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TRANSPORTERS AND RENAL DRUG ELIMINATION

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■ **Abstract** Carrier-mediated processes, often referred to as transporters, play key roles in the reabsorption and secretion of many endogenous and xenobiotic compounds by the kidney. The renal proximal tubule is the primary site of active transport for a wide variety of substrates, including organic anions/cations, peptides, and nucleosides. During the past decade, significant advances in molecular identification and characterization of transporter proteins have been made. Although it is generally noted that these transporters significantly contribute to renal drug handling and variability in drug disposition, the extent of our knowledge regarding the specific roles of such transporters in drug disposition and drug-drug interactions remains, for the most part, limited. In this review, we summarize recent progress in terms of molecular and functional characterization of renal transporters and their clinical relevance to drug therapy.

INTRODUCTION

Maintenance of fluid and electrolyte homeostasis is known to be a critical function provided by the kidney. In addition, the kidney plays an important role in the elimination of numerous endobiotics and xenobiotics. To accomplish this task, renal tubular epithelial cells express a variety of transporter proteins with diverse substrate specificities. Such transporters are predominantly localized to the proximal tubules and utilize ATP or transmembrane ion gradients to drive the vectorial movement of substrate compounds. Based on their preferential substrate selectivity, the renal transport systems have often been classified as either organic anion or cation transport systems (1). Application of molecular biology technologies has led to the molecular and functional characterization of many renal transporter proteins, including those for organic ions, peptides, and nucleosides (see Table 1). Moreover, these renal transporters have been shown to directly transport or interact with a number of clinically utilized drugs (1–5).

Despite our increasing knowledge of the molecular identity and substrate specificity of individual transporter proteins, the extent of our knowledge regarding the roles of these transporters in the overall renal handling of drugs and drug-drug interactions remains limited. In this review, we summarize some of the recent

TABLE 1 Molecular characteristics of renal transporters

Gene product		Gene symbol	Chromosome localization	Accession No.	Main location		Transport mechanism
					Tissue	Sub-cellular	
OAT1	Human	*SLC22A6*	11q13.1-13.2	NM_004790	K, B	BL	OA/HCO_3^- antiport
Oat1	Rat	*Slc22a6*	1	NM_017224		BL	
	Mouse		19	NM_008766			
OAT2	Human	*SLC22A7*	6p21.2-21.1	NM_006672	L, K	BL	
Oat2	Rat	*Slc22a7*	9q12	NM_053537		AP	
	Mouse		17	NM_144856			
OAT3	Human	*SLC22A8*	11q11.7	NM_004254	K, B	BL	
Oat3	Rat	*Slc22a8*	1	NM_031332		BL	
	Mouse		19	NM_031194			
OAT4	Human	*SLC22A11*	11q12.3	NM_018484	K, P	AP	
Oatp1	Rat	*Slc21a1*	4q44	NM_017111	L, K, B	AP	OA/GSH or HCO_3^- antiport
	Mouse		6	NM_013797			
Oatp3	Rat	*Slc21a7*	4	NM_030838	K, E	AP	
	Mouse		6	NM_130861			
OATP-A	Human	*SLC21A3*	12p12	NM_005075	B, L, K	AP	
OATP-B	Human	*SLC21A9*	11q13	NM_007256	B, L, K, I		
OATP-D	Human	*SLC21A11*	15q26	NM_013272	Ub		
Oatp-D	Mouse	*Slc21a11*	7	NM_023908			
OATP-E	Human	*SLC21A12*	20q13.33	NM_016354	Ub		
Oatp-E	Rat	*Slc21a12*		NM_133608			
	Mouse		2	NM_148933			

(*Continued*)

Oat-k1	Rat	*Slc21a4*	4	NM_030837	K	AP	
Oat-k2	Rat	*Slc21a4*			K	AP	
MRP1	Human	*ABCC1*	16p13.1	NM_004996	Ub	BL	Primary active
Mrp1	Mouse	*Abcc1*	16	NM_008576			
MRP2	Human	*ABCC2*	10q24	NM_000392	L, I, K, B	AP	Primary active
Mrp2	Mouse	*Abcc2*	19	NM_013806			
MRP3	Human	*ABCC3*	17q22	NM_003786	L, I, K, P, A	BL	Primary active
Mrp3	Mouse	*Abcc3*	11	NM_029600			
MRP4	Human	*ABCC4*	13q32	NM_005845	Ub	AP	Primary active
Mrp4	Rat	*Abcc4*	15	XM_224522			
MRP5	Human	*ABCC5*	3q27	NM_005688	Ub	BL	Primary active
Mrp5	Mouse	*Abcc5*	16	NM_013790			
MRP6	Human	*ABCC6*	16p13.1	NM_001171	K, L	BL	Primary active
Mrp6	Mouse	*Abcc6*	7	NM_018795			
MDR1	Human	*ABCB1*	7q21.1	NM_000927	B, I, K	AP	Primary active
mdr1a/	Rat	*Abcb1*	4	NM_012623		AP	Primary active
mdr1b	Mouse		5	NM_011075			
OCT1	Human	*SLC22A1*	6q26	NM_003057		BL	Potential driven, electrogenic
			17	NM_009202			
Oct1	Rat	*Slc22a1*	1	NM_012697		BL	
	Mouse		17	NM_009202			

(*Continued*)

TABLE 1 (*Continued*)

Gene product		Gene symbol	Chromosome localization	Accession No.	Main location		Transport mechanism
					Tissue	Sub-cellular	
OCT2	Human	*SLC22A2*	6q26	NM_003058	K, B, I	AP	Potential driven, electrogenic
Oct2	Mouse	*Slc22a2*	17	NM_013667			
OCT3	Human	*SLC22A3*	6q26-q27	NM_021977	P, K, B, I		
Oct3	Mouse	*Slc22a3*	17	NM_011395			
OCTN1	Human	*SLC22A4*	5q31.1	NM_003059	K, L	AP	OC/H^+ antiport
Octn1	Mouse	*Slc22a4*	11	NM_019687			
OCTN2	Human	*SLC22A5*	5q31	NM_003060	K, L, B, I	AP	OC/carnitine antiport
Octn2	Rat	*Slc22a5*	10	NM_019269			
	Mouse		11	NM_011396			
PEPT1	Human	*SLC15A1*	13q33-q34	NM_005073	I, K	AP	Peptide/H^+ symport
Pept1	Rat	*Slc15a1*	15	NM_057121		AP	
	Mouse		14	NM_053079			
PEPT2	Human	*SLC15A2*	3q13.33	NM_021082	K	AP	Peptide/H^+ symport
Pept2	Rat	*Slc15a2*	11	NM_031672			
	Mouse		16	NM_021301			
CNT1	Human	*SLC28A1*	15q25-26	NM_004213	K		Nucleoside/Na^+ cotransport
Cnt1	Rat	*Slc28A1*	1	NM_053863			
CNT2	Human	*SLC28A2*	15q15	NM_004212	K		Nucleoside/Na^+ cotransport
Cnt2	Mouse	*Slc28a2*	2	NM_172980			

