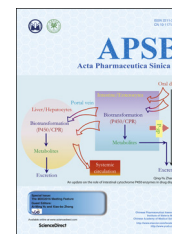




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## REVIEW

# 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.

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**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-phenylpyridinium; 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<sup>1</sup>. 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<sup>1-3</sup>. 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<sup>3,4</sup>. 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<sup>1,3</sup>. 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<sup>1,3</sup>. 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<sup>2,3,5</sup>. Drugs inhibiting renal drug transporters may cause marked changes in the pharmacokinetics of the affected drug, resulting in clinically significant DDIs<sup>1,2,5</sup>. 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)<sup>1,3</sup>. 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<sup>+</sup> and H<sup>+</sup>) or solute<sup>1</sup>. 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.

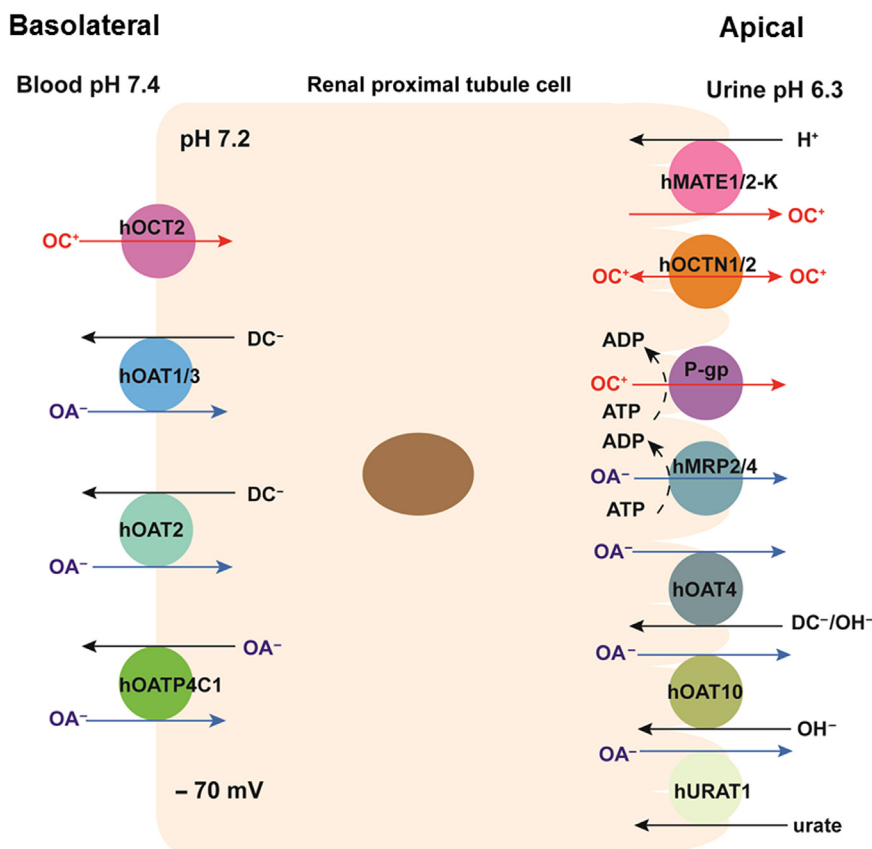
### 2.1. Cationic drug transporters

#### 2.1.1. hOCTs (SLC22A)

hOCTs belong to the SLC22 family<sup>6</sup>. Following the first cloning of rat OCT1 (rOCT1) in 1994<sup>7</sup>, 16 additional OCTs were cloned from different species<sup>6</sup>. In human, three OCT isoforms (hOCT1, 2, and 3) have been identified. hOCT2 is about 70% identical to hOCT1<sup>8</sup>, and hOCT3 is about 50% identical to hOCT1 and hOCT2<sup>9</sup>. hOCTs are membrane proteins with 553–556 amino acid residues<sup>8,9</sup> and are predicted to have 12 transmembrane domains (TMDs)<sup>6</sup>. In humans, hOCT2 is the major OCT isoform expressed in the kidney<sup>6,8</sup>. 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<sup>6,9,10</sup>. hOCT1-3 are polyspecific transporters with a large overlap in substrate specificity<sup>6</sup>. They typically translocate relatively small, hydrophilic, and structurally diverse organic cations<sup>2,6</sup>. In the kidney, hOCT2 is located in the basolateral membrane of renal proximal tubule cells<sup>1</sup>. It mediates the first step in OC secretion in the kidney by translocating drug molecules from systemic circulation into the renal tubule cells<sup>2,6,11</sup>. Transport by hOCT2 is electrogenic and Na<sup>+</sup>-independent, and facilitated by the inside-negative membrane potential existing in the kidney tubular cells<sup>8</sup>. Common substrates for hOCT2 include model cations tetraethylammonium (TEA) and 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>), endogenous monoamines, the antidiabetic drug metformin, the anti-hypertensive drug atenolol, the antiviral drug lamivudine, and the cytostatic drug oxaliplatin<sup>1,2,12,13</sup>. Most hOCT2 inhibitors are larger, more hydrophobic cations that may or may not be transported by the transporter<sup>1,2,6</sup>. Several clinically used drugs, including cimetidine, quinidine and dolutegravir, are known hOCT2 inhibitors<sup>2,14</sup>. The mRNA of hOCT3 is also detectable in the kidney but at a much lower level<sup>15,16</sup>. 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<sup>17</sup>. Soon after, two splice variants of hMATE2 were isolated from kidney and brain separately and were designated as hMATE2-K and hMATE2-B, respectively<sup>18</sup>. hMATE1 and hMATE2 are 47.5% identical<sup>17</sup>. hMATE1, hMATE2 and hMATE2-K are proteins of 570, 602 and 566 amino acids<sup>17,18</sup>, respectively, and are currently predicted to have 13 TMDs<sup>19,20</sup>. hMATE2-B is a truncated protein of 220 amino acids and is not functional with respect to transport<sup>18</sup>. 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<sup>17,18</sup>. 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<sup>17</sup>. The full-length hMATE2 and the kidney-specific splice variant hMATE2-K are predominantly expressed in the kidney<sup>17,18,21</sup>. Immunostaining showed



