Organic Cation Transporters (OCTs, MATEs), In Vitro and In Vivo Evidence for the Importance in Drug Therapy

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Contents

1 Introduction 106
2 Cloning and Molecular Characterization of OCT and MATE Transporters 108
2.1 OCT Transporters 108
2.2 MATE Transporters 125
3 Tissue Distribution and Subcellular Localization 125
3.1 OCT1 126
3.2 OCT2 126
3.3 OCT3 128
3.4 MATE1 and MATE2-K 128
4 Functional Characterization of OCT and MATE Transporters 128
4.1 Common Functional Properties of OCTs 128
4.2 Substrate and Inhibitor Specificities of Human OCTs 129
4.3 Drug–Drug Interactions Involving OCTs 130
4.4 Common Functional Properties of MATEs 131
4.5 Substrate and Inhibitor Specificities of MATEs 131
4.6 Drug–Drug Interactions Involving MATEs 131
5 Knockout Mouse Models 132
5.1 Oct1 Knockout Mice 132
5.2 Oct2 Single-Knockout and Oct1/Oct2 Double-Knockout Mice 133
5.3 Oct3 Knockout Mice 133
5.4 Mate1 Knockout Mice 134

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6 Pharmacogenomics of OCT and MATE Transporters 134
6.1 Identification of Genetic Variants, Their Predicted Consequences, and Their Effects In Vitro 134
6.2 Interethnic Variability 135
6.3 Phenotype–Genotype Correlations 140
References 157

Abstract Organic cation transporters (OCTs) of the solute carrier family (SLC) 22 and multidrug and toxin extrusion (MATE) transporters of the SLC47 family have been identified as uptake and efflux transporters, respectively, for xenobiotics including several clinically used drugs such as the antidiabetic agent metformin, the antiviral agent lamivudine, and the anticancer drug oxaliplatin. Expression of human OCT1 (SLC22A1) and OCT2 (SLC22A2) is highly restricted to the liver and kidney, respectively. By contrast, OCT3 (SLC22A3) is more widely distributed. MATEs (SLC47A1, SLC47A2) are predominantly expressed in human kidney. Data on in vitro studies reporting a large number of substrates and inhibitors of OCTs and MATEs are systematically summarized. Several genetic variants of human OCTs and in part of MATE1 have been reported, and some of them result in reduced in vitro transport activity corroborating data from studies with knockout mice. A comprehensive overview is given on currently known genotype–phenotype correlations for variants in OCTs and MATE1 related to protein expression, pharmacokinetics/-dynamics of transporter substrates, treatment outcome, and disease susceptibility.

Keywords Drug transporters · Organic cation transport · Excretion · OCT1 · OCT2 · OCT3 · MATE1 · MATE2-K · Liver · Kidney · tissue distribution · Knockout mice · Pharmacogenomics · Genotype–phenotype correlation · Metformin · Single nucleotide polymorphisms · Drug response · Interindividual variability · Drug–drug interaction · Pharmacokinetics

1 Introduction

A large number of clinically used drugs are administered orally, from which approximately 40% are cations or weak bases at physiological pH (Neuhoff et al. 2003). For absorption, distribution, metabolism, and elimination (ADME), they need to be taken up into and effluxed from various cell types in the body. Several families of membrane transporters have been recognized to play a role in the transport of organic cations across the plasma membrane. These include members of the solute carrier (SLC) family 22 (organic cation transporters, OCTs) and of the SLC family 47 (multidrug and toxin extrusion, MATEs) (Koepsell et al. 2007). The

human SLC22 family can be divided into several subgroups according to substrates and transport mechanisms (Koepsell and Endou 2004) (Fig. 1). One subgroup comprises OCT1, OCT2, and OCT3, which translocate organic cations and weak bases in an electrogenic manner. Human MATE transporters have only recently been identified as proton/cation antiporters participating in the excretion of organic cations in the liver and kidney (Otsuka et al. 2005; Masuda et al. 2006). Alterations in the expression and function of these transporters may significantly contribute to drug pharmacokinetics and the interindividual variability of drug response. This review summarizes current knowledge about the molecular characteristics, tissue

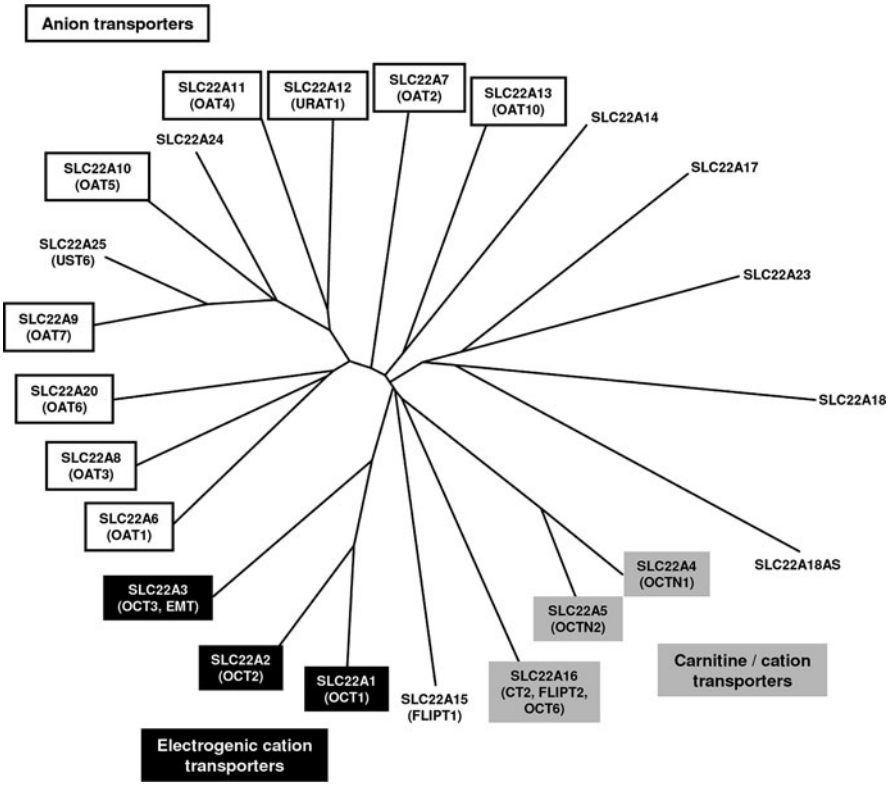

Fig. 1 Phylogenetic tree of the 23 transporters of the human SLC22 family. Protein sequences were downloaded from the NCBI gene database and aligned with the ClustalX2 program (Larkin et al. 2007). The tree was drawn with the "drawtree" program of the PHYLIP3.67 program package (http://evolution.genetics.washington.edu/phylip.html). The distance along the branches is inversely correlated to the degree of sequence identity. For example, the amino acid sequence identity of OCT1 and OCT2 is 70% and that of OCT1 and URAT1 31%. Electrogenic cation transporters are marked by *black boxes*, transporters for organic cations and carnitine by *gray boxes*, and transporters for organic anions by *white boxes*. Transporters whose function is as yet unknown are unmarked

distribution, (drug) substrates and inhibitors, drug–drug interactions, and the fast-growing field of pharmacogenomics of human OCT and MATE transporters.

2 Cloning and Molecular Characterization of OCT and MATE Transporters

A large number of physiological and biochemical studies had suggested the presence of different carrier systems mediating the transport of organic solutes in hepatocytes and renal proximal tubule cells (Giacomini et al. 1988; Boyer et al. 1992). However, molecular identification of these transporters succeeded not until molecular biology techniques became available in the late 1980s. The first member of the electrogenic OCT family was isolated from rat kidney by expression cloning (Gründemann et al. 1994). It took another 11 years until Otsuka et al. identified in 2005 human orthologs of the bacterial MATE family as proton/organic cation exchangers responsible for the electroneutral transport of organic cations into bile and urine.

2.1 OCT Transporters

The genes encoding human OCT1 (gene symbol: SLC22A1), OCT2 (SLC22A2), and OCT3 (SLC22A3) are located in a cluster on chromosome 6q26–q27 and have a common structure of 11 coding exons and 10 introns (Koehler et al. 1997; Gründemann et al. 1998; Hayer et al. 1999; Verhaagh et al. 1999; Gründemann and Schömig 2000). The amino acid sequence identity of OCT1 and OCT2 is 70%, and 50% for both OCT1/OCT3 and OCT2/OCT3. OCT orthologs have been cloned from other mammalian species as well (Koepsell et al. 2007) (Fig. 2).

Based on sequence and hydropathy analyses, OCTs have a predicted topology comprising 12 transmembrane helices, an intracellular amino and carboxyl terminus, and a large glycosylated extracellular loop between the first two transmembrane helices (Fig. 3a). The large intracellular loop between transmembrane helix 6 and 7 carries several putative phosphorylation sites that are used for short-term modulation of OCT activity (Koepsell et al. 2007; Ciarimboli 2008). Employing detailed mutagenesis and modeling of the tertiary structure in analogy to the crystallized structure of lactose permease from *Escherichia coli* (Abramson et al. 2003), several amino acids in the 4th, 10th, and 11th transmembrane helix of rat Oct1 were identified that are involved in substrate and/or inhibitor binding (Gorboulev et al. 1999, 2005; Popp et al. 2005; Sturm et al. 2007; Volk et al. 2009). These amino acids are localized within the center of a large cleft that may exist in an outward- or inward-facing conformation. The cleft contains high- and low-affinity substrate and/or inhibitor binding sites (Popp et al. 2005; Gorbunov

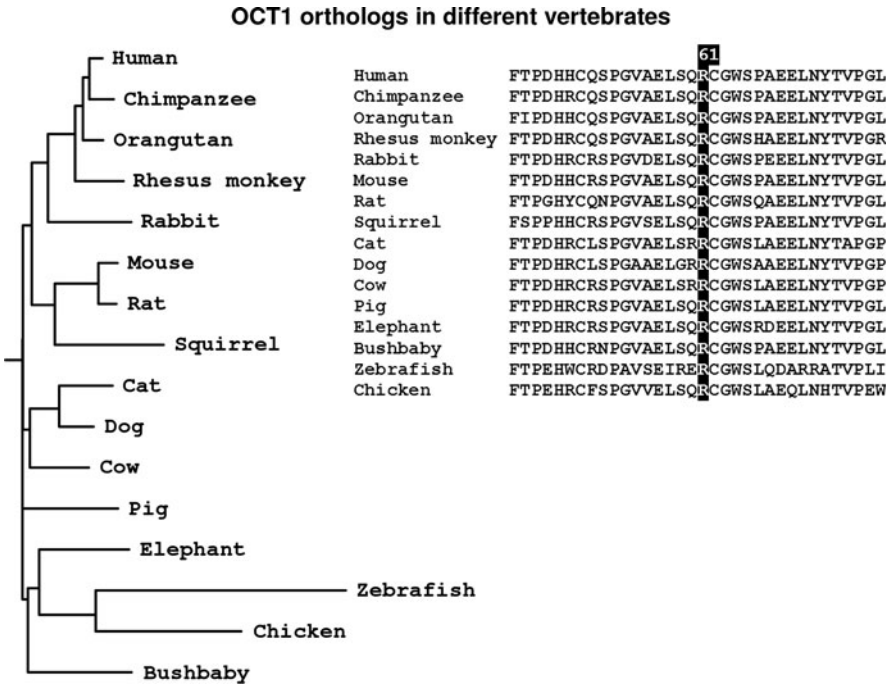

Fig. 2 OCT1 orthologs in different vertebrates. The phylogenetic tree on the left was constructed from OCT1/Oct1 protein sequences aligned using the ClustalX2 program (Larkin et al. 2007) and drawn with the "drawgram" program of the PHYLIP3.67 program package (http://evolution.genetics.washington.edu/phylip.html). The sequence comparison on the right shows the aligned sequences in the vicinity of amino acid arginine 61, which is highly conserved among species. A genetic variant was identified in human OCT1 that leads to a nonsynonymous exchange of arginine 61 to a cysteine (Kerb et al. 2002; Shu et al. 2003). OCT1-Cys61 shows a reduced in vitro transport function (Kerb et al. 2002; Shu et al. 2003, 2007), is associated with a significant decrease of hepatic OCT1 protein levels (Nies et al. 2009), and affects metformin pharmacokinetics in humans (Shu et al. 2008). For further details see Tables 4–12. The following protein sequences were used for alignments: human NP_003048; orangutan ENSPPYP00000019207; chimpanzee XP_527554; rhesus monkey ENSMMUP00000020546; dog XP_850971; mouse NP_033228; rat NP_036829; cow NP_001094568; pig NP_999154; elephant ENSLAFP00000009760; cat ENSFCAP00000002624; chicken XP_419621; rabbit ENSOCUP00000002189; bushbaby ENSOGAP00000004719; squirrel ENSSTOP00000008083; zebrafish ENSDARP00000048889. Accession numbers are either from the ENSEMBL genome server (http://www.ensembl.org; numbers starting with "ENS") or from the "Protein" database at http://www.ncbi.nlm.nih.gov/entrez. Sequences from elephant, cat, rabbit, bushbaby, and squirrel are in part incomplete

et al. 2008; Minuesa et al. 2009; Volk et al. 2009). Whereas the affinities of the low-affinity substrate binding sites are in the same range as the respective Michaelis-Menten constant values, the high-affinity binding sites may have a 10,000-fold higher affinity. The different substrate and inhibitor binding sites overlap and may exhibit competitive or allosteric interactions. Both the low- and high-affinity sites may be inhibitory (Minuesa et al. 2009). High-affinity binding sites may be also

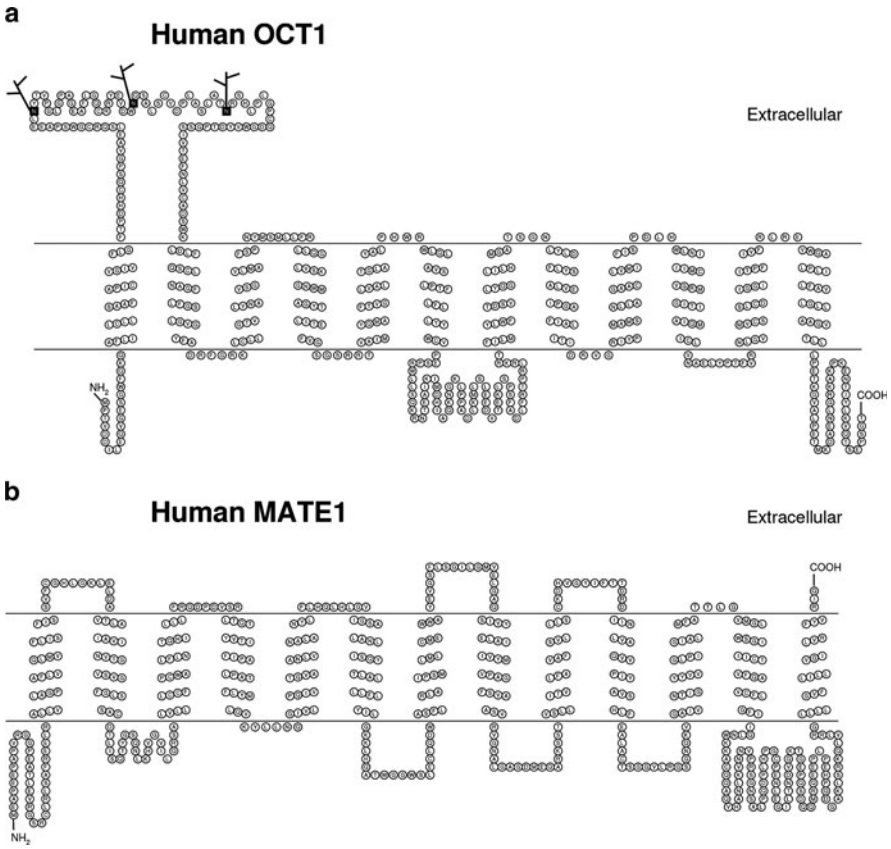

Fig. 3 Predicted membrane topology models of human OCT1 (**a**) and human MATE1 (**b**). Topology prediction was performed with the TMHMM algorithm (http://www.cbs.dtu.dk/services/TMHMM-2.0) and the model was drawn with TOPO2 (http://www.sacs.ucsf.edu/TOPO-run/wtopo.pl). (**a**) Tree-like structures indicate the location of putative *N*-glycosylation sites in OCT1. OCT2 and OCT3 have similar predicted secondary structures as OCT1. (**b**) There are no putative *N*-glycosylation sites in MATE1. Thirteen transmembrane segments are also predicted for human MATE2 and for most of the orthologs from other mammalian species (Terada and Inui 2008)

involved in transport since for inhibition of organic cation transport different IC_{50} values may be obtained when the uptake measurements were performed using different substrate concentrations far below the respective K_m values (see e.g. Table 2: inhibition of OCT2-mediated MPP uptake by flecainide or quinidine). The existence of various substrate and inhibitor binding sites and the complex interactions between different sites explains why largely different IC_{50} values were obtained for individual transporters when different substrates were used for transport measurements (see, e.g., Tables 1–2: inhibition of OCT1-mediated TEA uptake versus MPP uptake by dopamine or histamine, or inhibition of OCT1-mediated TEA uptake vs. ASP uptake by quinidine). Many naturally occurring