Abbreviations: A, adrenal gland; AP, apical; B, brain; BL, basolateral; I, intestine; K, kidney; L, Liver; OA, organic anion; OC, organic cation; P, placenta; Ub, ubiquitous.

advances relating to the molecular and functional characterization of renal drug transporters. We also specifically outline the key transporter families associated with renal transport of organic anions, organic cations, peptides, and nucleosides, focusing on their substrate and inhibitor specificities (see Tables 2–5). (A more extensive table is available by following the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org). The impact of renal transporters on drug elimination and drug-drug interactions, as well as a potential relevance of genetic polymorphisms in these transporters, is also examined.

ORGANIC ANION TRANSPORT SYSTEMS

The organic anion transport system includes a number of structurally divergent transporters with broad substrate specificity. Studies in this area have utilized competition for p-aminohippurate (PAH) secretion as a marker for renal organic anion transporters. However, renal anion transport has been shown to be mediated by a number of transporters expressed in renal tubular cells (1, 6, 7). Since the molecular cloning of a PAH transporter termed OAT1 (8, 9), additional organic anion-transporting proteins have been identified at both basolateral and apical membranes. These organic anion transporters belong to various transporter families, including the organic anion transporters (OATs), organic anion transporting polypeptides (OATPs), and multidrug resistance-associated proteins (MRPs) transporter families (Tables 2 and 3). Certain members of such transporter families have been shown to play critical roles in the elimination of a number of drugs [e.g., β-lactam antibiotics, anticancer agents, diuretics, nonsteroidal antiinflammatory drugs (NSAIDs), anti-HIV drugs, and angiotensin-converting enzyme inhibitors] and drug metabolites (especially conjugates to glutathione or glucuronide).

Functional Characteristics of Organic Anion Transport Systems

Renal tubular secretion of organic anions can be functionally described by two distinct processes: (*a*) cellular uptake of organic anions across the basolateral membrane and (*b*) efflux of organic anions into urine across the apical membrane (Figure 1, left panel). Because of the intracellular negative potential maintained by the renal tubular cells, the uptake of negatively charged anions across the basolateral membrane tends to require energy-dependent active transport. Uptake of PAH, a marker substrate for the renal organic anion transport system, is accomplished by a tertiary active process coupled to an outward α-ketoglutarate (α-KG) gradient. The outward gradient of α-KG is sustained mainly by the Na^+/α-KG cotransport system driven by the inward Na^+ gradient, established and maintained by the Na^+/K^+-ATPase (1). Besides this classical PAH transporter (OAT1), an additional Na^+-dependent uptake system has been characterized for bulky organic anions (OAT2/3). On the apical side, efflux of organic anions is thought to occur via anion exchange and/or facilitated diffusion and a Na^+-independent ATP-driven system (4). Currently, it is not known which of these transport mechanisms are

TABLE 2 Organic anion transporter (OAT) and organic anion transporting polypeptide (OATP) families

Name		Substrates	Inhibitors
OAT1 (*SLC22A6*)	Human	PAH, α-KG Drugs: anti-HIV drugs, MTX	Probenecid, urate Drugs: β-lactam antibiotics, NSAIDs, diuretics
Oat1 (*Slc22a6*)	Rat	PAH, α-KG, cAMP, cGMP, folate, ochratoxin A, PGE_2, urate Drugs: β-lactam antibiotics, anti-HIV drugs, MTX	Probenecid, glutarate Drugs: β-lactam antibiotics, NSAIDs, diuretics, antidiabetic agents
OAT2 (*SLC22A7*)	Human	PAH, α-KG, cAMP, PGE_2, $PGF_{2\alpha}$ Drugs: AZT, MTX	Probenecid, BSP Drugs: β-lactam antibiotics, NSAIDs
Oat2 (*Slc22a7*)	Rat	PAH, α-KG, PGE_2, $PGF_{2\alpha}$ Drugs: NSAIDs, AZT, MTX, zalcitabine	BSP, cholate Drugs: β-lactam antibiotics, NSAIDs, bumetanide, enalapril, glibenclamide, rifampicin, verapamil
OAT3 (*SLC22A8*)	Human	PAH, cAMP, estrone-S, $E_2 17\beta G$, ochratoxin A, PGE_2, urate Drugs: AZT, cimetidine, MTX, salicylate	Probenecid, BSP, cholate, corticosterone, TEA Drugs: β-lactam antibiotics, diuretics, NSAIDs, quinidine
Oat3 (*Slc22a8*)	Rat	PAH, estrone-S, ochratoxin A Drugs: benzylpenicillin, cimetidine	Probenecid, BSP, cholate, taurocholate Drugs: β-lactam antibiotics, diuretics, AZT, MTX, quinidine
OAT4 (*SLC22A11*)	Human	PAH, estrone-S, ochratoxin A Drugs: AZT, cimetidine, MTX	Probenecid, BSP, corticosterone Drugs: β-lactam antibiotics, diuretics, NSAIDs
Oatp1 (*Slc21a1*)	Rat	LTC_4, BSP, DNP-SG, aldosterone, cortisol, $E_2 17\beta G$, estrone-S, ochratoxin A, thyroid hormones, bile acids Drugs: BQ123, dexamethasone, cardiac glycosides, enalapril, fexofenadine, pravastatin	Probenecid, steroids Drugs: atorvastatin, furosemide, lovastatin, simvastatin

(*Continued*)