**Figure 1** Major drug transporters expressed in human renal proximal tubule cells. ADP, adenosine diphosphate; ATP, adenosine triphosphate; DC, dicarboxylate; OA, organic anion; and OC, organic cation.

both of them are expressed in the renal proximal tubule and hMATE2-K is localized to the luminal membrane of the tubule cells<sup>18,21</sup>. Different from hMATE1/2-K, hMATE2 was localized in intracellular vesicular structures upon expression in human embryonic kidney (HEK) 293 cells and only showed transport activity when reconstituted into liposomes<sup>21</sup>. hMATE1 and hMATE2-K are OC/proton exchangers and need an oppositely oriented proton gradient to drive the transport<sup>17,18,21</sup>. In the nephron, the tubular lumen is more acidic (~pH 6.3) than the cytosol, providing an inwardly directed proton gradient across the apical membrane of proximal tubule epithelial cells. hMATE-mediated influx of protons is coupled with the efflux of OCs into the urine. hMATE1/2-K share a broad spectrum of substrates and inhibitors with the hOCT2<sup>22</sup>. In the kidney, hMATE1/2-K mainly coordinate with hOCT2 to mediate OC secretion. However, hMATE1/2-K can also transport several anionic compounds and zwitterions<sup>22</sup>, which suggests that they may also partner with hOATs for renal excretion of anionic and zwitterionic drugs.

### 2.1.3. hOCTN (SLC22A)

Organic zwitterions/cation transporters (OCTNs) belong to the same SLC22 gene subfamily as OCTs. There are three OCTN isomers (OCTN1–3) in rodents, but humans only have OCTN1 and OCTN2<sup>6</sup>. The first human OCTN, hOCTN1, was cloned in 1997 from human fetal liver<sup>23</sup>. Soon after, hOCTN2 was cloned by screening a human kidney cDNA library<sup>24</sup>. hOCTN1 and hOCTN2 have 75.8% identity and both have high expression level in the kidney<sup>23,24</sup>, where they are located in the apical membrane of renal proximal tubule cells<sup>6,25,26</sup>.

Both hOCTN1 and hOCTN2 can transport OC and zwitterions, but the transport mechanisms are substrate-dependent and quite different for each transporter. hOCTN1 has a high affinity for the zwitterionic antioxidant ergothioneine, the uptake of which is stimulated by extracellular sodium<sup>27</sup>. hOCTN1 also appears to transport OCs such as TEA by an OC/H<sup>+</sup> exchange mechanism<sup>23,28</sup>. The exact role of hOCTN1 in the renal proximal tubules is unclear. It may participate in Na<sup>+</sup>-dependent reabsorption of ergothioneine from the filtrate; alternatively, it may contribute to tubular secretion by mediating OC efflux at the apical membrane driven by the acidic pH in the lumen<sup>23,27,28</sup>. hOCTN2 has a high affinity for L-carnitine and functions as a Na<sup>+</sup>-L-carnitine cotransporter<sup>24</sup>. In addition, hOCTN2 can also transport OCs in Na<sup>+</sup>-independent manner<sup>29</sup>. Similar to hOCTN1, hOCTN2 may participate in either renal reabsorption of zwitterions (*e.g.*, L-carnitine) or secretion of xenobiotic OCs depending on its mode of transport. While the proton/OC antiporters hMATE1/2-K are apparently the most important extrusion transporters for OC efflux at the luminal membrane<sup>30</sup>, hOCTN1/2 have different substrate selectivity and may contribute to the secretion of certain OC or zwitterion drugs. Interestingly, a recent pharmacogenomics study suggested that hOCTN1 is involved in active tubular secretion of gabapentin, an anticonvulsant widely prescribed for epilepsy and other neuropathic disorders<sup>31</sup>.