Table 1 Physiological substrates and inhibitors of OCTs and MATEs

Compound	Physiological function	OCT1	OCT2	OCT3	MATE1	MATE2-K	References
Corticosterone	Hormone	$7^{5\ TEA;\ B}$ $8.9^{1\ YM;\ E}$ $22^{0.025\ MPP;\ C}$	$5.4^{1\ YM;\ E}$ $34^{0.025\ MPP;\ C}$	$0.12^{MPP;\ A}$ $0.29^{0.025\ MPP;\ C}$	$>20^{50\ TEA;\ D}$		A: Gründemann et al. (1998), B: Zhang et al. (1998), C: Hayer-Zillgen et al. (2002), D: Otsuka et al. (2005) and E: Minematsu et al. (2010)
β-Estradiol	Hormone	$5.7^{0.025\ MPP}$	$>30^{0.025\ MPP}$	$2.9^{0.025\ MPP}$			Hayer-Zillgen et al. (2002)
Progesterone	Hormone	$3.1^{0.025\ MPP}$	$27^{0.025\ MPP}$	$4.3^{0.025\ MPP}$			Hayer-Zillgen et al. (2002)
Prostaglandin E_2	Hormone, locally acting	$\boldsymbol{K_m}$**: 0.66** controversial	$\boldsymbol{K_m}$**: 0.03** controversial				Kimura et al. (2002) and Harlfinger et al. (2005)
Prostaglandin $F_{2\alpha}$	Hormone, locally acting	$\boldsymbol{K_m}$**: 0.48** controversial	$\boldsymbol{K_m}$**: 0.33** controversial				Kimura et al. (2002) and Harlfinger et al. (2005)
Testosterone	Hormone	$10^{0.1\ MPP}$	$3^{0.1\ MPP}$	$44^{0.1\ MPP}$			Koepsell et al. unpubl.
Choline	Metabolite	$3{,}540^{0.05\ TEA;\ B}$ $16{,}700^{0.1\ MPP;\ D}$ potential substrate	$\boldsymbol{K_m}$**: 210**$^{\mathbf{Ooc;\ A}}$	$23{,}800^{0.1\ MPP;\ D}$	$>5{,}000^{50\ TEA;\ C}$		A: Gorboulev et al. (1997) B: Bednarczyk et al. (2003) C: Otsuka et al. (2005) and D: Koepsell et al. (unpublished)
Creatinine	Metabolite	$>1{,}000^{0.1\ MPP;\ D}$	$6{,}060^{5\ TEA;\ C}$ $42{,}400^{10\ AG;\ C}$	$15{,}700^{0.1\ MPP;\ D}$	Substrate^{A}	Substrate$^{A,\ B}$	A: Tanihara et al. (2007), B: Masuda et al. (2006), C: Kimura et al. (2009) and D: Koepsell et al. (unpublished)
Estrone sulfate	Metabolite				$\boldsymbol{K_m}$**: 470**	$\boldsymbol{K_m}$**: 850**	Tanihara et al. (2007)
Guanidine	Metabolite	$5{,}030^{0.1\ MPP;\ F}$	$2{,}200^{5\ Crea;\ B}$ $2{,}300^{10\ TEA;\ C}$ $2{,}300^{0.1\ MPP;\ F}$ $3{,}030^{5\ TEA;\ E}$ potential substrate	$6{,}201^{0.03\ MPP;\ A}$	$\boldsymbol{K_m}$**: 2,100**^{D}	$\boldsymbol{K_m}$**: 4,200**^{D}	A: Wu et al. (2000), B: Urakami et al. (2004), C: Suhre et al. (2005), D: Tanihara et al. (2007), E: Kimura et al. 2009 and F: Koepsell et al. (unpublished)
L-Carnitine	Metabolite	$12{,}400^{0.1\ MPP}$	$13{,}000^{0.1\ MPP}$	$5{,}590^{0.1\ MPP}$			Koepsell et al. (unpublished)

(*continued*)

Table 1 (continued)

Compound	Physiological function	OCT1	OCT2	OCT3	MATE1	MATE2-K	References
N-1-Methyl-nicotinamide	Metabolite	$1{,}035^{0.05\ TEA;\ C}$ $7{,}700^{5\ TEA;\ B}$	$266^{60\ TEA\ Ooc;\ A}$ $303^{10\ TEA;\ E}$ $310^{5\ Crea;\ D}$ $\sim 1{,}000^{61\ YM;\ G}$	$3{,}000^{0.1\ MPP;\ H}$		Substrate[F]	A: Gorboulev et al. (1997), B: Zhang et al. (1998), C: Bednarczyk et al. (2003), D: Urakami et al. (2004), E: Suhre et al. (2005), F: Masuda et al. (2006), G: Minematsu et al. (2010) and H: Koepsell et al. (unpublished)
Thiamine	Metabolite	$434^{0.05\ TEA;\ A}$			Substrate[C]	Substrate[B,C]	A: Bednarczyk et al. (2003), B: Masuda et al. (2006) and C: Tanihara et al. (2007)
Agmatine	Metabolite, neuromodulator	$24{,}000^{0.1\ MPP}$	**K_m: 1,400**	**K_m: 2,500**			Gründemann et al. (2003)
Cyclo(His-Pro)	Metabolite, neuromodulator	**K_m: 655**	**K_m: 74**	**K_m: 126**			Taubert et al. (2007)
Salsolinol	Metabolite, neuromodulator	**K_m: 440**	**K_m: 130**	**K_m: 139**			Taubert et al. (2007)
Tyramine	Metabolite, neuromodulator	$107^{0.05\ TEA;\ B}$		Substrate[A]			A: Gründemann et al. (1998) and B: Bednarczyk et al. (2003)
Acetylcholine	Neurotransmitter	$580^{0.2\ MPP\ Ooc;\ A}$	**K_m: 117**$^{Ooc;\ A}$ $149^{0.2\ MPP\ Ooc;\ A}$	$10{,}490^{0.1\ MPP;\ B}$			A: Lips et al. (2005) and B: Koepsell et al. (unpublished)
Dopamine	Neurotransmitter	$487^{0.05\ TEA;\ B}$ $>20{,}000^{0.1\ MPP;\ E}$	**K_m: 390**$^{Ooc;\ A}$ **K_m: 1,400**[D] $1{,}400^{5\ Crea;\ C}$	$1{,}200^{0.1\ MPP;\ E}$			A: Busch et al. (1998), B: Bednarczyk et al. (2003), C: Urakami et al. (2004), D: Amphoux et al. (2006) and E: Koepsell et al. (unpublished)

Epinephrine	Neurotransmitter	>30,000$^{0.1\ MPP;\ C}$	**K_m: 420**^{B}	**K_m: 240**^{A}		A: Gründemann et al. (1998), B: Amphoux et al. (2006), and C: Koepsell et al. (unpublished)
Histamine	Neurotransmitter	3,007$^{0.05\ TEA;\ C}$ >20,000$^{0.1\ MPP;\ E}$	**K_m: 940**^{D} **K_m: 1,300**$^{Ooc;\ A}$	**K_m: 180**^{B} **K_m: 220**^{D}		A: Busch et al. (1998), B: Gründemann et al. (1998), C: Bednarczyk et al. (2003), D: Amphoux et al. (2006) and E: Koepsell et al. (unpublished)
Norepinephrine	Neurotransmitter	7,100$^{0.1\ MPP;\ D}$	**K_m: 1,500**^{C} **K_m: 1,900**$^{Ooc;\ B}$	**K_m: 510**^{A} **K_m: 2,630**^{C}		A: Gründemann et al. (1998), B: Busch et al. (1998), C: Amphoux et al. (2006) and D: Koepsell et al. (unpublished)
Serotonin	Neurotransmitter	>20,000$^{0.025\ MPP;\ C}$	**K_m: 80**$^{Ooc;\ A}$ **K_m: 290**^{C}	1,000$^{0.025\ MPP;\ C}$	<100$^{50\ TEA;\ B}$	A: Busch et al. (1998), B: Otsuka et al. (2005) and C: Amphoux et al. (2006)

IC_{50} values and K_m values (explicitly stated) were measured in oocytes of *Xenopus laevis* or mammalian cell lines transfected with the respective transporter. Expression in oocytes is indicated (Ooc) when different results were obtained in the oocyte system. The substrates employed for inhibition measurements are indicated; abbreviations used are: *AG* aminoguanidine, *Crea* creatinine, *MPP* 1-methyl-4-phenylpyridinium, *TEA* tetraethylammonium, *YM* YM155. The employed substrate concentration is indicated when different results were obtained using different substrate concentrations far below the respective Michaelis-Menten constant. Bold face indicates cations, for which transport has been demonstrated. For example, corticosterone is an inhibitor of OCT1 with an IC_{50} value of 22 μM when measured with 0.025 μM MPP as the substrate

Table 2 Clinically used drugs as substrates and inhibitors of OCTs and MATEs

Therapeutic use	Compound	OCT1	OCT2	OCT3	MATE1	MATE2-K	References
Anesthetic	Ketamine	115[0.025 MPP]	23[0.025 MPP]	226[0.025 MPP]			Amphoux et al. (2006)
Anesthetic, local	Cocaine	85[0.025 MPP]	113[0.025 MPP]	>1,000[0.025 MPP]			Amphoux et al. (2006)
Anesthetic, local	Lidocaine		294[10 Metf; B]	**K_m: 139**[A] 656[0.2 His; A]			A: Hasannejad et al. (2004) and B: Umehara et al. (2008)
Antiallergic	Cetirizine				371[5 TEA]	818[5 TEA]	Tsuda et al. (2009b)
Antiallergic	Chlorpheniramine				88[5 TEA]	191[5 TEA]	Tsuda et al. (2009b)
Antiallergic	Clemastine	4.9[1 ASP]					Ahlin et al. (2008)
Antiallergic	Desloratidine		60[10 MPP]				Zolk et al. (2008)
Antiallergic	Fexofenadine				Substrate		Matsushima et al. (2009)
Antiallergic	Promethazine	35[1 ASP]					Ahlin et al. (2008)
Antiarrhythmic	Amiodarone			<100[10 MPP]			Sata et al. (2005)
Antiarrhythmic	Disopyramide	15–30[5 TEA; A] 82[1 ASP; C]	324[10 MPP; D]	457[0.2 His; B] substrate	84[5 TEA; E]	292[5 TEA; E]	A: Zhang et al. (1998), B: Hasannejad et al. (2004), C: Ahlin et al. (2008), D: Zolk et al. 2008 and E: Tsuda et al. (2009b)
Antiarrhythmic	Flecainide	42[0.001 MPP; A]	<191[10 MPP; B] >1,000[0.001 MPP; A]	60[0.001 MPP; A]			A: Umehara et al. (2008) and B: Zolk et al. (2008)
Antiarrhythmic	Mexiletine		55[10 MPP; B]	260[0.2 His; A]			A: Hasannejad et al. (2004) and B: Zolk et al. (2008)
Antiarrhythmic	Phenytoin			0.75[0.2 His]			Hasannejad et al. (2004)
Antiarrhythmic	Pilsicainide			66[0.2 His]			Hasannejad et al. (2004)
Antiarrhythmic	Procainamide	14.5[0.05 TEA; D] 51[1 YM; K] 74[5 TEA; B]	28[5 Crea; E] 50[60 TEA Ooc; A] 92[1 YM; K] 406[10 Metf; I]	355[0.2 His; F] 738[0.03 MPP; C] substrate[F]	217[5 TEA; J] **K_m: 1,230**[H]	178[5 TEA; J] **K_m: 1,580**[H] **K_m: 4,100**[G]	A: Gorboulev et al. (1997), B: Zhang et al. (1998), C: Wu et al. (2000), D: Bednarczyk et al. (2003), E: Urakami et al. (2004), F: Hasannejad et al. (2004), G: Masuda et al. (2006), H: Tanihara et al. (2007), I: Umehara et al. (2008), J: Tsuda et al. (2009b) and K: Minematsu et al. (2010)
Antiarrhythmic	Propafenone	11[1 ASP; A]	25[10 MPP; B]				A: Ahlin et al. (2008) and B: Zolk et al. (2008)

Antiarrhythmic	Quinidine	$5.4^{0.05\ TEA;\ B}$ $5.7^{1\ MPP;\ L}$ $6.7^{1\ MPP\ Ooc;\ G}$ $7.1^{1\ YM;\ K}$ $17^{0.001\ MPP;\ J}$ $18^{5\ TEA;\ A}$ $114^{1\ ASP;\ I}$	$7.1^{1\ YM;\ K}$ $8.7^{1\ MPP\ Ooc;\ G}$ $10^{5\ Crea;\ D}$ $13^{1\ MPP;\ L}$ $17^{10\ Metf;\ E}$ $87^{10\ MPP;\ H}$ $446^{0.001\ MPP;\ J}$	$14^{0.001\ MPP;\ J}$ $18^{1\ MPP\ Ooc;\ G}$ $22^{1\ MPP;\ L}$ $124^{0.2\ His;\ C}$ **K_m: 216**[C]	$29^{5\ TEA;\ F}$	$23^{5\ TEA;\ F}$	A: Zhang et al. (1998), B: Bednarczyk et al. (2003), C: Hasannejad et al. (2004), D: Urakami et al. (2004), E: Kimura et al. (2005a), F: Tsuda et al. 2009b, G: Bourdet et al. (2005), H: Zolk et al. (2008), I: Ahlin et al. (2008), J: Umehara et al. (2008), K: Minematsu et al. (2010) and L: Ming et al. (2009)
Antiarrhythmic	Verapamil	$1.2^{1\ YM;\ F}$ $2.9^{5\ TEA;\ A}$	$13.4^{1\ YM;\ F}$ $85^{10\ MPP;\ D}$		$28^{5\ TEA;\ E}$ $<100^{50\ TEA;\ B}$	$32^{5\ TEA;\ E}$ substrate[C]	A: Zhang et al. (1998), B: Otsuka et al. (2005), C: Masuda et al. (2006), D: Zolk et al. (2008), E: Tsuda et al. (2009b) and F: Minematsu et al. (2010)
Antiarrhythmic, antihypertensive	Oxprenolol	$29^{1\ ASP;\ A}$ $87^{0.001\ MPP;\ B}$	$>1{,}000^{0.001\ MPP;\ B}$	$326^{0.001\ MPP;\ B}$			A: Ahlin et al. (2008) and B: Umehara et al. (2008)
Antiarrhythmic, antihypertensive	Propranolol	$63^{1\ ASP;\ B}$ $113^{0.001\ MPP;\ C}$	$8.3^{10\ Metf;\ E}$ $229^{10\ MPP;\ D}$ $>300^{0.001\ MPP;\ C}$ substrate[A]	$133^{0.001\ MPP;\ C}$			A: Dudley et al. (2000), B: Ahlin et al. (2008), C: Umehara et al. (2008), D: Zolk et al. (2008) and E: Bachmakov et al. (2009)
Antiasthmatic	Beclomethasone		$4.4^{1\ TEA}$				Lips et al. (2005)
Antiasthmatic	Budesonide		$7.3^{1\ TEA}$				Lips et al. (2005)
Antibacterial	Cephalexin				6,500		Tanihara et al. (2007)
Antibacterial	Cephradine				4,040	10,400	Tanihara et al. (2007)
Antibacterial	Levofloxacin		$127^{5\ Crea;\ A}$		Substrate[B]		A: Okuda et al. (2006) and B: Tanihara et al. 2007
Antibacterial	Tetracycline					Substrate	Tanihara et al. (2007)
Antibacterial	Trimethoprim	$20^{MPP;\ D}$ $57^{1\ ASP;\ C}$	$21^{5\ Crea;\ A}$ $51^{MPP;\ D}$ $1{,}318^{10\ MPP;\ E}$	$<100^{10\ MPP;\ B}$			A: Urakami et al. (2004), B: Sata et al. (2005), C: Ahlin et al. (2008), D: Jung et al. (2008) and E: Zolk et al. (2008)
Anticoagulant	Nafamostat		20^{TEA}				Li et al. (2004)
Antidepressant	Citalopram	$3.1^{0.1\ MPP;\ B}$ $19^{1\ ASP;\ A}$	$12^{0.1\ MPP;\ B}$	$145^{0.1\ MPP;\ B}$			A: Ahlin et al. (2008) and B: Koepsell et al. (unpublished)
Antidepressant, tricyclic	Amitriptyline	$17^{1\ ASP;\ B}$	$14^{10\ MPP;\ C}$	$>100^{10\ MPP;\ A}$			A: Sata et al. (2005)B: Ahlin et al. (2008) and C: Zolk et al. (2008)

(*continued*)

Table 2 (continued)