Oatp3 (*Slc21a7*)	Rat	PGE_2, DHEA-S, $E_2 17\beta G$, estrone-S, LTC_4, BSP, thyroid hormones, bile acids Drugs: BQ123, cardiac glycosides, fexofenadine, rocuronium	6′,7′-Dihydroxybergamottin, furanocoumarins in grapefruit juice
OATP-A (*SLC21A3*)	Human	BSP, DHEA-S, $E_2 17\beta G$, estrone-S, PGE_2, thyroid hormones, ochratoxin A, bile acids Drugs: BQ123, CRC220, chlorambucil, fexofenadine, ouabain, rocuronium	Leu-Enkephalin Drugs: anti-HIV drugs, dexamethasone, erythromycin, lovastatin, naloxone, naltrindole, quinidine, verapamil
OATP-B (*SLC21A9*)	Human	Estrone-S, PGE_2 Drug: benzylpenicillin	
OATP-D (*SLC21A11*)	Human	Estrone-S, PGE_2 Drug: benzylpenicillin	
OATP-E (*SLC21A12*)	Human	Estrone-S, PGE_2, taurocholate, thyroid hormones Drug: benzylpenicillin	BSP
OAT-K1 (*Slc21a4*)	Rat	DHEA-S, $E_2 17\beta G$, estrone-S, folate, ochratoxin A, taurocholate, thyroid hormones Drugs: AZT, MTX	Probenecid, PAH, BSP, folate Drugs: NSAIDs, furosemide, valproate
Oat-k2 (*Slc21a4*)	Rat	DHEA-S, $E_2 17\beta G$, estrone-S, PGE_2, folate, ochratoxin A, taurocholate, thyroid hormones Drugs: AZT, digoxin, MTX	Probenecid, PAH, BSP, 17β-estradiol Drugs: cardiac glycosides, benzylpenicillin, dexamethasone, furosemide, indomethacin, levofloxacin, prednisolone, valproate

Abbreviations: α-KG, α-ketoglutarate; AZT, azidothymidine; BQ123, cyclo [Trp-Asp-Pro-Val-Leu]; BSP, bromosulfophthalein; DHEA-S, dehydroepiandrosterone-sulfate; DNP-SG, S-(dinitrophenyl)-glutathione; $E_2 17\beta G$, estradiol-17β-D-glucuronide; estrone-S, estrone sulfate; LTC_4, leukotriene C_4; MTX, methotrexate; PAH, p-aminohippurate; PGE_2, $PGF_{2\alpha}$, prostaglandin E2, F2α; TEA, tetraethylammonium.

TABLE 3 ABC transporter family

Name		Substrates	Inhibitors
MRP1 (*ABCC1*)	Human	LTC_4, bilirubin-glucuronide, glutathione conjugates, GSH, PAH, fluo-3, calcein Drugs: etoposide-glucuronide, *S*-(ethacrynic acid)-glutathione, MTX	Probenecid, ochratoxin A Drugs: benzbromarone, CSA, *S*-(decyl)-glutathione, indomethacin, MK571, sulfinpyrazone, valspodar
MRP1 (*Abcc1*)	Mouse	LTC_4, calcein, APA-SG Drugs: daunorubicin, vincristine	GSSG Drugs: arsenate, genistein, MK571
MRP2 (*ABCC2*)	Human	LTC_4, $E_2 17\beta G$, bilirubin-glucuronide, glutathione conjugates, GSH, PAH, ochratoxin A, fluo-3 Drugs: anti-HIV drugs, benzbromarone, furosemide, indomethacin, MTX, vinblastine	Probenecid, BSP Drugs: CSA, glibenclamide, MK571
Mrp2 (*Abcc2*)	Rat	LTC_4, LTD_4, $E_2 17\beta G$, anionic glucuronide conjugates, bilirubin-glucuronide, BSP, endothelin-1, fluo-3, folate, GSH, GSSG Drugs: cefpiramide, ceftriaxone, indomethacin, irinotecan and SN-38, MTX, pravastatin	Probenecid Drugs: CSA, glibenclamide, MK571
MRP3 (*ABCC3*)	Human	LTC_4, DNP-SG, $E_2 17\beta G$, folate, glycocholate Drug: MTX	Drugs: benzbromarone, MK571
Mrp3 (*Abcc3*)	Rat	LTC_4, $E_2 17\beta G$, bile acids Drugs: E3040-glucuronide, MTX	Anionic glucuronide/ GSH conjugates
MRP4 (*ABCC4*)	Human	$E_2 17\beta G$, cAMP, cGMP Drugs: adefovir, AZTMP, MTX	Probenecid, anionic glucuronide conjugates Drugs: benzbromarone, sildenafil, trequinsin, zaprinast
MRP5 (*ABCC5*)	Human	DNP-SG, cAMP, cGMP, GSH Drugs: adefovir, 6-MP	Probenecid Drugs: benzbromarone, sildenafil, trequinsin, zaprinast
MRP6 (*ABCC6*)	Human	LTC_4, NEM-SG Drug: BQ123	Probenecid Drugs: benzbromarone, indomethacin

(*Continued*)

TABLE 3 (*Continued*)

Name		Substrates	Inhibitors
MDR1 (*ABCB1*)	Human	$E_2 17\beta$G, calcein, fluo-3, rhodamine 123 Drugs: cardiac glycosides, anti-HIV drugs, anticancer agents, verapamil	Progesterone Drugs: amiodarone, amitriptyline, chlorpromazine, diltiazem, dipyridamole, elacridar, fluphenazine, fucidin, lovastatin, mefloquine, phenothiazines, pimozide, propafenone, propranolol, quinine, quinidine, reserpine, simvastatin, spironolactone, staurosporin, tamoxifen, trifluoperazine, triflupromazine, valspodar
mdr1a/ mdr1b (*Abcb1*)	Rat/Mouse	Rhodamine 123 Drugs: anti-HIV drugs, CSA, dexamethasone, digoxin, doxorubicin, fexofenadine, ivermectin, verapamil, vinblastine	

Abbreviations: APA-SG, azidophenacyl-S-glutathione; AZTMP, azidothymidine monophosphate; BQ123, (cyclo [Trp-Asp-Pro-Val-Leu]); BSP, bromosulfophthalein; CSA, cyclosporine A; DNP-SG, S-(dinitrophenyl)-glutathione; $E_2 17\beta$G, estradiol-17β-D-glucuronide; GSH, reduced glutathione; GSSG, oxidized glutathione; LTC_4/LTD_4, leukotriene C_4/D_4; MK571, 3-[3-[2-(7-chloroquinolin-2-yl)vinyl]phenyl]-(2-dimethylcarbamoyl-ethylsulfanyl) methylsulfanyl] propionic acid; 6-MP, 6-mercaptopurine; MTX, methotrexate; NEM-SG, N-ethylmaleimide glutathione; PAH, p-aminohippurate.

represented by the recently cloned apical organic anion transporters (e.g., OAT4, OATP, OAT-K1/K2).

Identification of Organic Anion Transporters

Molecular cloning studies have revealed that most of the organic anion transporters belong to OAT, OATP, and MRP transporter families. In this section, we summarize the available data relating to individual organic anion transporters and their possible roles in renal drug elimination.