### 2.1.4. P-gp (ABCB1)

P-glycoprotein (P-gp) is probably the most well studied ABC transporter to date. It was first identified in 1976 as a cell surface glycoprotein from Chinese hamster ovary (CHO) cells resistant to

colchicine<sup>32</sup>. Overexpressed in many cancer cells, P-gp decreases drug accumulation in multidrug-resistant cells and mediates the development of resistance to anticancer drugs<sup>32</sup>. As a typical ABC transporter, it has two membrane-spanning domains (MSDs) and two cytoplasmic nucleotide-binding domains (NBDs). Using energy generated from ATP hydrolysis, P-gp actively transports its substrates out of cells against their concentration gradients. A vast number of therapeutic drugs, such as anticancer drugs, HIV protease inhibitors, immunosuppressants, cardioactive drugs and antifungals, interact with P-gp<sup>33-35</sup>. Typical P-gp substrates are lipophilic or amphipathic large molecules (molecular weight > 400 Da) carrying a positive charge at pH 7.4. However, neutral drugs with bulky ring structures (steroids and cyclic peptides) are also transported by P-gp. Interestingly, many of drugs transported by P-gp are also substrate of drug-metabolizing cytochrome P450 (CYP) enzymes, especially CYP3A4/5<sup>33</sup>.

Besides cancer cells, P-gp is broadly expressed in many normal tissues including excretory organs and tissue barriers important for drug disposition. The transporter has been localized to the luminal membrane of brain endothelial cells forming the blood-brain barrier (BBB), canalicular membrane of hepatocytes, apical surface of intestinal columnar epithelial cells, the apical membrane of kidney proximal tubule cells, and the apical membrane of placental syncytiotrophoblast cells<sup>2,34,36</sup>. The expression of P-gp in organs important for drug elimination and distribution is consistent with a protective role of P-gp in promoting drug elimination from the body and preventing drug entry into critical organs such as the brain and the developing fetus<sup>33,37-39</sup>. In the human intestine, P-gp and CYP3A are co-localized to the mucosal epithelial cells<sup>36,40</sup>. It was suggested that P-gp and CYP3A work together to synergistically limit oral bioavailability of many drugs<sup>33</sup>. Both P-gp and CYP3A are inducible by pregnane X receptor ligands (*e.g.*, rifampin)<sup>41,42</sup>. In the kidney, P-gp has been identified in the apical membrane of human proximal tubule cells by immunostaining, consistent with a role in facilitating renal drug excretion<sup>34</sup>. There is also evidence that expression of P-gp is increased after ischemic reperfusion injury in kidney<sup>43</sup>.

## 2.2. Anionic drug transporters

### 2.2.1. hOATs (SLC22A)

Despite transporting a largely different group of anionic substrates, OATs belong to the same SLC22 family that also encodes the OCTs. OAT was first discovered in 1997 with the cloning of rat and flounder Oat1<sup>44-46</sup>. The cloned OAT/Oats are proteins of 536–556 amino acids and are predicted to have 12 TMDs<sup>47-49</sup>. In human, 10 OAT isoforms have been identified, including hOAT1–8, hOAT10, and the urate transporter 1 (hURAT1)<sup>47</sup>. Among them, hOAT1–4, hOAT7, hOAT10 and hURAT1 have been functionally characterized<sup>47,50</sup>. hOAT1, the first cloned human OAT<sup>51</sup>, has 4 splice variants, hOAT1-1, hOAT1-2, hOAT1-3 and hOAT1-4<sup>52</sup>. hOAT1-1 and hOAT1-2 are longer and showed similar transport activity while hOAT1-3 and hOAT1-4 are shorter and lack of transport activity<sup>52</sup>. Most hOATs have expression in the renal proximal tubule, except hOAT7, which is restrictedly expressed in the liver<sup>47,53</sup>. In the kidney, hOAT1–3 are located on the basolateral membrane of renal tubule cells whereas hOAT4, hOAT10 and hURAT1 are expressed on the luminal membrane<sup>47</sup>. Basally-expressed hOAT1–3 function as organic anion (OA)/dicarboxylate exchangers which mediate the first step of OA renal excretion by transporting OAs into renal tubule cells utilizing the

outward dicarboxylate (*e.g.*,  $\alpha$ -ketoglutarate for hOAT1/3, succinate for hOAT2) gradient established by the Na<sup>+</sup>-dicarboxylate cotransporter<sup>47</sup>. hOAT1 and hOAT3 have substantial overlap in their substrate specificities, accepting relatively small and hydrophilic OAs<sup>2,50</sup>. hOAT3 appears to be more tolerant in size and charge of its substrates than hOAT1 and can transport bulkier (*e.g.*, estrone sulfate) and even positively charged (*e.g.*, cimetidine) compounds<sup>2,50</sup>. Numerous drugs have been shown to be substrates of hOAT1/3, including antibiotics, antivirals, antihypertensive drugs, diuretics, cytostatics, H<sub>2</sub>-antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), statins and uricosurics<sup>1,54</sup>. The role of hOAT2 in renal handling of drugs is less clear. Reported substrates of hOAT2 include some endogenous compounds, such as glutamate, nucleobases, nucleosides and nucleotides, and some drug molecules, such as salicylate, bumetanide and erythromycin<sup>50</sup>.

Apically-expressed hOATs and hURAT1 may have multiple transport mechanisms. hOAT4 can transport in both influx and efflux modes<sup>55</sup>. As an influx transporter, it can take up estrone sulfate and urate through OA/dicarboxylate or OA/OH<sup>-</sup> exchange mode<sup>55,56</sup>. As an efflux transporter, it can release PAH into the tubule lumen via PAH/Cl<sup>-</sup> exchange<sup>55</sup>. hOAT10 is an antiporter, taking up p-aminohippurate (PAH), urate and nicotinate possibly by OA/OH<sup>-</sup> exchange<sup>57</sup>. Although hOAT4 and hOAT10 have both been implicated in drug transport in the kidney, their roles in tubular drug secretion and/or reabsorption still need to be clarified. hURAT1 is known to play an important role in urate homeostasis. It reabsorbs urate from lumen of renal tubule by exchanging extracellular urate with intracellular OAs such as lactate and nicotinate<sup>58</sup>.