Therapeutic use	Compound	OCT1	OCT2	OCT3	MATE1	MATE2-K	References
Antidepressant, tricyclic	Clomipramine	$19^{1\ ASP}$					Ahlin et al. (2008)
Antidepressant, tricyclic	Desipramine	$5.4^{5\ TEA;\ B}$ $57^{1\ ASP;\ D}$	$16^{60\ TEA;\ A}$	$14^{0.03\ MPP;\ C}$	$56^{5\ TEA;\ E}$	$283^{5\ TEA;\ E}$	A: Gorboulev et al. (1997), B: Zhang et al. (1998), C: Wu et al. (2000), D: Ahlin et al. (2008) and E: Tsuda et al. (2009b)
Antidepressant, tricyclic	Doxepin		$13^{10\ MPP}$				Zolk et al. (2008)
Antidepressant, tricyclic	Imipramine	$17^{1\ ASP;\ B}$	$6^{10\ MPP;\ C}$	$42^{0.03\ MPP;\ A}$	$42^{5\ TEA;\ D}$	$183^{5\ TEA;\ D}$	A: Wu et al. (2000), B: Ahlin et al. (2008), C: Zolk et al. (2008) and D: Tsuda et al. (2009b)
Antidepressant, tricyclic	Trimipramine	$28^{1\ ASP}$					Ahlin et al. (2008)
Antidiarrheal	Loperamide	$24^{1\ ASP}$					Ahlin et al. (2008)
Antiemetic	Diphenylhydramine	$3.4^{0.02\ MPP;\ A}$	$15^{0.02\ MPP;\ A}$	$695^{0.02\ MPP;\ A}$	$87^{5\ TEA;\ B}$	$267^{5\ TEA;\ B}$	A: Müller et al. (2005) and B: Tsuda et al. (2009b)
Antiemetic	Granisetron	$<100^{0.1\ MPP}$	$<100^{0.1\ MPP}$	$<100^{0.1\ MPP}$			Koepsell et al. (unpublished)
Antiemetic	Metoclopramide	$95^{1\ ASP;\ B}$		$<100^{10\ MPP;\ A}$			A: Sata et al. (2005) and B: Ahlin et al. (2008)
Antiemetic	Ondansetron	$20^{1\ ASP;\ A}$	$<100^{0.1\ MPP;\ B}$				A: Ahlin et al. (2008) and B: Koepsell et al. (unpublished)
Antiemetic	Promethazine	$17^{1\ ASP}$					Ahlin et al. (2008)
Antiemetic	Ramosetron			$<100^{10\ MPP}$			Sata et al. (2005)
Antiemetic	Tropisetron	$<100^{0.1\ MPP}$	$<100^{0.1\ MPP}$	$<100^{0.1\ MPP}$			Koepsell et al. (unpublished)
Antihypertensive	Bisoprolol		$2.4^{10\ Metf}$				Bachmakov et al. (2009)
Antihypertensive	Bucindolol	$27^{1\ ASP}$					Ahlin et al. (2008)
Antihypertensive	Captopril					Substrate	Masuda et al. (2006)
Antihypertensive	Carvedilol		$2.3^{10\ Metf;\ B}$ $63^{10\ MPP;\ A}$				A: Zolk et al. (2008) and B: Bachmakov et al. (2009)
Antihypertensive	Clonidine	$0.6^{1\ TEA;\ A}$ $0.7^{0.05\ TEA;\ C}$ $6.5^{0.02\ MPP;\ D}$ $23^{1\ ASP;\ F}$	$2.2^{10\ TEA;\ E}$ $16^{10\ MPP;\ G}$ $23^{0.02\ MPP;\ D}$	$110^{0.02\ MPP;\ D}$ $373^{0.03\ MPP;\ B}$			A: Zhang et al. (1998), B: Wu et al. (2000), C: Bednarczyk et al. (2003), D: Müller et al. (2005), E: Suhre et al. (2005), F: Ahlin et al. (2008) and G: Zolk et al. (2008)
Antihypertensive	Debrisoquine		$\boldsymbol{K_m}$**: 7.3**^{Ooc}				Koepsell et al. (unpublished)
Antihypertensive	Diltiazem	$12^{1\ ASP;\ B}$ $16^{0.001\ MPP;\ A}$	$>1{,}000^{0.001\ MPP;\ A}$	$50^{0.001\ MPP;\ A}$	$12.5^{5\ TEA;\ C}$	$117^{5\ TEA;\ C}$	A: Umehara et al. (2008), B: Ahlin et al. (2008) and C: Tsuda et al. (2009b)

Antihypertensive	Phenoxybenzamine	$2.7^{0.025\ MPP;\ A}$ $15^{1\ ASP;\ B}$	$4.9^{0.025\ MPP;\ A}$	$6.1^{0.025\ MPP;\ A}$			A: Hayer-Zillgen et al. (2002) and B: Ahlin et al. (2008)
Antihypertensive	Pindolol	$9.7^{0.05\ TEA;\ A}$ $39^{0.001\ MPP;\ B}$		$>1{,}000^{0.001\ MPP;\ B}$			A: Bednarczyk et al. (2003) and B: Umehara et al. (2008)
Antihypertensive	Prazosin	$1.6^{1\ YM;\ C}$ $1.8^{0.025\ MPP;\ A}$ $9.9^{1\ ASP;\ B}$	$80^{1\ YM;\ C}$ $>100^{0.025\ MPP;\ A}$	$13^{0.025\ MPP;\ A}$			A: Hayer-Zillgen et al. (2002), B: Ahlin et al. (2008) and C: Minematsu et al. (2010)
Antihypertensive	Terazosine	$24^{1\ ASP}$					Ahlin et al. (2008)
Antihypertensive, antiarrhythmic	Acebutolol	$96^{5\ TEA}$					Zhang et al. (1998)
Antihypertensive, antiarrhythmic	Metoprolol	$268^{0.001\ MPP;\ A}$	$50^{10\ Metf;\ B}$ $>1{,}000^{0.001\ MPP;\ A}$	$804^{0.001\ MPP;\ A}$			A: Umehara et al. (2008) and B: Bachmakov et al. (2009)
Antihypotensive	Etilefrine	$447^{0.02\ MPP}$	$4{,}009^{0.02\ MPP}$	**K_m: 2,800**			Müller et al. (2005)
Anti-inflammatory	Diclofenac	$<2{,}000^{5\ TEA}$	$<2{,}000^{5\ TEA}$				Khamdang et al. (2002)
Anti-inflammatory	Ibuprofen	$<2{,}000^{5\ TEA}$	$2{,}000–5{,}000^{5\ TEA}$				Khamdang et al. (2002)
Anti-inflammatory	Indomethacin	$<2{,}000^{5\ TEA}$	$<2{,}000^{5\ TEA}$				Khamdang et al. (2002)
Anti-inflammatory	Ketoprofen	$<2{,}000^{5\ TEA}$	$<2{,}000^{5\ TEA}$				Khamdang et al. (2002)
Anti-inflammatory	Mefenamic acid	$<2{,}000^{5\ TEA}$	$\sim2{,}000^{5\ TEA}$				Khamdang et al. (2002)
Anti-inflammatory	Piroxicam	$<2{,}000^{5\ TEA}$	$<2{,}000^{5\ TEA}$				Khamdang et al. (2002)
Anti-inflammatory	Salicylic acid				Substrate		Tanihara et al. (2007)
Anti-inflammatory	Sulindac	$<1{,}000^{5\ TEA}$	$<1{,}000^{5\ TEA}$				Khamdang et al. (2002)
Antimalarial	Chloroquine		$1{,}096^{0.01\ MPP}$				Zolk et al. (2008)
Antimalarial	Mefloquine		$204^{0.01\ MPP}$				Zolk et al. (2008)
Antimalarial	Pyrimethamine	$3.8^{30\ TEA}$	$10^{30\ TEA}$		$0.077^{30\ TEA}$ Substrate[G]	$0.046^{30\ TEA}$ Substrate[F]	Ito et al. (2010)
Antimalarial	Quinine	$13^{0.02\ MPP;\ E}$ $23^{5\ TEA;\ B}$ $45^{1\ ASP;\ D}$ $52^{1\ ASP;\ H}$	$3.4^{60\ TEA\ Ooc;\ A}$ $6.7^{1\ ASP;\ C}$ $23^{0.02\ MPP;\ E}$	$37^{0.02\ MPP;\ E}$			A: Gorboulev et al. (1997), B: Zhang et al. (1998), C: Cetinkaya et al. (2003), D: Ciarimboli et al. (2004), E: Müller et al. (2005), F: Masuda et al. (2006), G: Tanihara et al. (2007) and H: Ahlin et al. (2008)
Antineoplastic	Amsacrine	$5.0^{1\ ASP}$					Ahlin et al. (2008)
Antineoplastic	Cisplatin	$1{,}000–5{,}000^{50\ TEA;\ B}$	$1.5^{1\ ASP;\ A}$ $5{,}000–10{,}000^{50}$	$1{,}000–5{,}000^{50\ TEA;\ B}$	$1{,}000–5{,}000^{50\ TEA;\ B}$ substrate[B]	$>4{,}000^{50\ TEA;\ B}$ substrate[B]	A: Ciarimboli et al. (2005) and B: Yonezawa et al. (2006)

(*continued*)

Table 2 (continued)

Therapeutic use	Compound	OCT1	OCT2	OCT3	MATE1	MATE2-K	References
			TEA; B				
			substrate[A]				
Antineoplastic	Imatinib	Potential substrate[A, B] <50[100 TEA; C]					A: Wang et al. (2008a), B: Hu et al. (2008) and C: Nies et al. (unpublished)
Antineoplastic	Irinotecan			1.8[1 MPP]			Shnitsar et al. (2009)
Antineoplastic	Melphalan			366[1 MPP]			Shnitsar et al. (2009)
Antineoplastic	Mitoxantron	16[0.1 MPP]	800[0.1 MPP]	440[0.1 MPP]			Koepsell et al. (unpublished)
Antineoplastic	Oxaliplatin	Substrate	Substrate	Substrate	2,000–5,000[50 TEA]		Yonezawa et al. (2006)
Antineoplastic	Tamoxifen		87[10 MPP]				Zolk et al. (2008)
Antineoplastic	Topotecan				**K_m: 70**	**K_m: 60**	Tanihara et al. (2007)
Antineoplastic	Vincristine			17[1 MPP]			Shnitsar et al. (2009)
Antineoplastic; radiopharmaceutical	Metaiodobenzylguanidine	Substrate	Substrate	Substrate			Bayer et al. (2009)
Antiobesity	Fenfluramine		10[10 MPP]				Zolk et al. (2008)
Antiobesity	Sibutramine		29[10 MPP]				Zolk et al. (2008)
Antiparasitic	Furaminidine two positive charges	7.4[1 MPP] **K_m: 6.1**	182[1 MPP]	20[1 MPP]			Ming et al. (2009)
Antiparasitic	Pentamidine two positive charges	0.4[0.1 MPP; A] 16[1 MPP; B] **K_m: 36[B]**	3.8[0.1 MPP; A] 11[1 MPP; B]	15[1 MPP; B]			A: Jung et al. (2008) and B: Ming et al. (2009)
Anti-Parkinson	Memantine	3.7[0.025 MPP; B] 27[1 ASP; C]	7.3[0.025 MPP; B] **K_m: 34[Ooc; A]**	236[0.025 MPP; B]			A: Busch et al. (1998), B: Amphoux et al. (2006) and C: Ahlin et al. (2008)
Anti-Parkinson	Pramipexole				141[5 TEA]	24[5 TEA]	Tsuda et al. (2009b)
Anti-Parkinson	Talipexole				66[5 TEA]	120[5 TEA]	Tsuda et al. (2009b)
Anti-Parkinson; antiviral	Amantadine	18[0.05 TEA; B] 40[1 YM; E] 236[0.025 MPP; D]	20[10 TEA; C] 23[200 Dop; A] **K_m: 27[A]** 28[0.025 MPP; D] 46[1 YM; E]	>1,000[0.025 MPP; D]	112[5 TEA; F]	1,167[5 TEA; F]	A: Busch et al. (1998), B: Bednarczyk et al. (2003), C: Suhre et al. (2005), D: Amphoux et al. (2006), E: Minematsu et al. (2010) and F: Tsuda et al. (2009b)
Antipsychotic	Chlorpromazine	4.3[0.05 TEA; A] 27[1 ASP; C]	14[10 MPP; D]	<100[10 MPP; B]			A: Bednarczyk et al. (2003), B: Sata et al. (2005), C: Ahlin et al. (2008) and D: Zolk et al. (2008)

Antipsychotic	Chlorprotixen	78[1 ASP]					Ahlin et al. (2008)
Antipsychotic	Flupentixol	90[1 ASP]					Ahlin et al. (2008)
Antipsychotic	Fluphenazine	110[1 ASP]					Ahlin et al. (2008)
Antipsychotic	Haloperidol	142[1 ASP]					Ahlin et al. (2008)
Antipsychotic	Prochlorperazine	50[1 ASP]					Ahlin et al. (2008)
Antipsychotic	Sulpiride			<100[10 MPP]			Sata et al. (2005)
Antipsychotic	Tiapride			>100[10 MPP]			Sata et al. (2005)
Antispasmodic	Butylscopolamine	16[0.02 MPP]	764[0.02 MPP]				Müller et al. (2005)
Antispasmodic	Propantheline			~100[10 MPP]			Sata et al. (2005)
Antiulcer	Cimetidine	95[1 ASP; D] 166[5 TEA; A]	14[1 Amil; I] 26[1 ASP; I] 27[5 Crea; E] 36[1 ASP; C] **K_m: 67**[B] 70[5 TEA; G] **K_m: 73**[H] 120[10 MPP; M] 510[10 Metf; L] 1,380[1 Et; N]	240[1 Et; N]	1.1[5 TEA; O] ~10[50 TEA; F] **K_m: 170**[K]	7.3[5 TEA; O] **K_m: 120**[K] **K_m: 370**[J]	A: Zhang et al. (1998), B: Motohashi et al. (2002), C: Cetinkaya et al. (2003), D: Ciarimboli et al. (2004), E: Urakami et al. (2004), F: Otsuka et al. (2005), G: Suhre et al. (2005), H: Tahara et al. (2005), I: Biermann et al. (2006), J: Masuda et al. (2006), K: Tanihara et al. (2007), L: Umehara et al. (2008), M: Zolk et al. (2008), N: Lee et al. (2009) and O: Tsuda et al. (2009b)
Antiulcer	Famotidine		**K_m: 56**[D] 70[5 Crea; A] 111[10 TEA; C]	~20[10 MPP; B]	0.6[5 TEA; E]	9.7[5 TEA; E]	A: Urakami et al. (2004), B: Sata et al. (2005), C: Suhre et al. (2005), D: Tahara et al. (2005) and E: Tsuda et al. (2009b)
Antiulcer	Mepenzolate	65[1 ASP]					Ahlin et al. (2008)
Antiulcer	Ranitidine	22[0.05 TEA; A] 28[0.02 MPP; C]	31[10 Fam; E] 38[5 Crea; B] 40[10 TEA; D] 79[10 Cim; E] **K_m: 265**[E] 1,617[0.02 MPP; C]	372[0.02 MPP; C]	25[5 TEA; F]	25[5 TEA; F]	A: Bednarczyk et al. (2003), B: Urakami et al. (2004), C: Müller et al. (2005), D: Suhre et al. (2005), E: Tahara et al. (2005) and F: Tsuda et al. (2009b)
Antiviral	Acyclovir	**K_m: 151**[A]			**K_m: 2,640**[B]	**K_m: 4,320**[B]	A: Takeda et al. (2002) and B: Tanihara et al. (2007)
Antiviral	Ganciclovir	**K_m: 516**[A]			**K_m: 5,120**[B]	**K_m: 4,280**[B]	A: Takeda et al. (2002) and B: Tanihara et al. (2007)
Antiviral HIV	Abacavir	7.2×10^{-5}, 0.0013 MPP	4.1×10^{-5}, 0.0013 MPP	5×10^{-5}, 0.0013 MPP			Minuesa et al. (2009)

(*continued*)

Table 2 (continued)

Therapeutic use	Compound	OCT1	OCT2	OCT3	MATE1	MATE2-K	References
Antiviral HIV	Azidothymidine	1.6×10^{-4}, 0.0013 MPP	2.7×10^{-4}, 0.0013 MPP	4×10^{-4}, 0.0013 MPP			Minuesa et al. (2009)
Antiviral HIV	Emtricitabine	2×10^{-5}, 0.0013 MPP	2.4×10^{-3}, 0.0013 MPP	5.3×10^{-4}, 0.0013 MPP			Minuesa et al. (2009)
Antiviral HIV	Indinavir	$37^{0.1 \text{ MPP; B}}$ $62^{10 \text{ MPP; A}}$	$275^{0.1 \text{ MPP; B}}$				A: Zhang et al. (2000) and B: Jung et al. (2008)
Antiviral HIV	Nelfinavir	$7^{0.1 \text{ MPP; B}}$ $22^{10 \text{ MPP; A}}$	$13^{0.1 \text{ MPP; B}}$				A: Zhang et al. (2000) and B: Jung et al. (2008)
Antiviral HIV	Ritonavir	$5.2^{10 \text{ MPP; A}}$ $14^{0.1 \text{ MPP; B}}$	$25^{0.1 \text{ MPP; B}}$				A: Zhang et al. (2000) and B: Jung et al. (2008)
Antiviral HIV	Saquinavir	$8.3^{10 \text{ MPP; A}}$ $37^{0.1 \text{ MPP; B}}$	$205^{0.1 \text{ MPP; B}}$				A: Zhang et al. (2000) and B: Jung et al. (2008)
Antiviral HIV	Tenofovir	8.5×10^{-4}, 0.0013 MPP; B	5.7×10^{-4}, 0.0013 MPP; B	5×10^{-6}, 0.0013 MPP; B	Substrate[A]		A: Tanihara et al. (2007) and B: Minuesa et al. (2009)
Antiviral HIV	Zalcitabine	$24^{0.1 \text{ MPP}}$ **K_m: 242**	$131^{0.1 \text{ MPP}}$ **K_m: 232**				Jung et al. (2008)
Antiviral HIV, HBV	Lamivudine	1.2×10^{-5}, 0.0013 MPP; B $17^{0.1 \text{ MPP; A}}$ **K_m: 249[A]** **K_m: 1,250[B]** $1{,}900^{0.0013 \text{ MPP; B}}$	8.1×10^{-6}, 0.0013 MPP; B $33^{0.1 \text{ MPP; A}}$ **K_m: 248[A]** **K_m: 1,900[B]** $3{,}450^{0.0013 \text{ MPP; B}}$	2×10^{-5}, 0.0013 MPP; B $2{,}400^{0.0013 \text{ MPP; B}}$ **K_m: 2,140[B]**			A: Jung et al. (2008) and B: Minuesa et al. (2009)
Bronchodilator	Ipratropium		$15^{10 \text{ MPP}}$				Zolk et al. (2008)
Cardiotonic	Denopamine	$47^{1 \text{ ASP}}$					Ahlin et al. (2008)
CNS stimulant	3,4-Methylenedioxy-methamphetamine	$24^{0.025 \text{ MPP}}$	$1.6^{0.025 \text{ MPP}}$	$74^{0.025 \text{ MPP}}$			Amphoux et al. (2006)
CNS stimulant	D-Amphetamine	$202^{0.025 \text{ MPP}}$	$11^{0.025 \text{ MPP}}$	$460^{0.025 \text{ MPP}}$			Amphoux et al. (2006)
CNS stimulant	Phencyclidine	$4.4^{0.025 \text{ MPP}}$	$25^{0.025 \text{ MPP}}$	$333^{0.025 \text{ MPP}}$			Amphoux et al. (2006)
Diuretic	Amiloride	$57^{1 \text{ ASP; A}}$	$23^{1 \text{ ASP; B}}$ **K_m: 95[B]**				A: Ahlin et al. (2008) and B: Biermann et al. (2006)