OAT FAMILY The prototypical basolateral organic anion transporter in kidney was first cloned from the rat (Oat1) (8, 9), followed by the subsequent identification of a human ortholog (OAT1) (10–13). OAT1 is thought to mediate the uptake of the prototypical organic anion, PAH, using an exchange mechanism for intracellular dicarboxylates (HCO_3^-) (11, 12). Rat Oat1 has been shown to directly transport or interact with at least 100 known drugs/compounds from various classes: β-lactam antibiotics; diuretics; NSAIDs; antiviral drugs; and antidiabetic, antiepileptic, and antineoplastic agents (see Reference 8). The substrate specificity of human OAT1

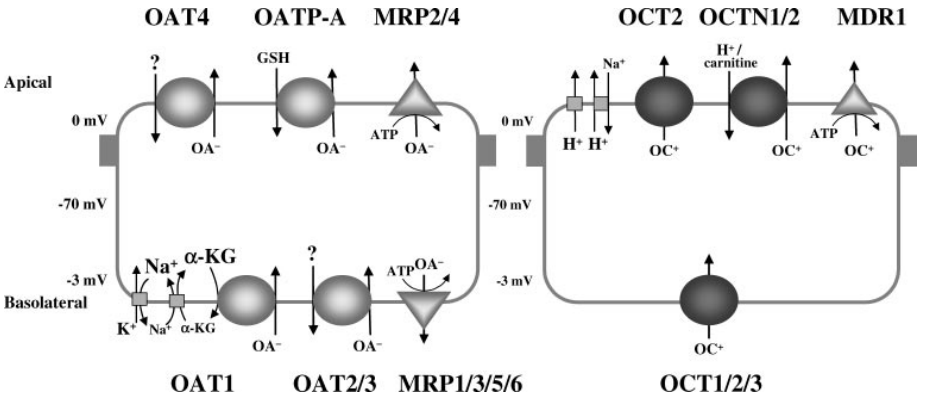

Figure 1 Functional models of organic anion (*left panel*) and cation (*right panel*) transporters in the renal proximal tubules.

appears to be more restricted relative to rat Oat1. However, reported substrates of OAT1 include antiviral agents, such as adefovir, cidofovir, zidovudine (AZT), acyclovir, and ganciclovir (14–16). It is possible that altered OAT1 function may be a risk factor for nephrotoxicity associated with the use of these antiviral agents. However, the extent of OAT1 contribution to the renal drug elimination remains to be clarified.

Variants of OAT1 have been identified as a result of alternative splicing (10, 13). The two major variants, OAT1-1 (563 amino acids) and OAT1-2 (550 amino acids), appeared to be functionally similar (10). The splice variants, OAT1-3 and OAT1-4, having a 132-bp deletion, have been reported to be nonfunctional when expressed in COS 7 cells (17).

Following the cloning of OAT1, three additional members of the OAT family, OAT2, OAT3, and OAT4, were recently identified. Oat2 was first isolated from a rat cDNA library and was named NLT (novel liver-specific transport protein) (18). Subsequently, Sekine and coworkers found that NLT transports organic anions and proposed to rename NLT as rat Oat2 (19). Rat Oat2 mRNA was highly expressed in the liver and low but significantly expressed in the kidney (18, 19). In contrast to OAT1, rat Oat2 does not appear to be driven by an outwardly directed α-KG gradient (19). It appears that transport via rat Oat2 may be facilitative or involve an as yet unidentified mechanism. Rat Oat2 is localized to the apical side of renal tubular cells (20) and transports PAH, methotrexate (MTX), acetylsalicylate, α-KG, and prostaglandin E_2 (PGE_2) (Table 2). The human ortholog, OAT2, was localized to the basolateral side of the proximal tubules (21). Human OAT2 and rat Oat2 appear to share some substrates, such as cephalosporin antibiotics (22) and NSAIDs (e.g., diclofenac, ibuprofen, ketoprofen) (23, 24). However, some NSAIDs appeared to have different affinity, in terms of Ki values, for rat Oat2 versus human OAT2 (23, 24).

OAT3 was initially cloned from both rat (Oat3) (25) and human (OAT3*/OAT3) kidney (12, 26). Rat Oat3 mRNA was detected in the liver, brain, and kidney (25). When expressed in oocytes, rat Oat3 mediated the uptake of organic anions (e.g., PAH, estrone sulfate, ochratoxin A) and the cationic drug cimetidine (25). Human OAT3*, bearing 84% similarity to rat Oat3, was cloned as the first human OAT3 transporter, and its expression was detected at high levels in the kidney and at low levels in other tissues (12). However, human OAT3* was found incapable of transporting PAH or any other previously tested organic anion substrates (12). Another OAT3 cDNA (OAT3) has been recently cloned with 85% similarity to OAT3* (26). Human OAT3 showed strong expression in the kidney, in particular, on the basolateral membrane of the proximal tubules (26). OAT3 mediated the transport of PAH, estrone sulfate, MTX, and cimetidine in a Na^+-independent manner (Table 2). OAT3 also interacted with chemically diverse compounds, such as NSAIDs, diuretics, bile salts, and tetraethylammonium (TEA) (26). These findings suggest that OAT3 may possess broader substrate specificity than OAT1. At present, it is not known whether OAT3 and OAT3* are formed by alternative splicing or encoded by different genes.

OAT4 cDNA was cloned from a human kidney and found to be abundantly expressed in both the placenta and kidney (27). Although OAT4 protein was localized to the apical proximal tubules (28), the driving force of OAT4-mediated transport is unknown. Steroid sulfates and ochratoxin A are high-affinity substrates of OAT4, whereas PAH is only weakly transported (27). OAT4 has also been shown to transport AZT and MTX (16, 29). Inhibition studies revealed that OAT4 interacts with a wide variety of organic anions, including probenecid, indomethacin, furosemide, and ibuprofen (Table 2). Unlike other OAT family members, OAT4 is expressed in the placenta, suggesting an important role of this transporter in the elimination or detoxification of harmful anionic compounds from the fetus. The role of OAT4 in regulating renal drug elimination and placental drug permeability has yet to be elucidated.

OATP FAMILY Rat Oatp1, the first member of the OATP family, was cloned from a rat liver cDNA library (30). Oatp1 mRNA was detected in various tissues, including the liver, kidney, and brain. In the rat kidney, Oatp1 protein was localized to the apical proximal tubules (31). The range of Oatp1 substrates is extremely broad in that Oatp1 transports anionic, cationic, and neutral compounds as well as drugs such as enalapril (32), fexofenadine (33), and pravastatin (34). The transport mechanism of Oatp1 may involve solute/HCO_3^- exchange, solute/GSH exchange, or another as yet unidentified mechanism (35, 36).