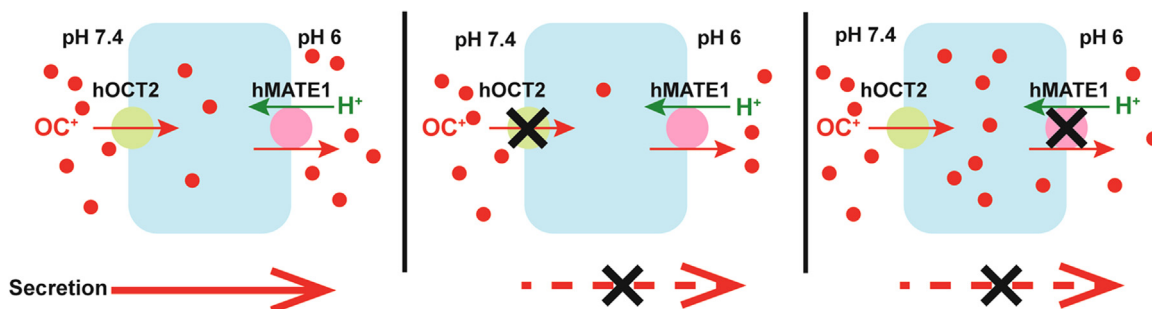
### 2.2.2. hMRPs (ABCC)

MRPs are ATP-dependent efflux transporters. They use energy generated from ATP hydrolysis to export molecules out of cells. They are part of the C branch of ABC family, which can be further divided into two subfamilies, “long” (MRP1, 2, 3, 6, and 7) and “short” (MRP4, 5, 8, 9, and 10)<sup>59</sup>. The short MRPs have the typical ABC transporter structure with two MSDs and two cytoplasmic NBDs, while the long MRPs have an additional MSD<sup>59</sup>. Among the 10 identified hMRP genes, 8 (hMRP1–8) have been confirmed to encode functional proteins<sup>59</sup>. Several hMRP isoforms are expressed in the kidney, including hMRP1, hMRP2, hMRP3, and hMRP4<sup>60,61-64</sup>. In particular, hMRP2 and hMRP4 are located in the apical membrane domain of renal proximal tubule cells, suggesting their role in efflux of molecules into the tubule lumen<sup>60,61</sup>. In mouse kidney, MRP1 was found in the basolateral membrane of the distal and collecting tubule cells, but not in proximal tubule cells<sup>65</sup>. Similarly, in human kidney, hMRP3 is located in the basolateral membrane of distal convoluted tubules<sup>66</sup>. The role of hMRP1 and hMRP3 in the kidney remains unclear. The typical substrates of hMRPs are the smaller unconjugated organic anions, such as PAH, and the larger conjugated organic anions, including glutathione (GSH) conjugates and glucuronides<sup>2</sup>. hMRP2/4 have some substrate overlap with hOAT1/3. Accordingly, hMRP2 and hMRP4 may coordinate with hOAT1/3 to mediate renal excretion of certain anionic drugs.

### 2.2.3. hOATPs (SLCO)

Organic anion-transporting peptides (OATPs) are SLC carriers predicted to have 12 TMDs<sup>67</sup>. The first OATP was cloned from rat in 1994<sup>68</sup>. One year later, the first human OATP, OATP1A2, was isolated from human liver<sup>69</sup>. Today, OATP superfamily consists of





**Figure 2** Hypothesized effects of transporter inhibition on tubular drug secretion and intracellular accumulation. When a basolateral uptake transporter such as hOCT2 is the main inhibition site, both renal secretion and intracellular drug accumulation are decreased. In contrast, when an apical efflux transporter such as hMATE1 is the primary inhibition site, tubular secretion is decreased but the intracellular drug level is increased.

more than 300 members from over 40 species, which form 6 families, OATP1–6<sup>70</sup>. In human, 11 members have been identified, which are hOATP1A2, hOATP1B1, hOATP1B3, hOATP1C1, hOATP2A1, hOATP2B1, hOATP3A1, hOATP4A1, hOATP4C1, hOATP5A1 and hOATP6A1<sup>70</sup>. OATPs can transport anionic and amphipathic molecules that are relatively large (>450) and have a high degree of albumin binding under physiological conditions<sup>71</sup>. The transport by OATPs is Na<sup>+</sup>-independent, but the exact transport mechanisms are unclear<sup>70</sup>. They are believed to act as an OA/OA exchanger, coupling cellular uptake of organic compounds with efflux of intracellular bicarbonate, GSH and GSH conjugates<sup>70</sup>. In addition, uptake by some OATPs is pH-sensitive and appears to have higher uptake rate at lower extracellular pH<sup>70</sup>. Among the 11 hOATPs, hOATP1B1 and 1B3 are considered to be liver-specific<sup>72</sup>, while hOATP4C1 was predicted to be kidney-specific<sup>73</sup>. hOATP4C1 can transport cardiac glycoside (digoxin and ouabain) and thyroid hormone (tri-iodothyronine) with high affinities<sup>73</sup>. Its rat counterpart OATP4C1 is localized to the basolateral membrane of rat kidney proximal tubule cells, suggesting that hOATP4C1 might mediate the first step in renal excretion of digoxin and other compounds<sup>73</sup>.