Emetic	Apomorphine	21[1 ASP]					Ahlin et al. (2008)
Hypoglycemic	Metformin	**K_m: 1,470**[C] 2,010[1 Cim Ooc; A] **K_m: 2,160**[H] 3,420[0.1 MPP; G] 9,480[10 AG; H]	339[10 TEA; D] **K_m: 990**[C] **K_m: 1,380**[B] 1,700[1 Cim; A] 2,370[10 AG; H]	**K_m: 2,260**[G] 2,980[0.1 MPP; G]	667[5 TEA; I] **K_m: 780**[F]	667[5 TEA; I] **K_m: 1,050**[E] **K_m: 1,980**[F]	A: Dresser et al. (2002), B: Kimura et al. (2005a), C: Kimura et al. (2005b), D: Suhre et al. (2005), E: Masuda et al. (2006), F: Tanihara et al. (2007), G: Kimura et al. (2009), H: Nies et al. (2009) and I: Tsuda et al. (2009b)
Hypoglycemic	Phenformin	10[1 Cim Ooc; A]	15[10 TEA; B] 65[1 Cim Ooc; A]				A: Dresser et al. (2002) and B: Suhre et al. (2005)
Hypoglycemic	Repaglinide	1.6[10 Metf; A] 1.8[30 MPP; A] 9.2[1 ASP; B]					A: Bachmakov et al. (2008) and B: Ahlin et al. (2008)
Hypoglycemic	Rosiglitazone	6.9[10 Metf] 30[30 MPP]					Bachmakov et al. (2008)
Muscle relaxant	Orphenadrine	13[1 ASP]					Ahlin et al. (2008)
Muscle relaxant	Vecuronium	127[1 MPP; B] 232[5 TEA; A]					A: Zhang et al. (1997) and B: Zhang et al. (1998)
Mydriatic	Atropine	1.2[0.02 MPP; A] 12[1 ASP; B]	29[0.02 MPP; A]	466[0.02 MPP; A]			A: Müller et al. (2005) and B: Ahlin et al. 2008
Narcotic	Morphine	28[1 ASP]					Ahlin et al. (2008)
Narcotic; analgesic	Tramadol	53[1 ASP]					Ahlin et al. (2008)
Sedative	Midazolam	3.7[5 TEA]					Zhang et al. (1998)
Smoking cessation	Varenicline		**K_m: 370**				Feng et al. (2008)
Tranquilizer	Flurazepam		60[10 MPP]				Zolk et al. (2008)

IC_{50} values and K_m values (explicitly stated) were measured in oocytes of *Xenopus laevis* or mammalian cell lines transfected with the respective transporter. Expression in oocytes is indicated (Ooc) when different results were obtained in the oocyte system. The substrates employed for inhibition measurements are indicated; abbreviations used are: *Amil* amiloride, *ASP* 4-(4-(Dimethylamino)styryl)-*N*-methylpyridinium, *AG* aminoguanidine, *Cim* cimetidine, *Crea* creatinine, *Dop* dopamine, *Et* ethidium bromide, *Fam* famotidine, *His* histamine, *Metf* metformin, *MPP* 1-methyl-4-phenylpyridinium, *TEA* tetraethylammonium, *YM* YM155. The employed substrate concentration is indicated when different results were obtained using different substrate concentrations far below the respective Michaelis-Menten constant. Bold face indicates cations, for which transport has been demonstrated. For example, ketamine is an inhibitor of OCT1 with an IC_{50} value of 115 μM when measured with 0.025 μM MPP as the substrate. Drug classification is according to the standard handbook Goodman & Gilman's: The Pharmacological Basis of Therapeutics (Hardman et al. 2001)

Table 3 Other selected xenobiotics as substrates and inhibitors of OCTs and MATEs

Compound	Classification	OCT1	OCT2	OCT3	MATE1	MATE2-K	References
Aflatoxin B1	Mycotoxin	Substrate $64^{5\ TEA}$	Substrate $121^{5\ TEA}$				Tachampa et al. (2008)
Aminoguanidine	Model cation	Substrate $<10{,}000^{5\ TEA}$	**K_m: 4,100** $800^{5\ TEA}$				Kimura et al. (2009)
Azidoprocainamide	Model cation	**K_m: 101**					van Montfoort et al. (2001)
Berberine	Fluorescent cation	**K_m: 14.8**	**K_m: 4.4**				Nies et al. (2008)
N-Butylpyridinium chloride	Model cation		$2.3^{0.015\ TEA}$				Cheng et al. (2009)
			K_m: 18				
Citreoveridine	Mycotoxin	$6.6^{5\ TEA}$	$18^{5\ TEA}$				Tachampa et al. (2008)
Decynium 22	Model cation	$1.0^{0.025\ MPP;\ D}$ $2.7^{5\ TEA;\ C}$ $4.7^{1\ MPP;\ A}$	$0.1^{60\ TEA\ Ooc;\ B}$ $1.1^{0.025\ MPP;\ D}$	$0.09^{0.025\ MPP;\ D}$			A: Zhang et al. (1997), B: Gorboulev et al. (1997), C: Zhang et al. (1998) and D: Hayer-Zillgen et al. (2002)
4-4-Dimethylaminostyryl-*N*-methylpyridinium (ASP)	Fluorescent model cation	**K_m: 2.3**[B]	$7^{1\ Amil;\ A}$ **K_m: 42**[A]				A: Biermann et al. (2006) and B: Ahlin et al. (2008)
Disprocynium 24	Model cation			$0.015^{1\ MPP}$			Gründemann et al. (1998)
Ethidium	Fluorescent xenobiotic	$0.6^{0.1\ MPP}$ **K_m: 0.8**	$1.2^{0.1\ MPP}$ **K_m: 1.7**	$1.4^{0.1\ MPP}$ **K_m: 2.0**			Lee et al. (2009)
Gliotoxin	Mycotoxin	$584^{5\ TEA}$	$117^{5\ TEA}$				Tachampa et al. (2008)
1-Methyl-4-phenylpyridinium (MPP)	Model cation	**K_m: 15**[A] $16^{0.05\ TEA;\ E}$ $30^{1\ YM;\ L}$ **K_m: 32**[D]	$2.4^{10\ TEA;\ F}$ $2.4^{60\ TEA;\ B}$ **K_m: 3.1**[J] $4.4^{1\ YM;\ L}$ **K_m: 7.8**[D] **K_m: 19**[Ooc; B] $20^{10\ MPP;\ K}$ $43–54^{Et;\ J}$	**K_m: 47**[C] **K_m: 83**[G]	**K_m: 100**[I]	**K_m: 94**[H] **K_m: 111**[I]	A: Zhang et al. (1997), B: Gorboulev et al. (1997), C: Wu et al. (2000), D: Gründemann et al. (2003), E: Bednarczyk et al. (2003), F: Suhre et al. (2005), G: Sata et al. (2005), H: Masuda et al. (2006), I: Tanihara et al. (2007), J: Lee et al. (2009), K: Zolk et al. (2008) and L: Minematsu et al. (2010)
N-Methylquinidine	Model cation	**K_m: 12**					van Montfoort et al. (2001)
N-Methylquinine	Model cation	**K_m: 20**					van Montfoort et al. (2001)
Nandrolone	Anabolic steroid	$35^{1\ ASP}$					Ahlin et al. (2008)
Nicotine	Tobacco toxin	$53^{0.05\ TEA;\ A}$ $186^{1\ TEA;\ B}$	$42^{1\ TEA;\ B}$	$101^{1\ TEA;\ B}$	$>500^{50\ TEA;\ C}$		A: Bednarczyk et al. (2003), B: Lips et al. (2005) and C: Otsuka et al. (2005)
Paraquat	Herbicide (two positive charges)		**K_m: 114**		**K_m: 212**		Chen et al. 2007

Rhodamine 123	Fluorescent cation				$<10^{50}$ TEA		Otsuka et al. (2005)
Tetrabutylammonium	Model cation	$6.5^{0.05}$ TEA; B 30^{1} MPP Ooc; A	20^{10} TEA; C 120^{1} MPP Ooc; A		$18^{4.5}$ PQ; D		A: Dresser et al. (2002), B: Bednarczyk et al. (2003), C: Suhre et al. (2005) and D: Chen et al. (2007)
Tetraethylammonium TEA	Model cation	158^{1} MPP Ooc; E **K_m: 168**[F] 173^{1} MPP; A 216^{1} MPP Ooc; H **K_m: 229**[I] $470^{0.1}$ MPP; N 673^{1} ASP; G $1{,}390^{10}$ AG; O	**K_m: 27**[Q] 30^{1} ASP; K **K_m: 46**[J] **K_m: 76**[Ooc; B] 98^{1} Amil; K 156^{1} MPP Ooc; E 160^{10} AG; O 161^{5} TEA; N $189^{0.1}$ MPP; N 222^{1} MPP Ooc; H	$1{,}237^{1}$ MPP Ooc; H $1{,}372^{0.03}$ MPP; D $1{,}477^{0.1}$ MPP; N	$121^{4.5}$ PQ; P **K_m: 220**[I] **K_m: 380**[M]	**K_m: 760**[M] **K_m: 830**[L]	A: Zhang et al. (1997), B: Gorboulev et al. (1997), C: Zhang et al. (1998), D: Wu et al. (2000), E: Dresser et al. (2002), F: Bednarczyk et al. (2003), G: Ciarimboli et al. (2004), H: Bourdet et al. (2005), I: Otsuka et al. (2005), J: Suhre et al. (2005), K: Biermann et al. (2006), L: Masuda et al. (2006), M: Tanihara et al. (2007), N: Ming et al. (2009), O: Kimura et al. (2009), P: Chen et al. (2007) and Q: Cheng et al. (2009)
Tetramethylammonium	Model cation	$12{,}400^{1}$ MPP Ooc; B	$24^{\text{Crea; C}}$ 150^{1} MPP Ooc; B 180^{60} TEA Ooc; A 525^{10} TEA; D		$5{,}073^{4.5}$ PQ; E		A: Gorboulev et al. (1997), B: Dresser et al. (2002), C: Urakami et al. (2004), D: Suhre et al. (2005) and E: Chen et al. (2007)
Tetrapentylammonium	Model cation	$1.8^{0.05}$ TEA; C 5.5^{1} ASP; E 7.5^{5} TEA; B	1.5^{60} TEA Ooc; A 2^{1} ASP; G 2.7^{1} ASP; D 7^{1} Amil; G 11^{10} TEA; F	$4.5^{0.1}$ MPP; H			A: Gorboulev et al. (1997), B: Zhang et al. (1998), C: Bednarczyk et al. (2003), D: Cetinkaya et al. (2003), E: Ciarimboli et al. (2004), F: Suhre et al. (2005), G: Biermann et al. (2006) and H: Koepsell et al. (unpublished)
Tetrapropylammonium	Model cation	$22^{0.05}$ TEA; B 102^{1} MPP Ooc; A	20^{10} TEA; C 128^{1} MPP Ooc; A		$63^{4.5}$ PQ; D		A: Dresser et al. (2002), B: Bednarczyk et al. (2003), C: Suhre et al. (2005) and D: Chen et al. (2007)
Tubocurarine		62^{1} YM	$>100^{1}$ YM				Minematsu et al. 2010
YM155	Survivin suppressant, experimental antineoplastic	**K_m: 22**[B] $24^{0.02}$ MPP; B **K_m: 39**[A]	**K_m: 2.7**[B] $16^{0.02}$ MPP; B	$108^{0.02}$ MPP; B			A: Iwai et al. (2009) and B: Minematsu et al. (2010)

(*continued*)

Table 3 (continued)

Compound	Classification	OCT1	OCT2	OCT3	MATE1	MATE2-K	References
YM758	I_f channel inhibitor	$41^{0.001\ MPP}$	$16^{10\ Metf}$ $651^{0.001\ MPP}$	$16^{0.001\ MPP}$			Umehara et al. (2008)
α-Zearalenol	Mycotoxin	$1.7^{5\ TEA}$	$34^{5\ TEA}$				Tachampa et al. (2008)
Zearalenone	Mycotoxin	$0.6^{5\ TEA}$	$25^{5\ TEA}$				Tachampa et al. (2008)

IC_{50} values and K_m values (explicitly stated) were measured in oocytes of *Xenopus laevis* or mammalian cell lines transfected with the respective transporter. Expression in oocytes is indicated (Ooc) when different results were obtained in the oocyte system. The substrates employed for inhibition measurements are indicated; abbreviations used are: *Amil* amiloride, *ASP* 4-(4-(Dimethylamino)styryl)-*N*-methylpyridinium, *AG* aminoguanidine, *Crea* creatinine, *Et* ethidium bromide, *Metf* metformin, *MPP* 1-methyl-4-phenylpyridinium, *PQ* paraquat, *TEA* tetraethylammonium, *YM* YM155. The employed substrate concentration is indicated when different results were obtained using different substrate concentrations far below the respective Michaelis-Menten constant. Bold face indicates cations, for which transport has been demonstrated. For example, aflatoxin B1 is an inhibitor of OCT1 with an IC_{50} value of 64 μM when measured with 5 μM MPP as the substrate

genetic variants of human OCT1, OCT2, and OCT3 exist that encode transporters with changed functions (Sect. 6).

2.2 MATE Transporters

The human MATE1 gene (SLC47A1) and the MATE2 gene (SLC47A2) are located in tandem on chromosome 17p11.2 and encode proteins of 570 and 602 amino acids, respectively (Otsuka et al. 2005). The amino acid sequence identity of MATE1 and MATE2 is 47.5%. Two additional human MATE2 isoforms have been cloned: MATE2-K (NM_001099646) coding for a 566-amino acid protein and MATE2-B encoding a truncated protein of 220 amino acids (Masuda et al. 2006). Of note, MATE2-K is currently the only isoform in the MATE2 subfamily, for which function has been demonstrated; MATE2-B is nonfunctional and MATE2 function has not been tested (Masuda et al. 2006; Tanihara et al. 2007). MATE orthologs have also been cloned from other mammalian species, including mouse (Otsuka et al. 2005; Kobara et al. 2008), rat (Terada et al. 2006; Ohta et al. 2006), and rabbit (Zhang et al. 2007).

The hydropathy analysis performed by Otsuka et al. (2005) suggested that MATE1 consists of 12 transmembrane helices. However, most of the current topology analysis programs predict 13 transmembrane helices with an extracellular location of the carboxyl terminus (Zhang et al. 2007; Terada and Inui 2008) (Fig. 3b). Immunocytochemical analyses using accessibility of an antibody to a carboxyl-terminal tag in nonpermeabilized cells proved the extracellular location of the carboxyl terminus of rabbit Mate1 (Zhang et al. 2007). Whether this holds true for other MATE orthologs awaits investigation. Several histidine, cysteine, and glutamate residues in different transmembrane helices of human MATE1 and MATE2-K are apparently involved in substrate binding and/or transport (Asaka et al. 2007; Matsumoto et al. 2008). As for the OCTs, naturally occurring genetic variants have been identified in human MATEs that lead to synthesis of functionally impaired transporters (Sect. 6).

3 Tissue Distribution and Subcellular Localization

By screening the abundance of human transcript sequences ("UniGene" database at http://www.ncbi.nlm.nih.gov) one can assess the approximate gene expression pattern for each OCT and MATE transporter. Northern blot and real-time quantitative PCR analyses have revealed the different mRNA expression profiles in more detail (Koepsell et al. 2007; Okabe et al. 2008). In addition to the mRNA expression profiles, knowledge of the protein expression profiles and the subcellular localization of each transporter in distinct cell types of a given tissue are of equal importance, and they have been analyzed to some extent as well. Although each

cell is equipped with a number of different transporters, it is of particular interest to identify transporters in the absorptive and secretory cells of the small intestine, liver, and kidney, because these are the major organs of drug absorption, metabolism, and excretion. The combined action of electrogenic OCT uptake and MATE efflux transporters, which function as proton/cation antiporters, results in the transcellular movement of organic cations in the small intestine, liver, and kidney (Fig. 4).

Because OCTs and MATEs also transport cationic cytostatic drugs such as platinum drugs (see Sect. 4), transporter expression may affect intracellular levels of anticancer drugs and, thus, response to chemotherapy. Therefore, several studies have analyzed transporter expression profiles in cancer-derived cells as well as in normal tissue in comparison to cancerous tissue (Hayer-Zillgen et al. 2002; Zhang et al. 2006; Ballestero et al. 2006; Yokoo et al. 2008; Okabe et al. 2008). Only recently, OCT1 expression was identified as an important clinical determinant of the response to imatinib in chronic myeloid leukemia (Wang et al. 2008a) (see Sect. 6).

3.1 OCT1

Rat Oct1, the first cloned member of the SLC22A family, is strongly expressed in liver, kidney, and intestine (Gründemann et al. 1994). In humans, on the contrary, OCT1 mRNA is most prominently expressed in the liver (Gorboulev et al. 1997; Nishimura and Naito 2005; Jung et al. 2008; Nies et al. 2009). The OCT1 protein has been localized in the sinusoidal (basolateral) membrane of rat and human hepatocytes (Meyer-Wentrup et al. 1998; Nies et al. 2008), where it mediates the uptake of substrates from the blood and, thereby, mediates the first step in hepatic excretion of many cationic drugs (Fig. 4a). Other reported locations of human OCT1 include the lateral membrane of intestinal epithelial cells (Müller et al. 2005) and the luminal (apical) membrane of ciliated cells in the lung (Lips et al. 2005) and of tubule epithelial cells in the kidney (Tzvetkov et al. 2009).

