British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2011.01724.x
www.brjpharmacol.org

REVIEW

OATPs, OATs and OCTs: the organic anion and cation transporters of the *SLCO* and *SLC22A* gene superfamilies

Megan Roth[1], Amanda Obaidat[1] and Bruno Hagenbuch[1,2]

[1]*Department of Pharmacology, Toxicology and Therapeutics, The University of Kansas Medical Center, Kansas City, KS, USA, and* [2]*The University of Kansas Cancer Center, Kansas City, KS, USA*

Correspondence
Bruno Hagenbuch, Department of Pharmacology, Toxicology and Therapeutics, The University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160, USA. E-mail: bhagenbuch@kumc.edu

Keywords
SLCO; *SLC22A*; OATP; OAT; OCT; drug transport; membrane transport

Received
5 July 2011
Revised
1 September 2011
Accepted
23 September 2011

The human organic anion and cation transporters are classified within two *SLC* superfamilies. Superfamily *SLCO* (formerly *SLC21A*) consists of organic anion transporting polypeptides (OATPs), while the organic anion transporters (OATs) and the organic cation transporters (OCTs) are classified in the *SLC22A* superfamily. Individual members of each superfamily are expressed in essentially every epithelium throughout the body, where they play a significant role in drug absorption, distribution and elimination. Substrates of OATPs are mainly large hydrophobic organic anions, while OATs transport smaller and more hydrophilic organic anions and OCTs transport organic cations. In addition to endogenous substrates, such as steroids, hormones and neurotransmitters, numerous drugs and other xenobiotics are transported by these proteins, including statins, antivirals, antibiotics and anticancer drugs. Expression of OATPs, OATs and OCTs can be regulated at the protein or transcriptional level and appears to vary within each family by both protein and tissue type. All three superfamilies consist of 12 transmembrane domain proteins that have intracellular termini. Although no crystal structures have yet been determined, combinations of homology modelling and mutation experiments have been used to explore the mechanism of substrate recognition and transport. Several polymorphisms identified in members of these superfamilies have been shown to affect pharmacokinetics of their drug substrates, confirming the importance of these drug transporters for efficient pharmacological therapy. This review, unlike other reviews that focus on a single transporter family, briefly summarizes the current knowledge of all the functionally characterized human organic anion and cation drug uptake transporters of the *SLCO* and the *SLC22A* superfamilies.

LINKED ARTICLES

BJP recently published a themed section on Transporters. To view the papers in this section visit http://dx.doi.org/10.1111/bph.2011.164.issue-7

Abbreviations

ABC, ATP-binding cassette; BSP, bromosulphophthalein; CCK-8, cholecystokinin-octapeptide; CoMFA, comparative molecular field analysis; HNF, hepatocyte nuclear factor; MPP, 1-methyl-4-phenylpyridinium; NSAID, non-steroidal anti-inflammatory drug; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; OCTN, organic cation and carnitine transporter; PAH, p-aminohippurate; SHP, small heterodimer partner; SLC, solute carrier; SNP, single nucleotide polymorphism; SXR, steroid and xenobiotic receptor; TEA, tetraethylammonium; URAT, urate transporter

General introduction

Numerous endo- and xenobiotics including many drugs are organic anions or cations. Their disposition and elimination depend on the proper function of multispecific drug transporters that belong to two major superfamilies: solute carrier (SLC) transporters and ATP-binding cassette (ABC) transporters. Although most are capable of bidirectional transport, in

© 2011 The Authors
British Journal of Pharmacology © 2011 The British Pharmacological Society

general, ABC transporters are considered to be responsible for efflux of substrates, while SLC transporters mediate uptake of substrates into cells. Within the SLC transporters, there are two gene superfamilies that contain the major organic anion and cation transporters. These are the *SLCO* superfamily, made up of the organic anion transporting polypeptides (OATPs), and the *SLC22A* superfamily, which contains the organic cation transporters (OCTs) and the organic anion transporters (OATs). Individual members of these superfamilies are expressed in essentially every epithelium throughout the body. The members of both superfamilies mediate transport of a broad range of structurally diverse compounds with overlapping substrate specificities within the superfamilies. In general, OCTs transport cations, OATPs transport large and fairly hydrophobic organic anions, and OATs transport the smaller and more hydrophilic organic anions. This brief review will summarize our current knowledge about the human members of these three transporter families, with an emphasis on tissue distribution, substrate specificity, regulation of expression, transporter structure and pathology.