Rat Oatp3 has been cloned independently by two groups (37, 38). Abe et al. (37) found high-level expression of Oatp3 in rat retina and kidney, whereas Walters et al. (38) detected Oatp3 in tissues other than retina and kidney from Sprague-Dawley rats. This apparent discrepancy in tissue distribution of Oatp3 has been attributed to possible differences between rat strains (39). Rat Oatp3 mediates the uptake of bile acids, which suggests its role as an intestinal bile acid transporter

(38). Xenobiotic substrates (e.g., fexofenadine, digoxin, ouabain) have also been reported to interact with rat Oatp3 (40, 41), but the role of Oatp3 in renal drug elimination remains to be clarified.

OATP-A (also known as human OATP or OATP1) was the first human OATP to be cloned and characterized (42). OATP-A mRNA has been detected in various tissues, including the brain, liver, and kidney (42). Based on chromosome mapping and amino acid similarity, OATP-A was proposed to be the human ortholog of rat Oatp3 (38). Whether this is the case for OATP-A requires further investigation (43). Functional studies indicated that OATP-A mediates the Na^+-independent uptake of a number of compounds, including bromosulfophthalein (BSP), bile acids, steroid conjugates, fexofenadine, ouabain, and rocuronium (30, 33, 42, 44).

Human OATP-B was cloned from a brain cDNA library (43) and was also noted to be expressed in various tissues, including the liver, lung, and kidney. OATP-B, however, exhibits very restricted substrate specificity (45); thus, its importance in renal drug elimination is currently unclear. Human OATP-D and OATP-E are ubiquitously expressed (43). Estrone-sulfate and PGE_2 are transported by OATP-D and OATP-E, but again, the importance of these transporters in renal drug elimination remains uncertain.

OAT-K1 and OAT-K2 are also members of the OATP family and encode kidney-specific transporters. Rat Oat-k1 was isolated from a rat kidney cDNA library and appeared to be exclusively expressed in the kidney (46). Oat-k1, localized to the apical side of the kidney, showed narrow substrate specificity (e.g., MTX, AZT, folate) but was inhibited by a large number of compounds, including NSAIDs (e.g., ibuprofen, flufenamate, phenylbutazone) (Table 3). This finding suggested that Oat-k1 could be one of the target sites for drug interactions between MTX and NSAIDs in the kidney. Oat-k2, a smaller Oat-k1 homolog, was isolated from a rat kidney (47). Similar to Oat-k1, Oat-k2 was expressed exclusively in the kidney and localized functionally to the apical side (47). Oat-k1 and Oat-k2 have been implicated as the major excretory route of MTX from the proximal tubular cells because these transporters are capable of transporting MTX coupled to the exchange of folic acid derivatives, contributing to so-called folinic acid rescue (48–50).

MRP FAMILY MRP1 was initially identified from a human multidrug-resistant cancer cell line (51). MRP1 mRNA was detected in numerous tissues, including the liver, lung, and kidney (52). MRP1 mediates ATP-dependent transport of a variety of glucuronide, sulfate, and GSH conjugates (53–57). MRP2 (also known as cMOAT) is involved in the ATP-dependent transport of anionic conjugates across the hepatocyte canalicular membrane (58). Rats lacking functional Mrp2 expression (e.g., Wistar TR^- and Sprague-Dawley EHBR strains) are hyperbilirubinemic as a result of their inability to excrete bilirubin conjugates into bile (59–61). Similarly, the absence of MRP2 in humans results in Dubin-Johnson syndrome, a disease noted for conjugated hyperbilirubinemia (62). These findings

indicate that bilirubin-glucuronide conjugates are important substrates for MRP2. In the kidney, MRP2 is expressed on the apical side of proximal tubules (63) and can also mediate the transport of nonconjugated compounds, such as PAH (55), vinblastine (64), and HIV protease inhibitors (e.g., saquinavir, ritonavir, indinavir) (65). A number of nonsynonymous single nucleotide polymorphisms (SNPs) resulting in loss of transporter function and aberrant RNA splicing have been identified in patients with Dubin-Johnson syndrome (66–68). However, due to the rarity of this syndrome, little is known regarding whether patients with Dubin-Johnson syndrome have significant alterations in the disposition of MRP2 substrate drugs.

Human MRP3 is expressed in various tissues, including the liver, kidney, and intestine (69). MRP3 appears to be an important basolateral MRP isoform in these tissues (70–73). Functional studies have demonstrated that MRP3 transports anionic glucuronide and glutathione conjugates as well as drugs, including MTX (Table 4). MRP3 was also shown to confer cellular drug resistance to etoposide, tenoposide, and vincristine (70, 71).

Expression of MRP4 mRNA has been detected in several tissues, including the kidney (74). MRP4 was localized to the apical side of renal proximal tubules (75). MRP4 can mediate probenecid-sensitive ATP-dependent transport of MTX, estradiol-17β-glucuronide ($E_2$17βG), cAMP, and cGMP (75, 76). MRP4 also

TABLE 4 Organic cation transporter (OCT) family

Name		Substrates	Inhibitors
OCT1 (*SLC22A1*)	Human	MPP^+, TEA Drugs: acylclovir, ganciclovir	Choline, creatinine, corticosterone, desipramine, dopamine, β-estradiol, nicotine, NMN, progesterone Drugs: anti-HIV drugs, acebutolol, amantadine, cimetidine, clonidine, disopyramide, midazolam, procainamide, prazosin, quinine, quinidine, vecuronium, verapamil
Oct1 (*Slc22a1*)	Rat	TEA, MPP^+, NMN, monoamine neurotransmitters Drugs: AZT, cimetidine, cladribine, cytarabine, D-tubocurarine	Corticosterone, guanidine, histamine, nicotine, *o*-methylisoprenaline Drugs: clonidine, desipramine, mepiperphenidol, procainamide, reserpine, quinine, quinidine
OCT2 (*SLC22A2*)	Human	TEA, MPP^+, NMN, agmatine, monoamine neurotransmitters Drugs: amantadine, memantine	Corticosterone, *o*-methylisoprenaline, progesterone, SKF550 Drugs: despramine, mepiperphenidol, phenoxybenzamine, procainamide, quinine

(*Continued*)

TABLE 4 (*Continued*)