3.2 OCT2

Human OCT2 mRNA is most strongly expressed in kidney (Gorboulev et al. 1997; Nishimura and Naito 2005; Jung et al. 2008), where the OCT2 protein has been localized in the basolateral membrane of proximal tubule epithelial cells (Motohashi et al. 2002; Nies et al. 2008). Analogous to OCT1 in hepatocytes, OCT2 plays an important role in the secretion of organic cations in the kidney by mediating the first step, that is, the uptake of organic cations across the basolateral membrane (Fig. 4b). OCT2 transcripts were also detected in several other human organs, including small intestine, lung, and different brain regions, and the inner ear

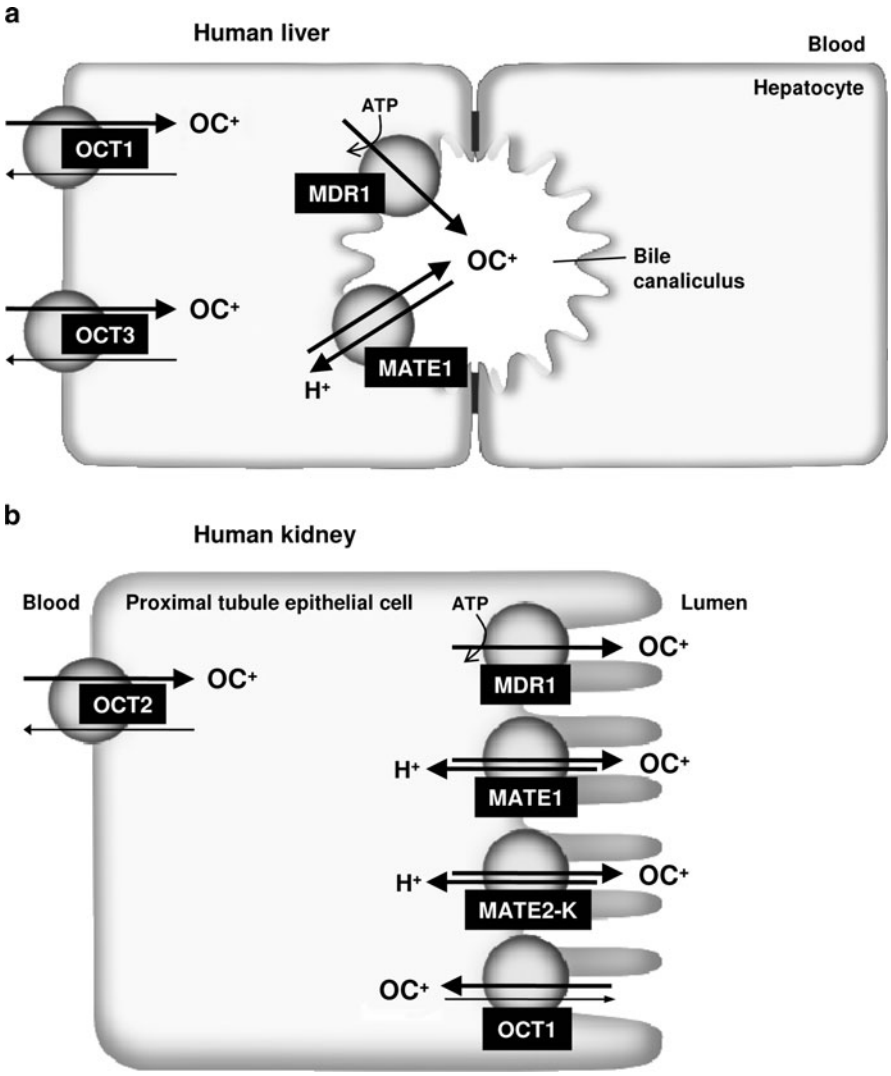

Fig. 4 Localization of OCT and MATE transporters in human hepatocytes (**a**) and proximal tubule epithelial cells in the kidney (**b**). The basolateral localization of OCT1 and OCT3 in hepatocytes and of OCT2 in proximal tubule epithelial cells together with the apical localization of MATE transporters results in the transcellular movement and, thereby, secretion of organic cations into bile and urine. MDR1 P-glycoprotein (ABCB1) is an ATP-dependent efflux pump for organic cations. In addition, OCTN1 (SLC22A4) and OCTN2 (SLC22A5) are present in the luminal membrane of proximal tubule cells, where they may exchange luminal carnitine plus sodium or luminal cations against intracellular cations. An apical OCT1 localization in proximal tubule cells was recently reported and was suggested to be involved in reabsorption of metformin from the urine

(Gorboulev et al. 1997; Busch et al. 1998; Lips et al. 2005; Taubert et al. 2007; Ciarimboli et al. 2010). The human OCT2 protein has been localized in the luminal membrane of ciliated epithelial cells in the lung (Lips et al. 2005) and in pyramidal cells of the hippocampus (Busch et al. 1998).

3.3 OCT3

Human OCT3 was initially cloned from a kidney-derived cell line and termed extraneuronal monoamine transporter (EMT) because substrate specificity is similar to monoamine uptake measured in extraneuronal tissues, neuronal expression of OCT3 was not established, and it was not known that monoamines are also transported by OCT2 (Gründemann et al. 1998); for discussion see Koepsell et al. (2003). Unlike OCT1 and OCT2, OCT3 has a broad tissue distribution (Verhaagh et al. 1999; Nies et al. 2009) and transcripts have been detected, among others, in placenta, adrenal gland, liver, kidney, heart, lung, brain, and intestine (Koepsell et al. 2007). The human OCT3 protein was identified in basolateral membrane vesicles from placenta (Sata et al. 2005), in the plasma membrane of normal human astrocytes (Inazu et al. 2003), in the luminal membrane of bronchial and intestinal epithelial cells (Müller et al. 2005; Lips et al. 2005), and in the sinusoidal membrane of hepatocytes (Nies et al. 2009) (Fig. 4).

3.4 MATE1 and MATE2-K

Human MATE1 is strongly expressed in liver and kidney as well as in skeletal muscle, adrenal gland, and testis (Otsuka et al. 2005; Masuda et al. 2006). Immunolocalization analyses identified the MATE1 protein in the canalicular membrane of hepatocytes (Otsuka et al. 2005) and in the luminal membrane of tubular epithelial cells in the kidney (Otsuka et al. 2005; Masuda et al. 2006). Human MATE2-K is almost exclusively expressed in the kidney and is localized in the luminal membrane of proximal tubular epithelial cells (Masuda et al. 2006) (Fig. 4).

4 Functional Characterization of OCT and MATE Transporters

4.1 Common Functional Properties of OCTs

The functional characteristics of OCTs have been studied in detail using cRNA-injected *Xenopus laevis* oocytes or OCT-transfected mammalian cell lines. Several transport characteristics are shared by all OCTs irrespective of their subtype or the

species. OCTs transport a broad range of organic cations with diverse molecular structures exhibiting K_m values in the micro- to millimolar range (Tables 1–3). Typically, the relative molecular masses of the substrates are below 500 (Suhre et al. 2005; Schmitt and Koepsell 2005; Ahlin et al. 2008; Zolk et al. 2008). OCTs are electrogenic facilitative diffusion systems that translocate organic cations in both directions across the plasma membrane (Busch et al. 1996; Nagel et al. 1997; Kekuda et al. 1998; Budiman et al. 2000; Lips et al. 2005). Transport of organic cations by OCTs is driven by the electrochemical potential but not accelerated by gradients of sodium or protons. For rat Oct2, a nonselective cotranslocation of inorganic cations together with transported organic cation substrates has been observed under depolarized conditions (Schmitt et al. 2009). OCTs are inhibited by a large number of cations and uncharged compounds that are not transported themselves. Partial or total inhibition of transport activity may be achieved (Volk et al. 2009). Transport inhibition may be competitive, partial competitive, or noncompetitive. Importantly, the affinities of the inhibitors are also dependent on the transported substrate (Tables 1–3). For human OCTs, IC_{50} values between 10 pM and 24 mM have been determined. Transported substrates and inhibitors of OCTs are of endogenous origin, xenobiotics, and clinically used drugs.

4.2 Substrate and Inhibitor Specificities of Human OCTs

Human OCT1, OCT2, and OCT3 have largely overlapping but distinctly different substrate and inhibitor specificities (Tables 1–3). The substrates of human OCTs (hOCT) are typically organic cations with one positive charge or two positive charges (furamidine and paraquat) or weak bases that are positively charged at physiological pH (Tables 1–3). Noncharged compounds such as cimetidine at alkaline pH (Barendt and Wright 2002) may also be transported. Whether OCTs may be also able to transport organic anions remains to be clarified. Transport of prostaglandins by hOCT1 and hOCT2 has been reported by Kimura et al. (2002) but was not confirmed by Harlfinger et al. (2005).

Transported endogenous substrates of human OCTs include monoamine neurotransmitters, neuromodulators, and other compounds such as choline, creatinine, and guanidine. Among the >120 clinically used drugs that were shown to interact with human OCTs, about 20 were identified as transport substrates (Table 2). These include antineoplastic platinum compounds, the histamine H_2 receptor antagonist cimetidine, the antiviral drugs acyclovir, ganciclovir, lamivudine, and zalcitabine, the antidiabetic drug metformin, and the antiarrhythmic drug quinidine. The neurotoxin 1-methyl-4-phenyl pyridinium (MPP), the antidiabetic drug metformin, and the antiviral drug lamivudine are transported with similar affinities by the three human OCT orthologs. The model cation TEA is transported with similar affinities by hOCT1 and hOCT2 but shows low-affinity interaction with hOCT3. At variance, epinephrine and norepinephrine are transported with similar affinity by hOCT2 and hOCT3, and only exhibit low-affinity interactions with hOCT1. Histamine is

transported with higher affinity by hOCT3 compared to hOCT2 and is apparently not transported by hOCT1 (Koepsell et al. unpublished data).

Inhibitors of OCTs may have larger molecular weights compared to substrates. They may bind to the central substrate binding pockets of the OCTs or to more peripheral regions in the clefts. Two or more inhibitor molecules may bind at the same time. Transport of a specific substrate may be inhibited partially after inhibitor binding to a high-affinity site and total inhibition may be observed when the inhibitor has bound to the low-affinity site (Minuesa et al. 2009).

It may be difficult to distinguish whether a compound that inhibits an OCT transporter is translocated or not. The reasons are (1) that transport rates may be low, (2) that the expression of endogenous cation transporters may be different in transfected and nontransfected cell lines, and (3) that OCT inhibitors that inhibit control substrates may have different affinities for other substrates. It has to be kept in mind that a correlation between transporter expression and the effect of a drug that interacts with the transporter does not prove that the drug is transported because the transporter inhibition may block cellular uptake of an endogenous compound that may critically influence drug effects on cell functions.

Thomas et al. (2004) observed that compounds that inhibit OCTs decreased uptake of imatinib, a first-generation tyrosine kinase inhibitor, into a human T-cell lymphoblast-like cell line. Similarly, imatinib uptake into blood cells from patients with chronic-phase chronic myeloid leukemia (CML) was blocked by OCT inhibitors (White et al. 2006). When the CML cell line KCL22 was transfected with hOCT1, imatinib uptake was about 1.6-fold higher compared to uptake into control transfectants (Wang et al. 2008a). At variance, expression of hOCT1 in *X. laevis* oocytes or in human embryonic kidney cells did not lead to a significant increase of imatinib uptake (Hu et al. 2008 and Koepsell, Nies, et al. unpublished data). Independent from the conflicting transport data, it was demonstrated that OCT1 mRNA levels and OCT1 genotype are important clinical determinants of treatment response in CML patients (Wang et al. 2008a; Kim et al. 2009) (Sect. 6.3).

4.3 Drug–Drug Interactions Involving OCTs

Various clinically used drugs were identified as inhibitors of OCT-mediated transport by investigating their potency to inhibit in vitro uptake of transported cations (Table 2). When these inhibitory drugs are coprescribed with drugs that are transported by OCTs, drug pharmacokinetics may be altered. Several studies, therefore, investigated the ability of drugs to inhibit transport of the OCT drug substrates metformin or cimetidine in vitro. For example, OCT2-mediated cimetidine transport is inhibited by ranitidine (Tahara et al. 2005) and OCT2-mediated metformin transport by sodium channel blockers (Umehara et al. 2008), β-adrenergic receptor antagonists (Bachmakov et al. 2009), and cimetidine (Zolk et al. 2009). The oral antidiabetics repaglinide and rosiglitazone inhibit OCT1-mediated metformin transport (Bachmakov et al. 2008).

Clinical studies suggest that drug–drug interactions involving OCTs also occur in vivo and may mainly affect cationic drugs that are predominantly eliminated by renal secretion (Ayrton and Morgan 2008; Kindla et al. 2009). For example, cimetidine decreases the renal tubular secretion of ranitidine (van Crugten et al. 1986), procainamide (Lai et al. 1988), dofetilide (Abel et al. 2000), and varenicline (Feng et al. 2008). The inhibition of tubular secretion of metformin by cimetidine was first described more than 20 years ago (Somogyi et al. 1987), but only recently this drug–drug interaction was attributed to OCT2 (Wang et al. 2008b). Other in vivo drug–drug interactions were reported between lamivudine and trimethoprim and between cisplatin and cimetidine or imatinib. It was shown that renal lamivudine clearance was decreased after coadministration of trimethoprim (Moore et al. 1996) and that the concomitant administration of imatinib has a protective effect against cisplatin-induced nephrotoxicity and ototoxicity (Tanihara et al. 2009; Ciarimboli et al. 2010).

4.4 Common Functional Properties of MATEs

MATE transporters are electroneutral transporters that operate independently of a sodium gradient, but use an oppositely directed proton gradient as driving force; translocation of organic cations across the plasma membrane may occur in both directions (Otsuka et al. 2005; Tanihara et al. 2007). MATEs are apparently the functionally long known but searched for proton-driven cation efflux transporters of the canalicular hepatocyte membrane and the luminal membrane of proximal tubule epithelial cells, which have been functionally described for many years (Koepsell 1998; Otsuka et al. 2005).

4.5 Substrate and Inhibitor Specificities of MATEs

MATE1 and MATE2-K have similar substrate and inhibitor specificities, which overlap with those of OCTs (Tables 1–3). The OCT substrates MPP and TEA are also transported by the two MATE orthologs. Endogenous substrates include the organic cations creatinine, guanidine, thiamine, and also the organic anion estrone sulfate. About 30 clinically used drugs have been shown to interact with MATE transporters, and several were identified as transport substrates such as metformin, cimetidine, oxaliplatin, acyclovir, and fexofenadine (Table 2).

4.6 Drug–Drug Interactions Involving MATEs

Information of drug–drug interactions involving MATEs is currently limited. In vitro, cimetidine inhibits MATE1-mediated transport of fexofenadine (Matsushima

et al. 2009) and metformin (Tsuda et al. 2009b). Thus, the clinical observation that metformin tubular secretion is inhibited by cimetidine (Somogyi et al. 1987) may not only be due to inhibition of OCT2-mediated metformin uptake (Wang et al. 2008b) but also to inhibition of MATE1-mediated luminal metformin efflux (Tsuda et al. 2009b).

5 Knockout Mouse Models

Knockout mouse models are valuable tools to identify the physiological and pharmacokinetic roles of transporters in vivo. For that purpose, *Oct1* (Jonker et al. 2001; Shu et al. 2007), *Oct2* (Jonker et al. 2003), *Oct3* (Zwart et al. 2001; Wultsch et al. 2009), and *Mate1* (Tsuda et al. 2009a) single-knockout mice and *Oct1/Oct2* double-knockout mice (Jonker et al. 2003) have been generated. All strains are viable and fertile and show no apparent phenotypical abnormalities, indicating that none of the transporters is essential for obvious physiological functions in mice. However, the tissue distribution and disposition of endogenous or exogenous organic cations may differ significantly between wild-type mice and the knockout mouse strains. These knockout mouse models may be used for the prediction of pharmacokinetics in humans, especially in those carrying genetic variants that encode transporters with reduced function (Sect. 6).

5.1 Oct1 Knockout Mice

Intravenous injection of the model cation TEA into *Oct1*(−/−) mice resulted in a fourfold to sixfold reduced hepatic accumulation and in a twofold reduced direct intestinal excretion of TEA in comparison to wild-type mice (Jonker et al. 2001). On the other hand, urinary TEA excretion was increased, probably because lack of hepatic Oct1 leads to increased availability of TEA to the kidney. Similar to TEA, the levels of the anticancer drug *meta*-iodobenzylguanidine, the neurotoxin MPP (Jonker et al. 2001), and the antidiabetic drug metformin (Wang et al. 2002; Shu et al. 2007) were also lower in livers from *Oct1*(−/−) mice than in those from wild-type mice. The decreased hepatic metformin uptake resulted in a reduced effect on AMP-activated protein kinase phosphorylation and gluconeogenesis, and, in consequence, the glucose-lowering effect of metformin was completely abolished (Shu et al. 2007). Thus, mouse Oct1 – as well as human OCT1 (see Sect. 6) – is a major determinant of the pharmacodynamic responses to metformin. It is of interest that *Oct1*(−/−) mice do not develop metformin-induced lactic acidosis, which is a severe and rare adverse drug reaction of metformin treatment in humans (Wang et al. 2003).

5.2 *Oct2 Single-Knockout and Oct1/Oct2 Double-Knockout Mice*

In contrast to the absence of Oct1, the targeted disruption of the murine *Oct2* gene had only little effect on the pharmacokinetics of intravenously injected TEA (Jonker et al. 2003). The hepatic and renal concentrations of TEA and the excretion of TEA in the urine and feces were similar in *Oct2*(−/−) and wild-type mice. Because Oct1 is expressed in mouse kidney in addition to Oct2 (Alnouti et al. 2006) and Oct1 and Oct2 have overlapping substrate specificities (Gründemann et al. 1999), renal Oct1 expression is apparently sufficient for secretion of most organic cations even in the absence of Oct2. In order to develop a mouse model for studying the renal secretion of organic cations, *Oct1*/*Oct2* double-knockout mice have been generated (Jonker et al. 2003). Renal tubular secretion of TEA was completely abolished and TEA was only eliminated by glomerular filtration in these double-knockout mice, which resulted in significantly elevated TEA plasma levels compared to wild-type mice. Similarly, urinary excretion of cisplatin was significantly impaired in *Oct1*/*Oct2*(−/−) mice so that the animals were protected from severe cisplatin-induced renal tubular damage and from cisplatin-induced loss of hearing (Filipski et al. 2009; Ciarimboli et al. 2010).