Nomenclature

OATPs are encoded by genes in the *SLCO/Slco* superfamily. This superfamily was originally named *SLC21A*; however, the nomenclature of its members was updated and standardized in 2004 based on phylogenetic relationships, and the superfamily was renamed to *SLCO*, the solute carrier family of the OATPs (Hagenbuch and Meier, 2004). Eleven human OATPs have been identified and are classified into six families based on their amino acid identity. The different proteins are named OATP (Oatp for the rodent proteins) followed by the family number (e.g. OATP1, OATP2), the subfamily letter (e.g. OATP1A, OATP1B) and then a consecutive number identifying the individual members within the family based on the historical order in which they have been identified (e.g. Oatp1a1, OATP1A2 and Oatp1a3). The corresponding gene symbols are *SLCO* followed by the same number–letter–number combination (e.g. *Slco1a1*, *SLCO1A2* and *Slco1a3*). The best characterized OATPs belong to family 1, which in humans contains OATP1A2, OATP1B1, OATP1B3 and OATP1C1. A significant amount of gene duplication and divergence has occurred in this family, especially in rodents, complicating direct comparisons between human (OATP) and rodent (Oatp) studies. OATP1A2 has five rodent orthologues: Oatp1a1, Oatp1a3 (in rats only), Oatp1a4, Oatp1a5 and Oatp1a6. OATP1B1 and OATP1B3 have a single rodent orthologue, Oatp1b2. The other OATPs and their rodent orthologues are OATP1C1 (Oatp1c1), OATP2A1 (Oatp2a1), OATP2B1 (Oatp2b1), OATP3A1 (Oatp3a1), OATP4A1 (Oatp4a1), OATP4C1 (Oatp4c1), OATP5A1 and OATP6A1 (Oatp6b1, Oatp6c1 and Oatp6d1).

The *SLC22A* family includes OCT1-3 (*SLC22A1-3*), OCTN1 and OCTN2 (*SLC22A4-5*), OCT6 (*SLC22A16*, also known as CT2), OAT1-4 (*SLC22A6-8, 11*), OAT7 (*SLC22A9*), URAT1 (*SLC22A12*) and several additional not well characterized putative transporters. Most of these proteins have a single rodent orthologue, but OAT4 is specific to humans. OAT5 (*SLC22A10*) was cloned in 2001 but has not been functionally characterized (Sun *et al.*, 2001); thus, it is considered an orphan OAT. It is believed that human OAT5 is not the orthologue of rodent Oat5 (Youngblood and Sweet, 2004). Additionally, in rodents, there is an Octn3 protein (*Slc22a21*) – although no human homologue has been conclusively identified, an antibody against mouse Octn3 cross-reacts in certain human tissues, which led the authors to suggest that a human OCTN3 does exist (Lamhonwah *et al.*, 2005). The human and rodent *SLCO* and *SLC* genes and their corresponding proteins are listed in Table 1. Unless otherwise stated, all information included in this review refers to the human transporters.

OATPs

Organic anion transporting polypeptides (OATPs in humans, Oatps in rodents) are multispecific transporters located in numerous epithelia throughout the body. They mediate the cellular uptake of a broad range of substrates, including bile acids, steroid conjugates and numerous xenobiotics.

Tissue distribution

Protein expression for OATPs is summarized in Figure 1. OATP1A2 is widely distributed throughout the body, with the highest mRNA expression in the brain, liver, lung, kidney and testes (Kullak-Ublick *et al.*, 1995; Steckelbroeck *et al.*, 2004). With this distribution, it is thought that OATP1A2 could play a critical role in the absorption, distribution and excretion of xenobiotics. OATP1A2 protein has been localized to the brush border membrane of enterocytes in the duodenum (Glaeser *et al.*, 2007), where it may mediate the absorption of xenobiotics. Within the liver, OATP1A2 is exclusively expressed in cholangiocytes (Lee *et al.*, 2005) and may be involved in the reabsorption of xenobiotics excreted into the bile. In the kidney, OATP1A2 is expressed at the apical membrane of the distal nephron (Lee *et al.*, 2005), where it could be responsible for either the reabsorption from or the secretion of xenobiotics into urine. OATP1A2 is also expressed at the luminal membrane of the endothelial cells of brain capillaries (Bronger *et al.*, 2005) and is thought to be part of the blood–brain barrier. OATP1B1 and OATP1B3 are both selectively expressed in the liver (Abe *et al.*, 1999; 2001; Hsiang *et al.*, 1999; Konig *et al.*, 2000a,b), where they are localized to the basolateral membrane of hepatocytes (Konig *et al.*, 2000b; Abe *et al.*, 2001; Kullak-Ublick *et al.*, 2001; Cui *et al.*, 2003). OATP1B1 is expressed in hepatocytes throughout the lobule, while OATP1B3 is primarily expressed around the central vein (Konig *et al.*, 2000a); consistent with this pattern, expression levels of OATP1B1 mRNA in liver homogenate are higher overall than are levels of OATP1B3 (Michalski *et al.*, 2002; Briz *et al.*, 2006). OATP1C1 mRNA expression was originally localized to the brain and testes (Pizzagalli *et al.*, 2002), and OATP1C1 protein has been detected at the basolateral membrane of choroid plexus epithelial cells (Roberts *et al.*, 2008) and to the Leydig cells of the testes (Pizzagalli *et al.*, 2002).