### 3. Renal transporter-mediated drug interactions

In the human kidney, elimination of drugs consists of passive glomerular filtration, active tubular secretion and passive or active reabsorption. For xenobiotics, reabsorption is believed to occur mainly through a passive process<sup>74</sup>. DDIs due to inhibition of tubular secretion thus represent the most common type of drug interactions at the renal level. Inhibition at a tubular secretion site decreases renal secretion clearance, which may result in increased drug concentrations in the plasma, altered pharmacological and toxicological responses. Furthermore, renal DDIs may change drug accumulation in proximal tubule cells, leading to drug-induced nephrotoxicity and kidney injury<sup>1,2</sup>. Although renal DDIs are often unwanted as they may lead to adverse drug reactions, occasionally, coadministration of an inhibitor (*e.g.*, probenecid) is used deliberately to either alter renal clearance or reduce nephrotoxicity of another drug<sup>75,76</sup>. Recognizing the important roles of transporters in drug disposition and interactions, the International Transporter Consortium (ITC) and the U.S. Food and Drug Administration (FDA) have recently published a series of papers and recommendations for assessing DDI potentials between a new molecular entity (NME) and clinically important transporters including the renal hOCT2 and hOAT1/3<sup>3,77-80</sup>.

Historically, numerous clinically significant DDIs in the kidney have been reported and attributed to the inhibition of renal organic cation and anion secretion systems<sup>1,2,5</sup>. Cimetidine has been historically used as the classic inhibitor for the OC system whereas probenecid is considered as the prototypical inhibitor of the OA system<sup>1,2,5</sup>. Inhibitors of the renal OC and OA secretion systems are often non-specific and interact with both apical and basolateral transporters. While inhibition of a basolateral or an apical transporter both decreases tubular secretion, the impact on intrarenal drug accumulation and toxicity is completely different. As illustrated in Fig. 2, inhibition of a basolateral uptake transporter reduces drug accumulation within renal tubular cells, thus is nephron-protective. In contrast, inhibition of apical efflux transporters diminishes drug exit from renal tubular cells, which can lead to increased drug accumulation and nephrotoxicity. Such scenarios are demonstrated in the clinical DDI examples later. Therefore, knowing the precise site of interaction (*i.e.*, apical *vs.* basolateral) is critical to predict whether an inhibitor has a nephron-toxic or a nephron-protective effect *in vivo*.

Clinically, several pharmacokinetic conditions must be satisfied for significant DDIs to occur at the level of renal transporters. First, the affected drug must be actively secreted in the kidney and transporter-mediated renal clearance must account for a significant portion of its total clearance. Second, clinical unbound concentrations of the interacting drug (*i.e.*, the inhibitor) must be high enough in order to produce a pronounced effect. When plasma concentrations of the inhibitor are much less than the inhibitory constant ( $K_i$ ), the potential for significant drug interactions is small. However, for drugs with a narrow therapeutic window, even small changes in their pharmacokinetic profiles may be clinically relevant. In the following section, we highlight the importance of renal OC and OA drug transporters in mediating clinically significant DDIs. The relevant consequences on pharmacokinetics, pharmacodynamics, and drug-induced nephrotoxicity are illustrated using several well-studied clinical DDI examples as summarized in Table 1<sup>14,76,81-90</sup>.

#### 3.1. Interactions involving hOCT2 and hMATE1/2-K

hOCT2 and hMATE1/2-K form a major pathway for renal elimination of small hydrophilic drugs carrying a positive charge. Inhibition of either hOCT2 or hMATE1/2-K has been implicated in many interactions involving cationic drugs<sup>1,2,5</sup>. In the current ITC and FDA recommendations, metformin is suggested as the *in vivo* probe for assessing the inhibition potential of a NME towards hOCT2 and hMATE1/2-K<sup>3,77,78</sup>. Metformin is the first-

**Table 1** Examples of clinically observed DDIs involving renal drug transporters.

Implicated transporters	Victim drug	Perpetrator drug	AUC fold increase	CL <sub>R</sub> decrease (%)	References
hOCT2, hMATE1, and hMATE2-K	Metformin	Cimetidine	1.5	28	81
	Metformin	Cimetidine	1.5	45	82
	Metformin	Pyrimethamine	1.4	35	83
	Metformin	Dolutegravir	2.5	N.D.	14
hOAT1 and hOAT3	Furosemide	Probenecid	2.7	66	84
	Furosemide	Probenecid	3.1	80	85
	Cidofovir	Probenecid	1.8	52	76
	Fexofenadine	Probenecid	1.5	73	86
	Fexofenadine	Probenecid	1.5	70	87
P-gp	Digoxin	Quinidine	N.D.	56	88
	Digoxin	Quinidine	N.D.	33	89
	Digoxin	Quinidine	N.D.	34	90

N.D.: not determined.

line treatment for type 2 diabetes. The drug is minimally metabolized *in vivo* and exclusively eliminated unchanged by the kidney<sup>91,92</sup>. Its reported renal clearance (CL<sub>R</sub>) is about 454 mL/min, which is much larger than its glomerular filtration clearance<sup>92</sup>. hOCT2-hMATE1/2-K-mediated active secretion plays an important role in metformin renal elimination. To date, some of the well-established DDIs involving renal OC transport system were observed with metformin. Besides DDIs, hOCT2-mediated drug uptake and accumulation in renal proximal tubule cells is known to contribute to drug-induced kidney injury as demonstrated in the case of cisplatin nephrotoxicity.