5.3 *Oct3 Knockout Mice*

After cloning human OCT3 it was hypothesized that the functional defined corticosterone-sensitive extraneuronal transport activity for monoamine neurotransmitters is mainly mediated by OCT3 (Gründemann et al. 1998; Koepsell et al. 2003). Interestingly, steady-state norepinephrine and dopamine levels did not differ between several tissues from wild-type and *Oct3*(−/−) mice whereas differences in MPP accumulation were observed (Zwart et al. 2001). Intravenous injection of MPP into *Oct3*(−/−) mice resulted in significantly reduced MPP levels in heart, but not in small intestine, liver, kidney, brain, and placenta in comparison to tissues from wild-type mice. Moreover, fetuses from pregnant *Oct3*(−/−) mice had three times lower MPP levels. Because MPP is a substrate of murine Oct1, Oct2, and Oct3, these data suggest a prominent role of Oct3 in the heart and fetoplacental interface, whereas in other tissues the lack of Oct3 is apparently well compensated by the function of other Octs. Although *Oct3*(−/−) mice did not show overt phenotypical abnormalities, Oct3 is probably critically involved in central nervous function. Vialou et al. (2004) showed that Oct3 is implicated in the appropriate neural and behavioral responses to environmentally induced changes in osmolarity. Whether Oct3 also plays a role in the regulation of fear and anxiety is being discussed (Vialou et al. 2008; Wultsch et al. 2009). Of note, there is compensatory upregulation of Oct3 in the brain of mice that lack the neuronal serotonin transporter Slc6a4/Sert (Schmitt et al. 2003; Baganz et al. 2008).

5.4 *Mate1 Knockout Mice*

Pharmacokinetic characterization of *Mate1*(−/−) mice (Tsuda et al. 2009a) was carried out with metformin, a typical drug substrate of human MATE1 (Table 2). After intravenous injection, renal and hepatic metformin concentrations were markedly increased in the *Mate1*(−/−) mice compared to wild-type mice. In addition, plasma metformin levels were increased in *Mate1*(−/−) mice, whereas urinary metformin excretion was significantly decreased. These data indicate a crucial role of Mate1 in the renal clearance of metformin and probably other drugs as well.

6 Pharmacogenomics of OCT and MATE Transporters

It is well accepted that drug response to the same medication differs among individuals (Kerb 2006). Besides factors such as age, organ function, concomitant therapy, drug–drug interactions, and the nature of the disease, genetic factors have been recognized as important determinants of interindividual variability of drug response. Because OCTs and MATEs function as drug uptake and efflux transporters, respectively (Sect. 4), genetic variants in these transporters may account for interindividual variability of pharmacokinetics of many drugs (Ho and Kim 2005; Giacomini and Sugiyama 2006; Kerb 2006). At present, major research efforts are being taken to identify OCT and MATE variants, to analyze their potential functional consequences, and to determine their contribution to a patient's response to pharmacotherapy.

6.1 *Identification of Genetic Variants, Their Predicted Consequences, and Their Effects In Vitro*

More than 1,100 and 450 single-nucleotide polymorphisms (SNPs) are currently listed for the OCT and MATE genes, respectively, in the NCBI-SNP database (National Center for Biotechnology Information, http://www.ncbi.nlm.nih.gov/SNP; build 130, January 2010). The Pharmacogenetics and Genomics Knowledge Base (PharmGKB, http://www.pharmgkb.org) is another public database comprising data and information related to all areas of pharmacogenetics including a large collection of DNA samples from ethnically diverse populations (Giacomini et al. 2007). Moreover, the International HapMap Consortium (http://www.hapmap.org) has generated a haplotype map of the human genome by identifying more than 3.1 million SNPs genotyped in 270 individuals from four geographically diverse populations (International HapMap Consortium et al. 2007). It is expected that the current next generation sequencing projects aiming at the complete sequencing

of 1,000 human genomes (Kaiser 2008; Siva 2008) will identify more variants, especially those with low frequencies between 0.1% and 1% (Ionita-Laza et al. 2009).

Whereas most sequence variants are present in the introns, others are located in the 5´- and 3´-flanking regions and may lead to an altered expression level of the respective OCT or MATE transporter (Ogasawara et al. 2008; Nies et al. 2009; Hesselson et al. 2009; Ha Choi et al. 2009). Sequence variants within the exons (coding SNPs, cSNPs) may result in amino acid substitutions. These nonsynonymous or missense variants are of considerable interest because they may affect the transport function of the OCT and MATE transporters. A comprehensive list of the currently known cSNPs in the genes encoding human OCTs and MATEs are given in Table 4.

PolyPhen (polymorphism phenotyping, http://genetics.bwh.harvard.edu/pph2; Ramensky et al. 2002) and SIFT (Sorting Intolerant from Tolerant, http://sift.jcvi.org/; Kumar et al. 2009) are two commonly used algorithms, with which the potential functional effects of single amino acid substitutions can be predicted in silico. Based on multiple sequence alignments and in part on information from known three-dimensional protein structures, the algorithms predict the probability that an amino acid substitution has an impact on protein structure and function. However, these in silico predictions cannot substitute for the experimental analysis of each amino acid variant to proof functional changes of the respective OCT or MATE transporter. For comparison, Table 4 lists the predicted functional consequences as well as in vitro transport data for many of the known nonsynonymous OCT and MATE variants. SIFT and PolyPhen predictions are similar for most variants though they differ for some (e.g., OCT1-Ser14Phe, OCT1-Leu23Val, OCT1-Pro341Leu, OCT2-Lys432Gln, MATE1-Leu125Phe). Moreover, amino acid substitutions that are predicted to be tolerated have no transport activity in vitro (e.g., OCT1-Gly220Val, MATE1-Val480Met). This shows limitations of the in silico predictions, which did not include recent structural analysis data (Popp et al. 2005; Volk et al. 2009). The differences may partly be due to the fact that several variants are not properly incorporated into the plasma membrane but are rather retained intracellularly (Shu et al. 2007; Kajiwara et al. 2009; Chen et al. 2009b). The observations that variants alter transport function in a substrate-dependent manner (e.g., OCT1-Ser189Leu, OCT1-Met420del) illustrate the difficulty to predict complex effects of mutagenesis on functions of polyspecific transporters.

6.2 Interethnic Variability

Geographic, ethnic, and racial differences in the frequency of genetic variants are well known and several examples in the field of ADME genes have been reported as a mechanistic basis for differences in drug response and/or drug toxicity (Schaeffeler et al. 2001; Klein et al. 2005).

Table 4 Characteristics of nonsynonymous *SLC22A1-A3/OCT1-3* and *SLC47/MATE* variants, their predicted functional consequences, and in vitro transport data

Gene	rs#	Amino acid change	SIFT prediction (score)	Polyphen prediction	Transport in vitro in comparison to refseq 60712.2 (MATE1)		References
					TEA	Metformin	
SLC22A1	rs34447885	Ser14Phe	Tolerated (1.00)	Possibly damaging	~190%[A]	~60%[B]	A: Shu et al. (2003) and B: Shu et al. (2007)
	rs72552761	Gln18His fs	NA	NA			
	rs34570655	Leu23Val	Deleterious (0.04)	Benign			
	rs35888596	Gly38Asp	Deleterious (0.01)	Possibly damaging			
	rs2297373	Phe41Leu	Deleterious (0.00)	Probably damaging			
	rs12208357	Arg61Cys	Deleterious (0.02)	Probably damaging	30%[A,B]	~5%[C]	A: Kerb et al. (2002), B: Shu et al. (2003) and C: Shu et al. (2007)
	rs35546288	Leu85Phe	Tolerated (0.30)	Benign	Similar		Shu et al. (2003)
	rs55918055	Cys88Arg	Deleterious (0.00)	Probably damaging	1.4%		Kerb et al. (2002)
	No refSNP ID	Pro117Leu	Deleterious (0.01)	Possibly damaging			Sakata et al. (2004)
	rs683369	Phe160Leu	Tolerated (0.66)	Benign	Similar[A, B]	Similar[C]	A: Kerb et al. (2002), B: Shu et al. (2003) and C: Shu et al. (2007)
	rs34104736	Ser189Leu	Tolerated (0.49)	Benign	Similar[A]	~20%[B]	A: Shu et al. (2003) and B: Shu et al. (2007)
	rs36103319	Gly220Val	Tolerated (0.10)	Benign	0%[A]	0%[B]	A: Shu et al. (2003) and B: Shu et al. (2007)
	rs4646277	Pro283Leu	Deleterious (0.00)	Probably damaging	0%		Itoda et al. (2004)
	rs4646278	Arg287Gly	Deleterious (0.00)	Probably damaging	0%		Itoda et al. (2004)
	rs2282143	Pro341Leu	Tolerated (0.07)	Probably damaging	~65%[A]	Similar[B]	A: Shu et al. (2003) and B: Shu et al. (2007)
	rs34205214	Arg342His	Tolerated (0.06)	Benign	Similar[A]	Similar[B]	A: Shu et al. (2003) and B: Shu et al. (2007)

	rs34130495	Gly401Ser	Tolerated (0.19)	Benign	0.9%,[A] 0%[B]	~10%[C]	A: Kerb et al. (2002), B: Shu et al. (2003) and C: Shu et al. (2007)
	rs628031	Met408Val	Tolerated (0.27)	Benign	Similar[A]	Similar[B]	A: Shu et al. (2003) and B: Shu et al. (2007)
	rs72552762	Gly414Ala	Deleterious (0.00)	Benign			
	No refSNP ID	Met420del	NA	NA	Similar[A,B]	~30%[C]	A: Kerb et al. (2002), B: Shu et al. (2003) and C: Shu et al. (2007)
	rs35956182	Met440Ile	Tolerated (0.12)	Probably damaging			
	rs34295611	Val461Ile	Tolerated (1.00)	Benign	Similar		Shu et al. (2003)
	rs34059508	Gly465Arg	Deleterious (0.00)	Probably damaging	0%[A]	0%[B]	A: Shu et al. (2003) and B: Shu et al. (2007)
	rs35270274	Arg488Met	Tolerated (0.14)	Benign	Similar[A]	Similar[B]	A: Shu et al. (2003) and B: Shu et al. (2007)
					Transport in vitro in comparison to refseq NP_003049.1 (OCT2)		
					MPP	Metformin	
SLC22A2	rs72552765	Phe45Leu fs	NA	NA			
	rs8177505	Phe45Ile fs	NA	NA			
	rs8177504	Pro54Ser	Deleterious (0.00)	Possibly damaging	Similar		Fujita et al. (2006)
	rs8177509	Phe161Leu	Tolerated (1.00)	Benign	Similar		Fujita et al. (2006)
	rs8177507	Met165Ile	Tolerated (0.44)	Benign	Decrease		Leabman et al. (2002)
	rs8177508	Met165Val	Tolerated (0.09)	Benign	Similar		Fujita et al. (2006)
	rs57371881	Arg176His	Deleterious (0.00)	Probably damaging			
	No refSNP ID	Thr199Ile	Deleterious (0.02)	Possibly damaging	~42%[A]	~31%[B]	A: Kang et al. (2007) and B: Song et al. (2008)
	No refSNP ID	Thr201Met	Tolerated (0.23)	Benign	~50%[A]	~40%[B]	A: Kang et al. (2007) and B: Song et al. (2008)
	rs316019	Ala270Ser	Tolerated (0.69)	Benign	Decrease,[A] ~62%[B]	~60%[C]	A: Leabman et al. (2002), B: Kang et al. (2007) and C: Song et al. (2008)

(*continued*)

Table 4 (continued)

Gene	rs#	Amino acid change	SIFT prediction (score)	Polyphen prediction	Transport in vitro in comparison to refseq 60712.2 (MATE1)		References
					TEA	Metformin	
	rs8177513	Ala297Gly	Tolerated (0.34)	Benign	Similar		Fujita et al. (2006)
	rs45599131	Leu351Trp	Deleterious (0.01)	Possibly damaging			
	rs8177516	Arg400Cys	Deleterious (0.00)	Benign	Decrease		Leabman et al. (2002)
	rs8177517	Lys432Gln	Tolerated (0.56)	Possibly damaging	Decrease		Leabman et al. (2002)
	rs3907239	Arg463Lys	Deleterious (0.00)	Probably damaging			
	rs17853948	Val502Gly	Deleterious (0.03)	Possibly damaging			
	rs17853948	Val502Glu	Deleterious (0.05)	Possibly damaging			
					Norepinephrine transport in vitro in comparison to refseq NP_068812.1 (OCT3)		
SLC22A3	rs8187715	Thr44Met	Tolerated (0.09)	Benign			
	rs8187717	Ala116Ser	Tolerated (1.00)	Benign			
	No refSNP ID	Met370Ile	Tolerated (0.21)	Probably damaging	~50%		Lazar et al. (2008)
	rs8187725	Thr400Ile	Tolerated (0.35)	Benign			
	rs12212246	Ala439Val	Tolerated (0.45)	Benign			
	rs9365165	Gly475Ser	Tolerated (1.00)	Benign			
					Transport in vitro in comparison to refseq NP_060712.2 (MATE1)		
					TEA	Metformin	
SLC47A1	No refSNP ID	Val10Leu	Tolerated (0.58)	Benign	Similar	Similar	Kajiwara et al. (2009)
	rs77630697	Gly64Asp	Deleterious (0.00)	Probably damaging	~1%,[A] ~14%[B]	~2%[A,B]	A: Kajiwara et al. (2009) and B: Chen et al. (2009b)
	rs77474263	Leu125Phe	Deleterious (0.00)	Benign	~50%	~50%	Chen et al. (2009b)
	rs11551331	Pro148Arg	Deleterious (0.00)	Benign			
	rs35646404	Thr159Met	Tolerated (0.33)	Benign			

	No refSNP ID	Ala310Val	Tolerated (0.31)	Benign	~20%	~41%	Kajiwara et al. (2009)
	No refSNP ID	Asp328Ala	Deleterious (0.02)	Probably damaging	~20%	~27%	Kajiwara et al. (2009)
	rs35790011	Val338Ile	Tolerated (0.51)	Benign	~40%	~40%	Chen et al. (2009b)
	No refSNP ID	Asn474Ser	Tolerated (0.35)	Benign	~63%	Similar	Kajiwara et al. (2009)
	rs76645859	Val480Met	Tolerated (0.16)	Benign	0%	0%	Chen et al. (2009b)
	rs35395280	Cys497Ser	Tolerated (0.64)	Benign	Similar	~65%	Chen et al. (2009b)
	rs35395280	Cys497Phe	Tolerated (0.12)	Probably damaging			
	rs78700676	Gln519His	Tolerated (0.12)	Benign	Similar	Similar	Chen et al. (2009b)
					Transport in vitro in comparison to refseq NP_001093116.2 (MATE2-K)		
					TEA	Metformin	
SLC47A2	No refSNP ID	Lys64Asn	Deleterious (0.00)	Benign	~48%	~66%	Kajiwara et al. (2009)
	No refSNP ID	Gly211Val	Deleterious (0.00)	Probably damaging	0%	0%	Kajiwara et al. (2009)
	rs34399035	Gly393Arg	Deleterious (0.00)	Probably damaging			

fs frameshift, *MPP* 1-methyl-4-phenylpyridinium, *NA* not applicable, *Polyphen* polymorphism phenotyping algorithm, http://genetics.bwh.harvard.edu/pph2. (Ramensky et al. 2002). Default settings were used for calculations, *SIFT* sorting intolerant from tolerant algorithm, http://sift.jcvi.org (Kumar et al. 2009). For prediction, the "SIFT sequence" single protein tool was used with default settings and the UniProt-Swiss Prot 56.6 database. Substitution values ≤ 0.05 are predicted to be intolerant and, thus, deleterious, *TEA* tetraethylammonium

Significant ethnic differences exist also in the frequency of allele and genotype distributions of SLC22A1, SLC22A2, and SLC47A1 variants as listed in Tables 5–8. For instance, whereas in European-Americans and Caucasians the allele frequency of the SLC22A1-Arg61Cys polymorphism is approximately 8%, in African-Americans as well as Asian-Americans, no variant subject including 260 individuals tested were identified. In contrast, for the SLC22A1-Pro341Leu variant a significant higher allele frequency was found in African-Americans and Asian-Americans (8% and 17%) than in Caucasians (up to 2%). Finally, the Met408Val polymorphism was detected with high-frequency distributions in all ethnic groups (Caucasians, Africans, Asians). Currently it is unclear whether these differences in allele frequencies between various ethnic groups are of any clinical importance and potentially may render individuals more susceptible to certain xenobiotics and/or environmental factors. For example, aflatoxin B1 is a substrate of OCT1 and it is well recognized that the incidence of hepatocellular carcinoma is significantly more frequent in Asians compared to Caucasians. One may assume that such a difference in disease frequency may be explained by functional relevant genetic variants of the uptake transporter OCT1 that are more common in Asian populations.

6.3 Phenotype–Genotype Correlations

Currently data on tissue expression of OCTs and MATEs correlated to genetic variants are limited. The only polymorphism identified so far that affects OCT1 expression in human liver on mRNA and protein levels is Arg61Cys (Nies et al. 2009; Table 9) after correction for nongenetic factors (such as cholestasis) and additional SLC22A1 variants. Of note, a total of 36 variants in the *SLC22A1* gene were tested including some SNPs, which showed reduced function in vitro (Table 4). It would be of major interest to analyze whether expression of OCT2, which is the predominant OCT uptake transporter in human kidney and involved in renal excretion of several drugs (e.g., metformin), is also influenced by genetic factors.