Name		Substrates	Inhibitors
Oct2 (*Slc22a2*)	Rat	TEA, MPP^+, adrenaline, agmatine, creatinine, monoamine neurotransmitters Drugs: amantadine, cimetidine, memantine	Corticosterone, dexoycorticosterone, β-estradiol, NMN, progesterone, monoamine neurotransmitters Drugs: cimetidine, cisplatin, procainamide, quinine
OCT3 (*SLC22A3*)	Human	MPP^+, guanidine, monoamine neurotransmitters Drugs: cimetidine, tyramine	Corticosterone, β-estradiol, MPTP, *o*-methylisoprenaline, progesterone, SKF550 Drugs: clonidine, desipramine, imipramine, phenoxybenzamine, prazosin, procainamide
Oct3 (*Slc22a3*)	Rat	MPP^+, TEA, guanidine	Monoamine neurotransmitters, corticosterone, dexoycorticosterone, β-estradiol, NMN, progesterone, testosterone Drugs: amphetamine, cimetidine, clonidine, desipramine, methamphetamine
OCTN1 (*SLC22A4*)	Human	TEA, MPP^+, L-carnitine, acetyl-L-carnitine Drugs: pyrilamine, quinidine, verapamil	D-carnitine, nicotine Drugs: cephaloridine, cimetidine, procainamide, quinine
Octn1 (*Slc22a4*)	Rat	TEA, MPP^+	DMA, nicotine Drugs: cimetidine, desipramine, imipramine, procainamide, verapamil
OCTN2 (*SLC22A5*)	Human	TEA, MPP^+, L, D-carnitine, acetyl-l-carnitine, betaine, choline, cysteine, lysine, methionine Drugs: pyrilamine, quinidine, valproate, verapamil	Aldosterone, corticosterone, MPTP, nicotine Drugs: cephalosporin antibiotics, cimetidine, clonidine, desipramine, emetine, procainamide, pyrilamine, quinine
Octn2 (*Slc22a5*)	Rat	L-carnitine, TEA	MPTP, nicotine Drugs: cephalosporin antibiotics, cimetidine, clonidine, despramine, procainamide

Abbreviations: AZT, azidothymidine; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NMN, N^1-methylnicotinamide; SKF550, (9-fluorenyl)-N-methyl-β-chloroethylamine; TEA, tetraethylammonium.

mediates cellular drug resistance to many antiviral drugs, including adefovir, PMEG [9-(2-phosphonylmethoxyethyl)-guanine], and AZT (77, 78). Pharmacokinetic studies in humans have indicated that the kidney is the primary excretory organ for antiviral drugs such as adefovir and cidofovir (79). Thus, it is possible that MRP4-mediated excretion of these antiviral drugs contributes, in part, to the nephrotoxicity associated with certain antiviral drugs.

MRP5 has been detected in numerous tissues, including the kidney, but immunolocalization analysis has yet to be performed (74, 80). Similar to human MRP1, MRP5 appears to traffic to the basolateral membrane upon expression in MDCKII cells and mediates the transport of *S*-(dinitrophenyl)-glutathione (DNP-SG) and GSH (81). Unlike MRP1, overexpression of MRP5 did not confer significant resistance to most anticancer agents (80). However, MRP5-transfected HEK293 cells were found to develop resistance against adefovir and the anticancer drugs 6-mercaptopurine and thioguanine (81). MRP5 was also shown to mediate ATP-dependent export of cAMP and cGMP (82). Furthermore, cGMP transport was blocked with phosphodiesterase inhibitors (e.g., sildenafil, trenquisin), which suggests a dual mode of action for this class of drugs. With its ubiquitous distribution in the body, MRP5 may play a role in the disposition and elimination of drugs.

MRP6 is an unusual member of the MRP family. Rat Mrp6 does not transport any of the prototypical MRP substrates, such as DNP-SG, leucotriene C_4 (LTC_4), or $E_2 17\beta G$ (83). The only substrate identified so far is the peptidomimetic compound BQ123 (83). Immunolocalization has detected MRP6 on the basolateral membrane of renal proximal tubules and hepatocytes (83, 84). Mutations in the *MRP6* gene have been linked to the connective tissue disorder Pseudoxanthoma elasticum (PXE) (85, 86). A variety of missense, splice, insertion, and deletion mutations have been associated with PXE. Whether MRP6 functions as a clinically relevant ATP-dependent drug transporter remains to be investigated.

ORGANIC CATION TRANSPORT SYSTEMS

In the kidney, the organic cation transport systems mediate the reabsorption and excretion processes of numerous structurally divergent cationic compounds. Substrates for the organic cation transporters include endogenous cations (e.g., guanidine, choline, N^1-methylnicotinamide, NMN, monoamine neurotransmitters), cationic toxins (e.g., 1-methyl-4-phenylpyridium, MPP^+), and cationic drugs (e.g., TEA, cimetidine, procainamide, quinidine, vecuronium, cardiac glycosides). The cationic compounds TEA and NMN have been used as model substrates for studying organic cation transport. Early studies using isolated rat hepatocytes have suggested that there exist two different transport systems for organic cations: a type 1 system for small hydrophilic organic anions and a type 2 system for hydrophobic organic cations (87, 88). A number of multispecific organic cation transporters have now been cloned and characterized at the molecular level.

Functional Characteristics of Organic Cation Transport Systems

Similar to the organic anion transport system, secretion of cationic compounds by renal tubular cells is maintained by two coordinate processes: the basolateral uptake and secretion across the apical membrane (Figure 1, right panel). Unlike anionic compounds, which require active transport, organic cations appear to enter proximal tubular cells by facilitated diffusion because the electrogenic membrane potential favors the inward movement of cationic solutes. OCT1 and OCT2 are likely to be the main basolateral facilitated diffusion carriers, although some controversy exists in terms of membrane localization of OCT2 (89–91). Secretion of organic cations across the apical membrane appears to be driven by the transmembrane H^+ gradient. The H^+ gradient is in turn generated by a Na^+/H^+ exchanger and/or H^+-ATPase. Another transport system involved in efflux of organic cations is the MDR1/P-glycoprotein. P-glycoprotein mediates the efflux of a broad spectrum of cationic and hydrophobic drugs via an ATP-dependent mechanism.

Identification of Organic Cation Transporters

In this section, we summarize the available data relating to key transporters involved in organic cation transport (OCT family and P-glycoprotein) and consider their possible roles in renal drug elimination.