### 3.1.1. Cimetidine–metformin interaction

Cimetidine, a histamine H<sub>2</sub>-receptor antagonist, is a classic inhibitor of renal OC secretion. Cimetidine is 20% protein bound in the plasma and the reported unbound maximum plasma concentration (C<sub>max</sub>) after a typical 400 mg oral dose is around 8 μmol/L<sup>93,94</sup>. There have been several reports of cimetidine–metformin interaction<sup>81,82</sup>. The largest observed area under the plasma concentration curve (AUC) increase and renal clearance (CL<sub>R</sub>) decrease is 1.5-fold and 45%, respectively<sup>82</sup>. Metformin is a substrate of both hOCT2 and hMATE1/2-K<sup>83</sup>, and is eliminated predominantly unchanged by the kidney. Historically, inhibition of basolateral hOCT2-mediated metformin uptake was thought to be the mechanism underlying the observed interaction<sup>2,3</sup>. In addition, the inhibitory effect of cimetidine on metformin renal clearance has been reported to depend on a genetic polymorphism of *hOCT2* in a cohort of Chinese subjects<sup>82</sup>. However, Ito et al.<sup>95</sup> recently demonstrated that cimetidine has much greater *in vitro* inhibition potencies towards the apical hMATE1/2-K (K<sub>i</sub>=1.1–6.9 μmol/L) than for the basolateral hOCT2 (K<sub>i</sub>=95–146 μmol/L). These data suggest that cimetidine inhibition of apical hMATE1/2-K, but not basolateral hOCT2, is the likely mechanism underlying clinically observed cimetidine–metformin DDIs<sup>95</sup>. However, cimetidine is a substrate of hOCT2 and hMATE1/2-K, and it has been proposed that cimetidine interferes with hMATE1/2-K through an intracellular binding site<sup>96,97</sup>. Therefore, hOCT2-mediated uptake into kidney cells could have an impact on cimetidine's inhibitory effect towards hMATE1/2-K, which may explain the hOCT2 genotype-dependent effect on cimetidine–metformin interaction<sup>82</sup>.

### 3.1.2. Pyrimethamine–metformin interaction

Pyrimethamine is an antiparasitic commonly used for malarial infection. Co-administration of pyrimethamine and metformin has been reported to result in clinically significant DDIs, leading to a 1.4-fold increase of AUC and a 35% decrease of CL<sub>R</sub> of metformin<sup>83</sup>. Pyrimethamine is a selective inhibitor of hMATE1/2-K, and its potency toward hMATE1/2-K is about 100-fold higher than that of hOCT2<sup>83</sup>. Thus inhibition of apical hMATE1/2-K has been proposed to be the underlying mechanism of pyrimethamine–metformin interaction<sup>83</sup>. However, pyrimethamine is highly protein bound, the unbound concentration of the drug in the plasma is low at clinically used doses. This may explain the relative small magnitudes of changes in metformin AUC and CL<sub>R</sub> when co-administrated with pyrimethamine<sup>83</sup>. Whether pyrimethamine is actively transported into renal tubule cells is still unknown, but its lipophilic nature (log*P* = 2.7) and small molecular weight (MW=248.7) may allow passive diffusion into the renal cells, leading to significant inhibition of the apical hMATE1/2-K.

### 3.1.3. Dolutegravir–metformin interaction

Dolutegravir is a newly approved anti-HIV drug and also an inhibitor of hOCT2 and hMATE1/2-K. *In vitro*, dolutegravir is a more potent inhibitor for hOCT2 (half maximal inhibitory concentration (IC<sub>50</sub>) is ~1.9 μmol/L) than for hMATE1/2-K (IC<sub>50</sub> ~6.3–25 μmol/L)<sup>14</sup>. Co-administration of dolutegravir increased metformin AUC by 2.5-fold<sup>14</sup>, a magnitude well exceeded what has been observed for cimetidine and pyrimethamine. The observed metformin AUC change in the presence of dolutegravir is higher than anticipated. Based on its IC<sub>50</sub> values and its unbound C<sub>max</sub>, dolutegravir is predicted to be an irrelevant *in vivo* inhibitor of hMATE1/2-K but a moderate *in vivo* inhibitor of hOCT2<sup>14,98</sup>. Therefore, inhibition of hOCT2 only partially explains the observed AUC change of metformin. Evaluation of the effect of dolutegravir on putative transporters involved in absorption and distribution of metformin also showed negative results<sup>14,99,100</sup>. Thus, it is possible that other unidentified mechanism(s) may be involved in dolutegravir–metformin interaction. Nevertheless, based on the significant metformin AUC change caused by dolutegravir, it is recommended that dose adjustments of metformin be considered when patients are starting or stopping dolutegravir while on metformin therapy.