Several studies addressed the association of OCT genotypes with pharmacokinetic parameters of OCT substrates in humans (Tables 9–12). These investigations were based on initial observations that some variants alter OCT function in in vitro cell experiments (Table 4). A key publication in this field showed that metformin AUC and C_{max} are significantly higher in OCT1-variant healthy subjects as compared to individuals with *OCT1* reference gene sequence (Shu et al. 2008). In addition and in line with *Oct1* knockout mice experiments, OCT1 variant human subjects revealed poor response to metformin measured by the oral glucose tolerance test (Shu et al. 2007). These data suggested for the first time that OCT1 may be a promising candidate gene for better prediction of the response to the antidiabetic agent metformin. Although some studies including type 2 diabetes patients were subsequently performed, unfortunately the results are inconsistent (Tables 9–12). A second clinically highly relevant agent, which was related to OCT1 expression and

Table 5 Allele frequencies of *SLC22A1* (*OCT1*) genetic variants in different ethnic populations

SLC22A1 (OCT1)[a]	rs#	Allele frequency (%)				References
		European-American/ Caucasian	African-American	Asian-American	Chinese, Japanese, Korean, Vietnamese	
5′ near gene	rs6935207	14 ($n = 55$)[A] 27 ($n = 150$)[B]			59 ($n = 150$ Koreans)[C]	A: Kerb et al. (2002), B: Nies et al. (2009) and C: Kang et al. (2007)
5′ near gene	rs9457840	2 ($n = 150$)				Nies et al. (2009)
5′ near gene	rs6899549	0 ($n = 150$)				Nies et al. (2009)
5′ UTR, C>A g.160462864	No refSNP ID				0.4 ($n = 116$ Japanese)	Itoda et al. (2004)
Ser14Phe	rs34447885	0 ($n = 200$)[A] 0 ($n = 150$)[B]	3.1 ($n = 200$)[A]	0 ($n = 60$)[A]		A: Shu et al. (2003) and B: Nies et al. (2009)
Leu23Val	rs34570655	0 ($n = 150$)				Nies et al. (2009)
Gly38Asp	rs35888596	0.3 ($n = 150$)				Nies et al. (2009)
Phe41Leu	rs2297373	0 ($n = 150$)[A]			0.4 ($n = 116$ Japanese)[B]	A: Nies et al. (2009) and B: Itoda et al. (2004)
Ser52Ser	rs1867351	23 ($n = 243$)[A]			44.4 ($n = 116$ Japanese)[B] 35 ($n = 150$ Koreans)[C]	A: Kerb et al. (2002), B: Itoda et al. (2004) and C: Kang et al. (2007)
Arg61Cys	rs12208357	9.1 ($n = 243$)[A] 7.2 ($n = 200$)[B] 9.7 ($n = 150$)[C]	0 ($n = 200$)[B]	0 ($n = 60$)[B]		A: Kerb et al. (2002), B: Shu et al. (2003) and C: Nies et al. (2009)
Leu85Phe	rs35546288	0 ($n = 200$)[A] 0 ($n = 150$)[B]	1 ($n = 200$)[A]	0 ($n = 60$)[A]		A: Shu et al. (2003) and B: Nies et al. (2009)
Cys88Arg	rs55918055	0.6 ($n = 243$)[A] 0.3 ($n = 150$)[B]				A: Kerb et al. (2002) and B: Nies et al. (2009)
Pro117Leu, C>T g.160463307	No refSNP ID				0.4 ($n = 116$ Japanese)	Itoda et al. (2004)
Intron	rs4646272	6.7 ($n = 150$)[A]			62.9 ($n = 116$ Japanese)[B]	A: Nies et al. (2009) and B: Itoda et al. (2004)
Intron, T>C g.160471091					8.2 ($n = 116$ Japanese)	Itoda et al. (2004)

(*continued*)

Table 5 (continued)

SLC22A1 (OCT1)[a]	rs#	Allele frequency (%)				References
		European-American/ Caucasian	African-American	Asian-American	Chinese, Japanese, Korean, Vietnamese	
Phe160Leu	rs683369	22 ($n = 241$)[A] 6.5 ($n = 200$)[B] 23 ($n = 150$)[C]	0.5 ($n = 200$)[B]	1.7 ($n = 60$)[B]	8.6 ($n = 116$ Japanese)[D] 13 ($n = 150$ Koreans)[E]	A: Kerb et al. (2002), B: Shu et al. (2003), C: Nies et al. (2009), D: Itoda et al. (2004) and E: Kang et al. 2007
Intron	rs4646273				45.7 ($n = 116$ Japanese)	Itoda et al. (2004)
Intron	rs3737088				1.7 ($n = 116$ Japanese)	Itoda et al. (2004)
Ala187Ala, G>A g.160473299					0.9 ($n = 116$ Japanese)	Itoda et al. (2004)
Intron	rs4646276				47 ($n = 116$ Japanese)	Itoda et al. 2004
Intron	rs2282142				16.8 ($n = 116$ Japanese)	Itoda et al. (2004)
Ser189Leu	rs34104736	0.5 ($n = 200$)[A] 0 ($n = 150$)[B]	0 ($n = 200$)[A]	0 ($n = 60$)[A]		A: Shu et al. (2003) and B: Nies et al. (2009)
Gly220Val	rs36103319	0 ($n = 200$)[A] 0 ($n = 150$)[B]	0.5 ($n = 200$)[A]	0 ($n = 60$)[A]		A: Shu et al. (2003) and B: Nies et al. (2009)
Pro283Leu	rs4646277	0 ($n = 150$)[A]			1.3 ($n = 150$ Koreans)[B] 0 ($n = 100$ Vietnamese)[B] 0.5 ($n = 100$ Chinese)[B]	A: Nies et al. (2009) and B: Kang et al. (2007)
Arg287Gly	rs4646278	0 ($n = 150$)				Nies et al. (2009)
Pro341Leu	rs2282143	0 ($n = 200$)[A] 1.7 ($n = 150$)[B]	8.2 ($n = 200$)[A]	11.7 ($n = 60$)[A]	16.8 ($n = 116$ Japanese)[C] 16.7 ($n = 150$ Koreans)[D] 5.5 ($n = 100$ Vietnamese)[D] 11 ($n = 100$ Chinese)[D]	A: Shu et al. (2003), B: Nies et al. (2009), C: Itoda et al. (2004) and D: Kang et al. (2007)
Intron, C>G g.160477747					2.2 ($n = 116$ Japanese)	Itoda et al. (2004)
Arg342His	rs34205214	0 ($n = 200$)[A] 0 ($n = 150$)[B]	3.1 ($n = 200$)[A]	0 ($n = 60$)[A]		A: Shu et al. (2003) and B: Nies et al. (2009)

Gly401Ser	rs34130495	3.2 ($n = 232$)[A] 1.1 ($n = 200$)[B] 1 ($n = 150$)[C]	0.7 ($n = 200$)[B]	0 ($n = 60$)[B]		A: Kerb et al. 2002, B: Shu et al. (2003) and C: Nies et al. (2009)
Met408Val	rs628031	59.7 ($n = 232$)[A] 59.8 ($n = 200$)[B] 42.9 ($n = 150$)[C]	73.5 ($n = 200$)[B]	76.2 ($n = 60$)[B]	81 ($n = 116$ Japanese)[D] 74 ($n = 150$ Koreans)[E]	A: Kerb et al. (2002), B: Shu et al. (2003), C: Nies et al. (2009), D: Itoda et al. (2004) and E: Kang et al. (2007)
Ala413Ala	rs34888879	0 ($n = 150$)				Nies et al. (2009)
Gly414Ala	rs72552762	0.2 ($n = 232$)				Kerb et al. (2002)
Intron	rs4646281				81 ($n = 116$ Japanese)	Itoda et al. (2004)
Met420del g.160480871-160480873delATG	No refSNP ID	15.7 ($n = 232$)[A] 18.5 ($n = 200$)[B] 17 ($n = 150$)[C]	2.9 ($n = 200$)[B]	0 ($n = 60$)[B]		A: Kerb et al. (2002), B: Shu et al. (2003) and C: Nies et al. (2009)
Met440Ile	rs35956182	0 ($n = 200$)	0.5 ($n = 200$)	0 ($n = 60$)		Shu et al. (2003)
Intron, A>G g.160484779					0.4 ($n = 116$ Japanese)	Itoda et al. (2004)
Intron	rs2297374				30.2 ($n = 116$ Japanese)	Itoda et al. (2004)
Intron	rs622591				59.1 ($n = 116$ Japanese)	Itoda et al. (2004)
Val461Ile	rs34295611	0 ($n = 200$)[A] 0 ($n = 150$)[B]	1 ($n = 200$)[A]	0 ($n = 60$)[A]		A: Shu et al. (2003) and B: Nies et al. (2009)
Gly465Arg	rs34059508	1.5 ($n = 236$)[A] 4 ($n = 200$)[B] 4.3 ($n = 150$)[C]	0 ($n = 200$)[B]	0 ($n = 60$)[B]		A: Kerb et al. (2002), B: Shu et al. (2003) and C: Nies et al. (2009)
Arg488Met	rs35270274	0 ($n = 200$)[A] 0 ($n = 150$)[B]	5 ($n = 200$)[A]	0 ($n = 60$)[A]		A: Shu et al. (2003) and B: Nies et al. (2009)
Val501Val	rs41267797	3.6 ($n = 56$)				Kerb et al. (2002)
3′ UTR, delATG, g.160499610-160499612					0.4 ($n = 116$ Japanese)	Itoda et al. (2004)
3′ UTR	rs9457846	0 ($n = 150$)				Nies et al. (2009)
3′ UTR	rs34108432	0 ($n = 150$)				Nies et al. (2009)

UTR untranslated region

The work by Itoda et al. (2004) describes arrhythmic patients

[a]In case that no refSNP ID is available, the genomic localization on chromosome 6 is given (NC_000006.10)

Table 6 Allele frequencies of *SLC22A2* (*OCT2*) genetic variants in different ethnic populations

SLC22A2 (OCT2)[a]	rs#	Allele frequency (%)				References
		European-American/ Caucasian	African-American	Asian-American	Chinese, Japanese, Korean, Vietnamese	
5′ UTR	rs8177506	0 ($n = 200$)	0 ($n = 200$)	1.7 ($n = 60$)		Leabman et al. (2002)
Phe45 fs	rs8177505	0.5 ($n = 200$)[A]	0 ($n = 200$)[A]	0 ($n = 60$)[A]	0 ($n = 116$ Japanese)[B]	A: Leabman et al. (2002) and B: Fukushima-Uesaka et al. (2004)
Pro54Ser	8177504	0 ($n = 200$)[A]	0.5 ($n = 200$)[A]	0 ($n = 60$)[A]	0 ($n = 116$ Japanese)[B]	A: Leabman et al. (2002) and B: Fukushima-Uesaka et al. (2004)
Thr130Thr	rs624249	39.4 ($n = 200$)[A]	20.5 ($n = 200$)[A]	18.3 ($n = 60$)[A]	15 ($n = 150$ Koreans)[B] 18.4 ($n = 112$ Chinese)[C]	A: Leabman et al. (2002), B: Kang et al. (2007) and C: Wang et al. (2008b)
Phe161Leu	rs8177509	0.5 ($n = 200$)	0 ($n = 200$)	0 ($n = 60$)		Leabman et al. (2002)
Met165Val	rs8177508	0 ($n = 200$)	0.5 ($n = 200$)	0 ($n = 60$)		Leabman et al. (2002)
Met165Ile	rs8177507	0 ($n = 200$)[A]	1 ($n = 200$)[A]	0 ($n = 60$)[A]	0 ($n = 116$ Japanese)[B]	A: Leabman et al. (2002) and B: Fukushima-Uesaka et al. (2004)
Intron	rs2774230	29.6 ($n = 200$)[A]	41.9 ($n = 200$)[A]	3.3 ($n = 60$)[A]	15.8 ($n = 112$ Chinese)[B]	A: Leabman et al. (2002) and B: Wang et al. (2008b)
Intron	rs8177511	0 ($n = 200$)	2.5 ($n = 200$)	0 ($n = 60$)		Leabman et al. (2002)
Thr199Ile, C>T g.160591647	No refSNP ID				0.9 ($n = 116$ Japanese)[A] 0.7 ($n = 150$ Koreans)[B] 0 ($n = 100$ Vietnamese)[B] 0 ($n = 100$ Chinese)[B]	A: Fukushima-Uesaka et al. (2004) and B: Kang et al. (2007)
Thr201Met, C>T g.160591641	No refSNP ID				1.3 ($n = 116$ Japanese)[A] 0.7 ($n = 150$ Koreans)[B] 1.5 ($n = 100$ Vietnamese)[B] 0 ($n = 100$ Chinese)[B] 0.4 ($n = 112$ Chinese)[C]	A: Fukushima-Uesaka et al. (2004), B: Kang et al. (2007) and C: Wang et al. (2008b)
Ile223Ile	rs8177510	0 ($n = 200$)	0 ($n = 200$)	1.7 ($n = 60$)		Leabman et al. (2002)
Ala270Ser	rs316019	15.7 ($n = 200$)[A] 8.7 ($n = 150$)[B]	11 ($n = 200$)[A]	8.6 ($n = 60$)[A]	16.8 ($n = 116$ Japanese)[C] 11.0 ($n = 150$ Koreans)[D] 13.5 ($n = 100$	A: Leabman et al. (2002), B: Nies et al. (2009), C: Fukushima-

					Vietnamese)[D]	Uesaka et al. (2004), D: Kang et al. (2007) and E: Wang et al. (2008b)
					14.0 (n = 100 Chinese)[D]	
					13.3 (n = 112 Chinese)[E]	
Intron	rs8177514	0 (n = 200)	0.5 (n = 200)	0 (n = 60)		Leabman et al. (2002)
Intron	rs2279463				12.4 (n = 112 Chinese)	Wang et al. (2008b)
Ala297Gly	rs8177513	0.5 (n = 200)	0 (n = 200)	0 (n = 60)		Leabman et al. (2002)
Intron	rs45437591	13.1 (n = 200)	14.5 (n = 200)	1.7 (n = 60)		Leabman et al. (2002)
Intron	rs8177512	13.1 (n = 200)	14.5 (n = 200)	1.7 (n = 60)		Leabman et al. (2002)
Intron	rs3219195				13.4 (n = 112 Chinese)	Wang et al. (2008b)
Intron	rs316021	23 (n = 150)[A]			17.4 (n = 112 Chinese)[B]	A: Nies et al. 2009 and B:Wang et al. 2008b
Intron	rs11422119				75.3 (n = 112 Chinese)	Wang et al. (2008b)
Arg400Cys	rs8177516	0 (n = 200)[A]	1.5 (n = 200)[A]	0 (n = 60)[A]	0 (n = 116 Japanese)[B]	A: Leabman et al. (2002) and B: Fukushima-Uesaka et al. (2004)
Ile401Ile	rs8177515	0.5 (n = 200)	0 (n = 200)	0 (n = 60)		Leabman et al. (2002)
Intron	rs8177518	0 (n = 200)[A]	0.5 (n = 200)[A]	6.7 (n = 60)[A]	4.5 (n = 112 Chinese)[B]	A: Leabman et al. (2002) and B: Wang et al. (2008b)
Lys432Gln	rs8177517	0 (n = 200)[A]	1 (n = 200)[A]	0 (n = 60)[A]	0 (n = 116 Japanese)[B]	A: Leabman et al. (2002) and B: Fukushima-Uesaka et al. (2004)
Gly466Gly	rs8177520	0 (n = 200)	0.5 (n = 200)	0 (n = 60)		Leabman et al. (2002)
Intron	rs11342198				15.5 (n = 112 Chinese)	Wang et al. (2008b)
Intron	rs315991				15.5 (n = 112 Chinese)	Wang et al. (2008b)
Intron	rs10532482				15.5 (n = 112 Chinese)	Wang et al. (2008b)
Intron	rs8177519	0 (n = 200)	0.5 (n = 200)	6.7 (n = 60)		Leabman et al. (2002)
Intron	rs3219197				15.5 (n = 112 Chinese)	Wang et al. (2008b)
Val502Val	rs316003	29 (n = 200)[A] 22 (n = 150)[B]	50 (n = 200)[A]	11.7 (n = 60)[A]	15 (n = 150 Koreans)[C] 15.5 (n = 112 Chinese)[D]	A: Leabman et al. (2002), B: Nies et al. (2009), C: Kang et al. (2007) and D: Wang et al. (2008b)
Ala529Ala	rs8177521	0 (n = 200)	0 (n = 200)	1.7 (n = 60)		Leabman et al. (2002)
3′ UTR, C>A	rs8177524	2 (n = 200)	0.5 (n = 200)	0 (n = 60)		Leabman et al. (2002)
3′ UTR, G>A	rs8177523	0 (n = 200)	0.5 (n = 200)	0 (n = 60)		Leabman et al. (2002)
	No refSNP ID	0 (n = 200)	3 (n = 200)	0 (n = 60)		Leabman et al. (2002)

(*continued*)

Table 6 (continued)

SLC22A2 (OCT2)[a]	rs#	Allele frequency (%)				References
		European-American/ Caucasian	African-American	Asian-American	Chinese, Japanese, Korean, Vietnamese	
3′ UTR, insT g.160558192						
3′ UTR	rs3219198	0.5 ($n = 200$)	0.5 ($n = 200$)	0 ($n = 60$)		Leabman et al. (2002)

fs frameshift, *UTR* untranslated region

[a]In case that no refSNP ID is available, the genomic localization on chromosome 6 is given (NC_000006.10)

Table 7 Allele frequencies of *SLC22A3*(*OCT*) genetic variants in different ethnic populations

SLC22A3 (OCT3)[a]	rs#	Allele frequency (%)		References
		Caucasian	Korean	
5′ near gene	rs10455781	3 ($n = 150$)		Nies et al. (2009)
5′ near gene	rs555754	47.5 ($n = 100$)		Lazar et al. (2003)
Thr44Met	rs8187715	0 ($n = 150$)		Nies et al. (2009)
Arg120Arg	rs668871	48.5 ($n = 100$)[A]	73 ($n = 150$)[B]	A: Lazar et al. (2003) and B: Kang et al. (2007)
Gly193Gly	rs76026925		2 ($n = 150$)	Kang et al. (2007)
g.160748108				
Phe201Phe	rs3918291	0.5 ($n = 100$)		Lazar et al. (2003)
Met370Ile	No refSNP ID	0 ($n = 100$)[A]		A: Lazar et al. (2008) and B: Nies et al. (2009)
g.160778055		0 ($n = 150$)[B]		
Thr400Ile	rs8187725	0.3 ($n = 150$)		Nies et al. (2009)
Ala411Ala	rs2292334	36.5 ($n = 100$)[A] 34.3 ($n = 150$)[B]	50 ($n = 150$)[C]	A: Lazar et al. (2003), B: Nies et al. (2009) and C: Kang et al. (2007)
Ala439Val	rs12212246	0 ($n = 150$)		Nies et al. (2009)
Gly475Ser	rs9365165	0 ($n = 150$)		Nies et al. (2009)
Leu498Leu	rs8187722	0.7 ($n = 150$)		Nies et al. (2009)
3′ UTR	rs3088442	33.7 ($n = 150$)		Nies et al. (2009)

UTR untranslated region

[a]In case that no refSNP ID is available, the genomic localization on chromosome 6 is given (NC_000006.10)

Table 8 Allele frequencies of *SLC47/MATE* genetic variants in different ethnic populations.