OCT FAMILY The first member of the OCT family, OCT1, was cloned from rat kidney (89). Rat Oct1 mRNA was detected in the liver, intestine, and kidney. Immunolocalization studies demonstrated that rat Oct1 was localized to the basolateral membrane of the renal proximal tubular cells (92, 93). When expressed in oocytes, rat Oct1 stimulated the uptake of TEA, inhibitable by various model organic cations (89). A novel splice variant of rat Oct1, termed Oct1A (104-bp deletion at the 5′ end), was later cloned by Zhang and coworkers (94). The human ortholog, OCT1, was found to be expressed most strongly in the liver, although other tissues, including the kidney and intestine, were found to have detectable levels of OCT1 (94, 95). Although it has been shown that hydrophobicity is a major determinant of drug interactions with OCT1 (96), significant differences have been found among the cloned OCT1 transporters from different species in terms of the kinetics and substrate selectivities (97). These findings suggest that OCT1 may be responsible, in part, for interspecies differences in disposition of organic cations. Recently, genetic variations of *OCT1* have been identified, including nonsynonymous polymorphisms in *OCT1* associated with altered transport function and substrate selectivity in vitro (98). Whether these variations lead to alterations in renal drug handling remains to be examined.

Other gene products with significant homology with OCT1 have also been identified. Okuda et al. (99) isolated rat Oct2 from a rat kidney cDNA library. Rat Oct2 mRNA was detected predominantly in the kidney, but not in the liver, lung,

or intestine. Immunolocalization of rat Oct2 indicated that it was localized to the basolateral membrane of the proximal tubules (90, 100). Rat Oct2 has been shown to interact with structurally divergent cationic compounds, such as MPP^+, cimetidine, NMN, nicotine, quinine, and quinidine (93). The human ortholog, OCT2, has also been identified (95). Interestingly, unlike rat Oct2, human OCT2 was localized to the apical side of the distal tubule (95). The reason for the observed species differences in the localization of OCT2 in the kidney has not been determined. In the brain, OCT2 was found to mediate the Na^+-independent transport of monoamine neurotransmitters and the antiparkinsonian drug, amantadine (101). Recently, genetic variations in human *OCT2* associated with altered activity in vitro have been defined (102). Because OCT2 appears to be the most abundant OCT isoform expressed in the kidney, it is possible that altered OCT2 function could lead to changes in renal handling of certain cationic drugs.

OCT3 was first cloned from a rat placental cDNA library (103). Subsequently, the human and mouse orthologs were identified (104–106). Unlike OCT1 and OCT2, OCT3 was expressed at high levels in placenta. Assessment of rodent Oct3 and human OCT3 mRNA revealed expression in multiple tissues, including the kidney (103, 106). Cell membrane localization of OCT3 has not been determined. Functional expression studies have demonstrated OCT3-mediated transport of prototypical organic cations, such as TEA, guanidine, and MPP^+ (103, 105). Rat Oct3 interacted with dopamine, the neurotoxins amphetamine and methamphetamine, as well as a variety of steroids (107). Although human OCT3 transports a variety of organic cations, including catecholamines (104, 105), compared to other OCT isoforms, OCT3 appears to be selectively inhibited by corticosterone and *o*-methylisoprenaline (108).

Two additional members of the OCT family, OCTN1 and OCTN2, have been identified based on their homology to OCT. OCTN1 was first cloned from human fetal liver by Tamai and coworkers (109). Initial studies suggested that OCTN1 has a broad tissue distribution, in that high levels of OCTN1 mRNA were detected in fetal kidney, lung, and liver as well as adult kidney, trachea, and bone marrow (109). When expressed in HEK293 cells, TEA efflux mediated by OCTN1 was stimulated by acidic pH in the external media, which suggests that transport via OCTN1 might be driven by a H^+ gradient (110). OCTN1 transported other drugs and endogenous compounds, including quinidine, verapamil, and carnitine (110). In addition, OCTN1 was inhibited by a number of drugs, including cimetidine, procainamide, pyrilamine, quinine, cephaloridine, and verapamil (110).

Human OCTN2 was originally cloned from a human placental trophoblast cell line using homology screening. Since then, the mouse and rat homologs of OCTN2 have also been isolated (111, 112). OCTN2 was strongly expressed in adult human brain, kidney, skeletal muscle, placenta, heart, prostate, and thyroid gland (113). When expressed in HEK293 cells, unlike most organic cation transporters, OCTN2 mediated the uptake of L-carnitine in a sodium-dependent fashion, whereas it mediated only minor uptake of TEA (113). Interestingly, the rat ortholog, Octn2, mediated the uptake of TEA to a greater extent than carnitine (112). It was found

that rat Octn2 can function as a Na^+-independent organic cation transporter and as a Na^+-dependent carnitine transporter (112). Wagner and coworkers (114) have shown that carnitine transport via OCTN2 is electrogenic, but additional experiments suggested that OCTN2 does not function as an organic cation/H^+ antiporter (114). Mutations in the *OCTN2* gene have been causally linked to primary systemic carnitine deficiency, an autosomal recessive disease characterized by low serum and intracellular concentrations of carnitine (115–119). Seth et al. (120) demonstrated that two mutations in OCTN2, namely P478L and L352R, resulted in complete loss of carnitine transport function, but P478L actually had higher organic cation transport activity than the wild type. These findings suggest that the binding sites for carnitine and organic cations in OCTN2 significantly overlap but are not identical.

MDR1/P-GLYCOPROTEIN MDR1/P-glycoprotein (P-gp), a member of the ATP-binding cassette (ABC) multidrug transporter superfamily, mediates active secretion of drugs with diverse structures (e.g., anthracyclines, vinca alkaloids, taxol, actinomycin D, digoxin). Although the cellular drug efflux mediated by P-gp was first identified in cancer cells, P-gp was found to be highly expressed in a number of normal tissues. P-gp plays an important role in limiting the entry of xenobiotics into specific anatomic sites, such as the brain and gastrointestinal tract, and in facilitating the systemic removal of xenobiotics from the liver and kidney (121). In the kidney, P-gp is expressed on the apical side of proximal tubules, where it secretes various drug substrates into the lumen (122). The observation that digoxin is actively secreted by the renal proximal tubules via P-gp is of particular clinical importance for drug-drug interactions (123). Genetic variations in the *MDR1* gene have been extensively studied. The reader is referred to the recent reviews on the pharmacogenetics of the *MDR1* gene (124, 125). However, it appears that the observed effects of known *MDR1* polymorphisms are variable and conflicting in some cases (126). Further investigation is required to assess the effects of the *MDR1* genetic variations on renal drug elimination.

PEPTIDE TRANSPORT SYSTEMS

Peptide transporters are expressed on the apical membranes of intestinal and renal epithelial cells, mediating the efficient absorption of oligopeptides. Peptide transporters also mediate the uptake of peptidelike drugs, such as β-lactam antibiotics (127, 128), angiotensin-converting enzyme (ACE) inhibitors (129), and the dipeptidelike anticancer drug bestatin (130, 131). Early studies with renal apical membrane vesicles established that the apical uptake of peptides is an electrogenic, H^+-dependent system (132). Additionally, it has been shown that the uptake of glycylsarcosine in renal apical membranes is mediated by at least two distinct peptide transport systems: a high-affinity/low-capacity and a low-affinity/high-capacity system (Table 5) (133).