### 3.1.4. Cisplatin nephrotoxicity

Cisplatin is a chemotherapeutic agent used in the treatment of lung, bladder, colon, testis, and brain cancer<sup>101–103</sup>. However, nephrotoxicity, primarily in proximal tubules, is a major dose limiting toxicity of cisplatin<sup>104,105</sup>. *In vitro*, cisplatin is an excellent OCT2 substrate; however, it is a poor substrate of either MATE1 or MATE2-K<sup>106–108</sup>. In animal studies, *Oct1/Oct2*-deficient mice exhibited impaired urinary excretion of cisplatin and were protected from severe cisplatin-induced renal tubular necrosis<sup>109,110</sup>. In addition, a nonsynonymous single-nucleotide polymorphism (SNP) 808 G>T in *hOCT2* gene was associated with reduced cisplatin-induced nephrotoxicity in cancer patients<sup>109</sup>. All these evidence supports a significant role of hOCT2 in renal handling and nephrotoxicity of cisplatin. The discovery of the critical role of OCT2 in cisplatin toxicity provided a rationale for using OCT2-selective inhibitors to mitigate the debilitating side effect of cisplatin<sup>109,111,112</sup>. In fact, co-administration of cisplatin and high dose cimetidine has been reported to lead to partial protection against cisplatin-induced nephrotoxicity<sup>113</sup>. These findings collectively support future exploration of hOCT2 inhibitors as potential therapeutic agents to prevent cisplatin-induced nephrotoxicity. However, as stated earlier, many OCT inhibitors also inhibit MATEs, which may increase intracellular cisplatin accumulation and toxicity. In needed, selective inhibition of MATE transporters with pyrimethamine or ondansetron was shown to increase the nephrotoxicity of cisplatin in mice<sup>114,115</sup>. Therefore the risk of using chemical inhibitors as a cisplatin nephroprotectant should be carefully addressed given the opposing effect of hOCT2 and hMATEs in cisplatin intrarenal accumulation and toxicity (Fig. 2).

## 3.2. Interactions involving hOATs

Probenecid is the prototype inhibitor for the renal organic anion secretion system<sup>2,3,77</sup>. During World War II, probenecid was first developed as a penicillin-sparing agent to prevent the rapid urinary loss of the antibiotic. Numerous interactions between probenecid and penicillin-derivatives, or other anionic drugs, have been reported<sup>1,2,5</sup>. Clinically, inhibition of renal anion secretion by probenecid has also been employed to produce beneficial drug interactions to either enhance activity of antibiotics or reduce renal accumulation and nephrotoxicity of certain antiviral drugs<sup>1,2</sup>. Probenecid exhibits similar inhibition potencies towards hOAT1 and hOAT3 with  $K_i$  values around 4–12  $\mu\text{mol/L}$ <sup>1,2</sup>. Less inhibitory effects were reported with apical hMRP2, hMRP4 and hOAT4 ( $K_i$  of 44.6, 2300, and 54.9  $\mu\text{mol/L}$ , respectively)<sup>2,116–118</sup>. At typical oral doses (*e.g.*, 0.5–2 g), probenecid produces unbound plasma concentrations in the range of 3–50  $\mu\text{mol/L}$ <sup>119</sup>, suggesting that both hOAT1 and hOAT3 are likely to be the site of drug interactions with probenecid *in vivo*. Nevertheless, as probenecid at higher doses also inhibits other transporters and some phase II drug metabolizing enzymes, cautions should be taken when interpreting *in vivo* DDI data with probenecid.

### 3.2.1. Probenecid–furosemide interaction

Furosemide is a loop diuretic, which exerts its pharmacological effects by inhibiting  $\text{Na}^+\text{-K}^+\text{-2Cl}^-$  cotransporter located in the luminal membrane of loop of Henle<sup>120</sup>. Renal excretion is the major elimination pathway for furosemide with fraction of the absorbed dose excreted unchanged in urine ( $f_e$ ) 71%<sup>121</sup>. Due to high protein binding, glomerular filtration of furosemide is very limited<sup>121</sup>. Thus, active tubular secretion may represent the major route for both furosemide renal elimination and delivery of the diuretic to its

effective site. *In vitro*, furosemide has been shown to be a substrate of hOAT1 and hOAT3<sup>120</sup>. *Oat1*-knockout mice also showed impaired furosemide renal excretion and diuretic responsiveness<sup>122</sup>, further supporting involvement of OATs in furosemide renal excretion. In humans, probenecid markedly reduces furosemide  $\text{CL}_R$  and urinary excretion while increases its system exposure and half-life<sup>84,85</sup> (Table 1). Intriguingly, mixed results were reported regarding the effect of probenecid on the diuretic effect of furosemide<sup>85,123–125</sup>. In some studies, pretreatment with probenecid even increased the overall response to furosemide<sup>124,125</sup>. A detailed analysis of the time-course of the increased diuresis and natriuresis showed that probenecid decreased the response for the first 60–90 min after furosemide but increased the subsequent response sufficiently to result in a greater overall effect<sup>124</sup>. Thus, the effect of probenecid on the pharmacodynamics of furosemide in humans is complex and may not be simply predicted from changes in plasma or urinary drug levels.

