drug molecules.

2.1.2. *hMATEs (SLC47A)*

hMATEs belong to SLC47 family. Two human orthologues of the bacterial MATE proteins, MATE1 and MATE2 were first cloned in 2005[17]. Soon after, two splice variants of hMATE2 were isolated from kidney and brain separately and were designated as hMATE2-K and hMATE2-B, respectively[18]. hMATE1 and hMATE2 are 47.5% identical[17]. hMATE1, hMATE2 and hMATE2-K are proteins of 570, 602 and 566 amino acids[17,18], respectively, and are currently predicted to have 13 TMDs[19,20]. hMATE2-B is a truncated protein of 220 amino acids and is not functional with respect to transport[18]. hMATE1 has the highest expression level in the kidney and is also strongly expressed in other tissues including the liver, skeleton muscle and adrenal gland[17,18]. Immunohistochemistry of human tissue revealed that in the kidney, hMATE1 is localized to the apical membrane of renal proximal tubule cells and distal convoluted tubules; and in the liver, it is expressed in bile canaliculi[17]. The full-length hMATE2 and the kidney-specific splice variant hMATE2-K are predominantly expressed in the kidney[17,18,21]. Immunostaining showed