TABLE 5 Peptide transporter (PEPT) and nucleoside transporter families

Name		Substrates	Inhibitors
PEPT1 (*SLC15A1*)	Human	Glycylsarcosine, di-, tripetides Drugs: β-lactam antibiotics, cyclacillin, valacyclovir	Valine, pentaglycine Drugs: β-lactam antibiotics, bestatin, ACE inhibitors
Pept1 (*Slc15a1*)	Rat	Glycylsarcosine, di-, tripetides Drugs: bestatin, β-lactam antibiotics	Drugs: β-lactam antibiotics, ACE inhibitors, tolbutamide, chlorpropamide
PEPT2 (*SLC15A2*)	Human	Glycylsarcosine, ALA Drugs: bestatin, cephalexin, valacyclovir	Drugs: β-lactam antibiotics
Pept2 (*Slc15a2*)	Rat	Glycylsarcosine Drug: valacylclovir	Drugs: β-lactam antibiotics, bestatin, chlorpropamide, glibenclamide, tolbutamide
CNT1 (*SLC28A1*)	Human	Adenosine, thymidine, uridine, Drugs: AZT, zalcitabine	
Cnt1 (*Slc28a1*)	Rat	Adenosine, thymidine, uridine Drug: AZT	Drugs: cytarabine, floxidine, gemcitabine, idoxuridine, zalcitabine
CNT2 (*SLC28A2*)	Human	Adenosine, uridine, inosine, thymidine Drugs: cladribine, didanosine	
Cnt2 (*Slc28a2*)	Rat	Adenosine, guanosine, inosine, thymidine, uridine Drug: didanosine	

Abbreviations: ACE, angiotensin converting enzyme; ALA, delta-aminolevulinic acid; AZT, azidothymidine.

Molecular cloning studies have identified two homologous peptide transporters, designated as PEPT1 and PEPT2. PEPT1 was first cloned from the rabbit intestine (134), and subsequently rat (131) and human (135) orthologs were identified. Rat Pept1 was localized to the apical side of intestinal epithelial cells (136) and in early regions (S1 segments) of apical proximal tubules (137). The substrates for PEPT1 include β-lactam antibiotics (138, 139), the antiviral drugs (e.g., valacyclovir, valganciclovir) (140, 141), and the ACE inhibitor captopril (142).

PEPT2, first identified by Liu et al. (143), appeared to have different tissue localization than PEPT1 in that PEP2 is highly expressed in the kidney but not in the intestine. Rat Pept2 was localized to the apical side of the proximal tubule in more distal regions (S3 segments) compared to rat Pept1 (137). Aside from differential localization in the proximal tubule, rat Pept1 versus Pept2 appear to have differential substrate selectivity. For example, rat Pept1 and Pept2 expressed in LLC-PK1 cells interacted differently with β-lactam antibiotics (138, 139). Differences in transport affinity between PEPT1 versus PEPT2 have also been observed with ACE inhibitors (e.g., quinapril, enalapril) (144, 145) and valacyclovir (146).

NUCLEOSIDE TRANSPORT SYSTEMS

Most nucleosides, including those with antineoplastic or antiviral activities, are hydrophilic and require specialized nucleoside transporter proteins for their uptake into or release from cells (147). To date, two general mechanisms of nucleoside transport have been identified: the concentrative inwardly directed Na^+/nucleoside cotransport system (CNT family) and the equilibrative bidirectional facilitators (ENT family) (148). Members of both the CNT and ENT family are found in renal epithelium (147, 148). CNT1 and CNT2 are responsible for the concentrative Na^+-dependent high-affinity transport of pyrimidine and purine nucleosides, respectively (148). These nucleoside transporters may play a critical role in the absorption, disposition, and targeting of therapeutically used nucleosides and nucleoside analogs.

CLINICAL IMPLICATIONS OF TRANSPORTERS-MEDIATED DRUG INTERACTIONS

Many drugs are dependent on renal transporters for their ultimate urinary elimination. Combined use of drugs that interact with renal transporters may increase the risk for drug interactions. Indeed, probenecid inhibits renal secretion of other anionic drugs through inhibition of the organic anion transport system(s). Renal excretion of penicillin derivatives and various other drugs (e.g., cidofovir, ciprofloxacin, cisplatin) was decreased by coadministration of probenecid in humans (see Reference 4). Combination therapy with MTX and NSAIDs can often result in severe MTX toxicity, such as bone marrow depression, hepatitis, or renal insufficiency (149). This MTX-NSAID interaction may be explained by the inhibitory effect of NSAIDs on the renal excretion of MTX (via OAT-K1 and/or OAT-K2) (150). Other drugs, such as cimetidine and trimethoprim, appear to be potent inhibitors of the renal tubular secretion of a number of cationic drugs (e.g., procainamide and its active metabolite N-acetylprocainamide), which results in adverse drug side effects (151).

Also, as noted above, clinical use of digoxin has been complicated by drug interactions leading to severe digoxin toxicity. When coadministered with compounds that inhibit P-gp transport activity [e.g., quinidine (152), clarithromycin (153), ritonavir (154)], tubular secretion of digoxin is diminished, thereby leading to an increase in plasma digoxin concentration. It should be noted that for the same drugs, inhibition of P-gp may enhance the CNS entry of clinically useful drugs such as HIV protease inhibitors (155–157).

PERSPECTIVES

Focused studies of drug transporters in the kidney have significantly enhanced our understanding of the cellular and molecular basis of transporter-mediated drug elimination and interactions. A large number of drug transporters, including OAT,

OATP, OCT, and ABC transporter families, as well as peptide/nucleoside transporters have been shown to play a role in renal drug disposition (Tables 2–5). Additional studies on the physiological and pharmacological roles of each cloned transporter to the overall renal handling of drugs are needed. A better understanding of the extent of species differences in terms of substrate selectivity, tissue distribution, and expressed level of drug transporters is required to better predict the in vivo kinetic profile of substrate drugs. Furthermore, future studies focused on transporter genotype versus phenotype may also provide valuable insights into the structure-function relationship of drug transporters and the in vivo relevance of genetic heterogeneity in drug transporters. Similarly, a better insight into the molecular mechanisms governing renal drug elimination is likely to aid in the design or use of drugs with greater safety profiles.

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