### 3.2.2. Probenecid–cidofovir interaction

Cidofovir is an acyclic nucleotide analog used in the treatment of cytomegalovirus infection of the eye. Cidofovir is eliminated largely through renal excretion with approximately 90% of intravenous dose recovered in urine unchanged<sup>76</sup>. Nephrotoxicity, due to excessive drug accumulation in renal proximal tubule cells, is the dose-limiting toxicity for cidofovir<sup>126</sup>. Cidofovir is an hOAT1 substrate and hOAT1-mediate cytotoxicity was markedly reduced with probenecid treatment<sup>75,127</sup>. Co-administration of high-dose probenecid with cidofovir in HIV patients reduced cidofovir  $\text{CL}_R$  to a level approaching glomerular filtration, supporting the clinical use of probenecid as a nephroprotectant during cidofovir therapy<sup>76</sup>. Nowadays, co-administration of probenecid with cidofovir is required by FDA to protect patients against cidofovir-induced nephrotoxicity<sup>1</sup>.

### 3.2.3. Probenecid–fexofenadine interaction

Fexofenadine, an active metabolite of terfenadine, is a selective histamine H<sub>1</sub> receptor antagonist used for the treatment of allergic rhinitis and chronic idiopathic urticaria. After oral administration, fexofenadine is mainly eliminated through biliary excretion, but renal clearance also makes a significant contribution to its total body clearance<sup>128</sup>. Several reports showed that probenecid could increase fexofenadine AUC by 1.5-fold and decrease its  $\text{CL}_R$  by approximately 70%<sup>86,87</sup>. Although fexofenadine is a known substrate of P-gp and OATPs, probenecid appears to be a weak inhibitor for these transporters. *In vitro*, fexofenadine showed significant accumulation in hOAT3-expressing HEK cells but not in hOAT1- and hOAT2-expressing HEK cells<sup>128</sup>. Probenecid also showed high inhibition potency toward fexofenadine uptake in hOAT3 cells with  $K_i$  value of 1.3  $\mu\text{mol/L}$ <sup>128</sup>, which is much lower than the maximum unbound concentration of probenecid at typical clinical dosages<sup>119</sup>. It is likely that inhibition of hOAT3-mediated renal uptake of fexofenadine contributes to the observed probenecid–fexofenadine interactions.

## 3.3. Interaction involving P-gp

As an efflux pump with broad substrate specificity, P-gp plays an important role in drug disposition<sup>1</sup>. In the kidney, P-gp is located in the apical membrane of proximal tubule cells where it can actively export hydrophobic drug molecules into the urine<sup>36</sup>. There have been many reports of P-gp-mediated DDIs, but the most well studied interaction is probably P-gp-mediated interaction with

digoxin<sup>2,3</sup>, a well-established P-gp substrate. Digoxin, a commonly used cardiac glycoside, is metabolically stable and primarily eliminated through renal excretion<sup>129</sup>. Because digoxin has a narrow therapeutic window, even small changes in serum levels of digoxin may lead to clinically significant toxicities that can affect multiple organ systems<sup>130</sup>. Thus cautions must be taken when using other co-medications with digoxin.

Quinidine is a substrate and inhibitor of P-gp<sup>131</sup>. There have been several reports of quinidine–digoxin interactions with the largest reported plasma clearance (CL) decrease of digoxin being 64%<sup>132</sup>. Serum digoxin levels can reach dangerously high concentrations when co-administered with quinidine. In Caco-2 monolayers, basal-to-apical transport of digoxin was strongly inhibited by quinidine<sup>133</sup>. In addition, quinidine at same *in vivo* concentration markedly increased digoxin plasma concentration in wild-type mice, but not in *P-gp* knockout mice<sup>133</sup>. Both *in vitro* and *in vivo* data strong support that inhibition of P-gp–mediated digoxin efflux is the major underlying mechanism of quinidine–digoxin interaction. Similar digoxin–drug interactions with reduced renal clearance and have also been observed with other P-gp inhibitors such as verapamil and clarithromycin<sup>134,135</sup>.

#### 4. Conclusions

In conclusion, renal drug transporters play an important role in drug disposition, efficacy and toxicity. Like drug-metabolizing enzymes, they are also the target sites for DDIs. Despite the significant progresses made in our understanding on drug transporters, our knowledge of renal drug transporters and our comprehension of their roles in the kidney and the mechanisms of renal transporter-mediated DDIs are still limited. There are still significant challenges to predict and understand DDIs mediated by renal drug transporters. For example, it is still difficult to precisely locate the actual sites (apical vs. basal membranes) of renal DDIs *in vivo*. While the plasma concentrations of the inhibitor drug are used for DDI prediction, the actual concentrations of inhibitor that the transporter encounters at the site of inhibition may be significantly different and difficult to measure. Lastly, substrate-dependent and time-dependent inhibitions have been recently reported<sup>136–139</sup>, which further complicates the assessment and *in vitro*–to–*in vivo* prediction of DDIs. Nevertheless, the field of drug transporters is rapidly evolving. With the conceptual and technological advancements in drug transport research, we are now at the forefront to gain a better understanding of renal drug transporters, predict and ameliorate adverse renal DDIs, and design beneficial DDIs to improve drug efficacy and minimize drug toxicity.

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