SLC47A1 (MATE1)[a]	rs#	Allele frequency (%)					References
		European-American/ Caucasian	Mexican-American	African-American	Chinese-American	Japanese	
5′ UTR	rs2252281	32.1 ($n = 68$)	28.9 ($n = 68$)	44.5 ($n = 68$)	23.1 ($n = 68$)		Ha Choi et al. (2009)
5′ UTR	rs78572621	5.4 ($n = 68$)	7.8 ($n = 68$)	1.7 ($n = 68$)	3.1 ($n = 68$)		Ha Choi et al. (2009)
5′ UTR	rs76654011	0 ($n = 68$)	0 ($n = 68$)	2.5 ($n = 68$)	0 ($n = 68$)		Ha Choi et al. (2009)
5′ UTR	rs75517315	1.5 ($n = 68$)	0.8 ($n = 68$)	1.5 ($n = 68$)	2.9 ($n = 68$)		Ha Choi et al. (2009)
Val10Leu, G>T g.19377872	No refSNP ID					2.2 ($n = 89$)	Kajiwara et al. (2009)
Arg11Arg, C>T g.19377877	No refSNP ID					0.6 ($n = 89$)	Kajiwara et al. (2009)
Ser29Ser	rs61733934	2.2 ($n = 68$)	0.7 ($n = 68$)	0 ($n = 68$)	0 ($n = 68$)		Chen et al. (2009b)
Ala42Ala, T>C g.19377970	No refSNP ID					0.6 ($n = 89$)	Kajiwara et al. (2009)
Gly64Asp	rs77630697	0 ($n = 68$)[A]	0 ($n = 68$)[A]	0 ($n = 68$)[A]	0.7 ($n = 68$)[A]	0.6 ($n = 89$)[B]	A: Chen et al. (2009b) and B: Kajiwara et al. (2009)
Phe90Phe	rs34012597	0 ($n = 68$)	0 ($n = 68$)	5.1 ($n = 68$)	0.7 ($n = 68$)		Chen et al. (2009b)
Leu125Phe	rs77474263	0 ($n = 68$)	5.1 ($n = 68$)	0 ($n = 68$)	0.7 ($n = 68$)		Chen et al. (2009b)
Leu236Leu	rs16960203	0 ($n = 68$)[A]	7.6 ($n = 68$)[A]	0.7 ($n = 68$)[A]	8.3 ($n = 68$)[A]	9.6 ($n = 89$)[B]	A: Chen et al. (2009b) and B: Kajiwara et al. (2009)
Ile297Ile,	rs76420645	0 ($n = 68$)	0 ($n = 68$)	0.8 ($n = 68$)	0 ($n = 68$)		Chen et al. (2009b)
Ala310Val, C>T g.19404100	No refSNP ID					2.2 ($n = 89$)	Kajiwara et al. (2009)
Asp328Ala, A>C g.19404154	No refSNP ID					0.6 ($n = 89$)	Kajiwara et al. (2009)
Val338Ile	rs35790011	0 (n = 68)	0 (n = 68)	5.1 (n = 68)	0 (n = 68)		Chen et al. (2009b)
Asn474Ser, A>G g.19416701	No refSNP ID					0.6 ($n = 89$)	Kajiwara et al. (2009)

Val480Met	rs76645859	0 ($n = 68$)	0 ($n = 68$)	0 ($n = 68$)	0.8 ($n = 68$)	Chen et al. (2009b)
Cys497Ser	rs35395280	0 ($n = 68$)	0 ($n = 68$)	2.4 ($n = 68$)	0 ($n = 68$)	Chen et al. (2009b)
Gln519His	rs78700676	0 ($n = 68$)	0 ($n = 68$)	0.8 ($n = 68$)	0 ($n = 68$)	Chen et al. (2009b)

The work by Kajiwara et al. (2009) describes subjects with renal diseases

[a]In case that no refSNP ID is available, the genomic localization on chromosome 17 is given (NC_000017.9). *UTR*, untranslated region

Table 9 Phenotype-genotype correlations of *SLC22A1*(*OCT1*) in humans

	SLC22A1 (OCT1)	Population (*n*)	Results	References
Tissue expression				
Liver	rs4646272 (intron) Met408Val	Nondiabetic donors (Caucasian $n = 33$, Japanese $n = 25$)	OCT1 mRNA tended to be lower in 408Met carriers	Shikata et al. (2007)
Liver	36 variants	Caucasian surgical liver samples ($n = 150$)	By multivariate analysis adjusted for multiple testing, Arg61Cys significantly correlated with decreased OCT1 protein expression ($p < 0.0001$)	Nies et al. (2009)
Pharmacokinetics/pharmacodynamics				
Metformin (two doses, total 1,850 mg)	Arg61Cys Gly401Ser Met420del Gly465Arg	Healthy subjects ($n = 20$)	Plasma glucose AUC for OGTT ($p = 0.004$) and insulin levels 2 h after glucose administration ($p < 0.05$) were higher in OCT1-variant subjects (carrier of any of the SNPs tested) vs. subjects with only OCT1-reference alleles	Shu et al. (2007)
Metformin (two doses, total 1,850 mg)	Arg61Cys Gly401Ser Met420del Gly465Arg	Healthy subjects ($n = 20$)	Significant higher AUC, higher $C_{max,}$ and lower V/F in OCT1-variant subjects (carrier of any of the SNPs tested) vs. subjects with only OCT1-reference alleles	Shu et al. (2008)
Metformin (single dose, 500 mg)	Ser52Ser Arg61Cys Gly401Ser Met420del Gly465Arg and other tagging SNPs	Healthy male caucasians ($n = 103$)	CL_{ren} ($p = 0.032$) and net CL by tubular secretion ($p = 0.03$) increased with the number of inactive OCT1 alleles defined by the presence of one or more of the amino acid substitutions at positions 61, 401, 420, and 465	Tzvetkov et al. (2009)
Imatinib	Arg61Cys Gly465Arg	Patients with GIST ($n = 74$)	No difference in oral clearance at steady state in patients with at least one of both variants compared to patients with the reference allele on both positions	Hu et al. (2008)
Treatment outcome				
Metformin	Phe41Leu Ser52Ser Gly81Gly Pro117Leu rs4646272 (intron)	Patients with type 2 diabetes ($n = 33$)	The intron variant (rs4646272 T>G) was a negative and Met408Val a positive outcome predictor in a stepwise discriminant functional analysis	Shikata et al. (2007)

	Phe160Leu Pro341Leu Met408Val rs36056065 (intron) rs622591 (intron)			
Metformin	11 tagging SNPs (Illumina 550k SNP array) rs3798174 (intron) rs6937722 (intron) rs3798168 (intron) rs628031 (Met408Val) rs9457843 (intron) rs3798167 (intron) rs2197296 (intron) rs622342 (intron) rs1443844 (intron) rs2297374 (intron) rs1564348 (intron) rs622591 (intron)	Incident metformin users ($n = 102$, Rotterdam Study)	Only the rs622342 A>C variant was associated with metformin response. For each minor C allele, the reduction in HbA1c levels was 0.28% less ($p = 0.005$). After Bonferroni correction, the p-value was 0.045	Becker et al. (2009b)
Metformin	Arg61Cys Met420del	Patients with type 2 diabetes and definable metformin response ($n = 1531$, GoDARTS study)	No clinically significant reduction to lower HbA1c levels, to influence the chance of achieving a treatment target or the hazard of therapy failure in patients carrying both SNPs compared to reference genotype	Zhou et al. (2009)
Metformin	OCT1: rs622342 (intron) MATE1: rs2289669 (intron)	Incident metformin users ($n = 98$, Rotterdam Study)	The effect of MATE 1 rs2289669 polymorphism on glucose-lowering effect was larger in patients with the OCT1 rs622342 CC genotype ($p = 0.005$) than in patients with the AA genotype	Becker et al. (2010)
Imatinib	Arg61Cys	Patients with CML ($n = 32$)	No association with the Arg61Cys variant and imatinib response (cytogenetic/major molecular response)	Zach et al. (2008)
Imatinib oral				

(*continued*)

Table 9 (continued)

	SLC22A1 (OCT1)	Population (*n*)	Results	References
	Arg61Cys Ser52Ser Phe160Leu Pro341Leu Met408Val	Patients with CML ($n = 229$), median duration of therapy 40.8 months, median follow-up 47.3 months	Patients with the GG genotype for Phe160Leu showed a higher risk of LOR (HR, 4.86; $p = 0.0008$) or treatment failure (HR, 3.24; $p = 0.02$) compared to patients carrying at least one C allele. No correlation with SLC22A1 haplotypes	Kim et al. (2009)

CML chronic myeloid leukemia, *GIST* gastrointestinal stromal tumor, *OGTT* oral glucose tolerance test, *LOR* loss of response, *HR* hazard ratio

Table 10 Phenotype-genotype correlations of *SLC22A2* (*OCT2*) in humans

	SLC22A2 (OCT2)	Population (*n*)	Results	References
Pharmacokinetics/pharmacodynamics				
Metformin (single dose, 500 mg)	Thr199Ile Thr201Met Ala270Ser	Healthy Korean subjects ($n = 26$)	Subjects with variant genotypes for the three SNPs showed higher values for C_{max} ($p = 0.0005$) and for AUC ($p = 0.0003$), but lower values for CL/F ($p = 0.0335$), Vd/F ($p = 0.0316$), CL_{ren} ($p = 0.0018$), and net CL by tubular secretion ($p = 0.001$) as compared to the reference genotype group	Song et al. (2008)
Metformin (single dose, 500 mg)	Ala270Ser	Healthy Chinese subjects ($n = 14$)	Mean CL_{ren} and net CL by tubular secretion were 26.1% ($p = 0.022$) and 28% ($p = 0.036$), resp., lower in TT vs. GG carriers After cimetidine coadministration CL_{ren} and net CL were significantly decreased in GG and GT carriers, respectively. Metformin $AUC_{0-\infty}$ increased in GG carriers ($p = 0.043$).	Wang et al. (2008b)
Metformin (single dose, 850 mg)	Ala270Ser	Healthy subjects ($n = 23$)	Mean CL_{ren} ($p = 0.005$) net CL by tubular secretion ($p = 0.002$) were lower in GG vs GT carriers	Chen et al. (2009a)
Metformin (single dose, 500 mg)	14 variants including Ala270Ser	Healthy male Caucasians ($n = 103$)	No significant association between CL_{ren} and OCT2 variants	Tzvetkov et al. (2009)
Treatment outcome				
Metformin	Thr201Met Ala270Ser	Patients with type 2 diabetes ($n = 33$)	No association with metformin response was found	Shikata et al. (2007)
Cisplatin	Ala270Ser	Patients with solid tumors and cisplatin-based therapy ($n = 78$)	Ala270Ser variant was associated with reduced cisplatin-induced nephrotoxicity and only patients with the reference sequence showed significant increase in serum creatinine level ($n = 68$, $p = 0.0009$)	Filipski et al. (2009)
Susceptibility				
Essential hypertension	Ala270Ser	Caucasian patients with cardiovascular diseases ($n = 607$)	Essential hypertension was less prevalent among patients carrying at least one Ser270 allele compared to patients with the reference sequence ($p = 0.028$). The effect was more prominent in patients without type 2 diabetes ($p = 0.013$)	Lazar et al. (2006)

Table 11 Phenotype-genotype correlations of *SLC22A3* (*OCT3*) in humans

	SLC22A3 (OCT3)	Population (*n*)	Results	References
Tissue expression				
Liver	34 variants including rs3088442 (3′ UTR)	Caucasian surgical liver samples ($n = 150$)	By multivariate analysis adjusted for multiple testing, four variants (rs2292334, rs2048327, rs1810126, rs3088442) were associated with reduced mRNA levels ($p = 0.03$)	Nies et al. (2009)
Pharmacokinetics/pharmacodynamics				
Metformin (single dose, 500 mg)	6 variants	Healthy male Caucasians ($n = 103$)	No significant association between CL_{ren} and OCT3 variants	Tzvetkov et al. (2009)
Susceptibility				
Methamphetamine dependence	rs655185 (intron) rs509707 (intron) rs4709426 (intron) rs7745775 (intron) rs3106164 (intron) rs2292334 (Ala411Ala) rs3918286 (intron) rs3088442 (3′ UTR)	Japanese subjects with methamphetamine (MAP) dependence ($n = 213$) and healthy controls ($n = 443$)	Genotype ($p = 0.024$) and allele ($p = 0.011$) frequency of rs509707, allele frequency of rs4709426 ($p = 0.037$), and haplotypic frequencies for both SNPs ($p = 0.0438$) differed significantly between polysubstance and single-MAP users	Aoyama et al. (2006)
Obsessive-compulsive disorder (OCD)	rs60515630 (5′ near gene) rs555754 (5′ near gene) rs668871 (Arg120Arg) rs3918291 (Phe201Phe) Met370Ile rs2292334 (Ala411Ala) rs3918287 (intron) rs2457574 (intron) rs1810126 (3′ UTR)	Children/adolescents ($n = 84$) with childhood-onset OCD vs healthy Caucasian subjects ($n = 100$)	Known SNPs and frequent haplotypes were not associated with OCD. Two novel variants (rs60515630, Met370Ile) were exclusively found in OCD patients	Lazar et al. (2008)
Prostate cancer	GWA study	Prostate cancer patients vs population-screened controls stage 1: 1854 cases vs 1894 controls Stage 2: 3268 cases vs 3366 controls	Significant association of variant rs9364554 (intron) with prostate cancer susceptibility (stage 1: $p = 9.3 \times 10^{-7}$, stage 1 + 2: $p = 5.5 \times 10^{-10}$)	Eeles et al. (2008)

Coronary artery disease (CAD)	GWHA study	Stage 1: WTCC CAD study (1,926 CAD cases vs 2,938 controls) Stage 2: GerMIFS I study (875 CAD cases vs 1,644 controls) Stage 3: four additional studies (total numbers: 6,198 CAD cases vs 5,681 controls)	Significant association of the haplotypes derived from 4 SNPs of SLC22A3 (rs2048327)-LPAL2-LPA gene cluster with CAD in independent studies	Tregouet et al. (2009)

GWA genomewide association, *GWHA* genomewide haplotype association

Table 12 Phenotype-genotype correlations of *SLC47/MATE* in humans

	SLC47A1 (MATE1)	Population (*n*)	Results	References
Tissue expression				
Kidney Liver	rs2252281 (5′ UTR)	Surgical kidney samples ($n = 38$), post-mortem liver samples ($n = 34$)	mRNA in TC ($n = 21$) or CC ($n = 5$) kidneys were significantly lower ($p = 0.015$) compared to TT genotype ($n = 12$). No effect was found in human liver	Ha Choi et al. (2009)
Pharmacokinetics/pharmacodynamics				
Metformin (single dose, 500 mg)	rs2289669 (intron)	Healthy male Caucasians ($n = 103$)	No significant association between CL_{ren} and the rs2289669 G>A variant	Tzvetkov et al. (2009)
Treatment outcome				
Metformin	12 tagging SNPs (Illumina 550k SNP array) rs894680 (intron) rs2018675 (intron) rs2440154 (intron) rs2440155 (intron) rs16960201 (intron) rs2453568 (intron) rs2244280 (intron) rs2289669 (intron) rs1961669 (intron) rs2453594 (intergenic region) rs2453589 (intergenic region) rs2165894 (intergenic region)	Incident metformin users ($n = 116$, Rotterdam Study)	Only the rs2289669 G>A variant was associated with metformin response. For each minor A allele, the reduction in HbA1c levels was 0.30% larger ($p = 0.005$). After Bonferroni correction, the p-value was 0.045	Becker et al. (2009a)

activity (White et al. 2007; Wang et al. 2008a), is the tyrosine kinase inhibitor imatinib, a mainstay in treatment of patients with chronic myeloid leukemia (CML). Although one study suggests a significant contribution of the OCT1-Phe160Leu variant related to loss of response to imatinib or treatment failure (Kim et al. 2009), further confirmatory studies are still missing, which are mandatory to support such an association.

Regarding OCT2 variants, the Ala270Ser polymorphism was investigated in several pharmacokinetic metformin studies with discrepant results (Table 10). The study with the most representative number of subjects included ($n=103$) did not show any association (Tzvetkov et al. 2009). Interestingly, the OCT2-Ala270Ser variant was also related to a significantly reduced cisplatin-induced nephrotoxicity in patients with solid tumors, which fits to the fact that cisplatin is indeed an OCT2 substrate and OCT2 is highly expressed in human kidney (Filipski et al. 2009).

Although the physiological role of OCTs and MATEs is not fully resolved, it is conceivable that membrane transporters determine intracellular concentration of potentially efficient and/or toxic agents and metabolites. In this context it is plausible to hypothesize that genotype-dependent OCT/MATE expression may also contribute to a certain disease susceptibility. Of interest, susceptibility for diseases was repeatedly related to OCT3 (Table 11), whereas convincing data for both, OCT1 and OCT2, are lacking. The *SLC22A3* gene was identified as a potential risk factor for prostate cancer as well as coronary artery disease by genomewide association studies (GWA), including thousands of index cases and confirmed by independent control groups (Eeles et al. 2008; Tregouet et al. 2009).

Taken together, compared with other transport proteins the research on the impact of OCT and MATE variants is only at the beginning. Comprehensive genotype–phenotype correlation studies including different human tissues as well as clinical response data are required in the future.

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