OATP2A1, also known as the prostaglandin transporter (PGT), is ubiquitously expressed throughout the body (Nomura *et al.*, 2004; 2005). As shown by Northern blot analysis, mRNA of OATP2A1 was found in several tissues including brain, colon, heart, kidney, liver, lung, ovary, pan-

Table 1

Gene and protein names of human and rodent organic anion and cation transporters

Human gene	Human protein	Rodent gene	Rodent protein
		Slco1a1	Oatp1a1
SLCO1A2	OATP1A2		
		Slco1a3 (rat only)	Oatp1a3
		Slco1a4	Oatp1a4
		Slco1a5	Oatp1a5
		Slco1a6	Oatp1a6
SLCO1B1	OATP1B1		
		Slco1b2	Oatp1b2
SLCO1B3	OATP1B3		
SLCO1C1	OATP1C1	*Slco1c1*	Oatp1c1
SLCO2A1	OATP2A1	*Slco2a1*	Oatp2a1
SLCO2B1	OATP2B1	*Slco2b1*	Oatp2b1
SLCO3A1	OATP3A1	*Slco3a1*	Oatp3a1
SLCO4A1	OATP4A1	*Slco4a1*	Oatp4a1
SLCO4C1	OATP4C1	*Slco4c1*	Oatp4c1
SLCO5A1	OATP5A1		
SLCO6A1	OATP6A1		
		Slco6b1	Oatp6b1
		Slco6c1	Oatp6c1
		Slco6d1	Oatp6d1
SLC22A1	OCT1	*Slc22a1*	Oct1
SLC22A2	OCT2	*Slc22a2*	Oct2
SLC22A3	OCT3	*Slc22a3*	Oct3
SLC22A4	OCTN1	*Slc22a4*	Octn1
SLC22A5	OCTN2	*Slc22a5*	Octn2
SLC22A6	OAT1	*Slc22a6*	Oat1
SLC22A7	OAT2	*Slc22a7*	Oat2
SLC22A8	OAT3	*Slc22a8*	Oat3
SLC22A9	OAT7		
SLC22A10	OAT5		
SLC22A11	OAT4		
SLC22A12	URAT1	*Slc22a12*	Urat1
SLC22A13	OAT10	*Slc22a13*	Oat10
SLC22A16	OCT6 (CT2)		
		Slc22a19	Oat5
SLC22A20	OAT6	*Slc22a20*	Oat6
		Slc22a21	Octn3

creas, placenta, prostate, skeletal muscle, spleen and small intestine (Schuster, 2002). Recently, OATP2A1 protein expression was shown in the upper gastrointestinal tract, localized in the pyloric glands of the antrum and parietal cells of the gastric corpus (Mandery *et al.*, 2010). OATP2A1 is thought to be involved in terminating prostaglandin signalling by transporting prostaglandins into cells (Nomura *et al.*, 2004; 2005). OATP2B1 is also widely expressed throughout the body (Tamai *et al.*, 2000; Kullak-Ublick *et al.*, 2001). The highest levels of mRNA are found in the liver, where the protein is located at the basolateral membrane of hepatocytes (Kullak-Ublick *et al.*, 2001). Protein expression has also been reported at the apical membrane of intestinal epithelial cells (Kobayashi *et al.*, 2003), at the basolateral membrane of syncytiotrophoblasts in the placenta (St-Pierre *et al.*, 2002), in epidermal keratinocytes (Schiffer *et al.*, 2003), in the myoepi-

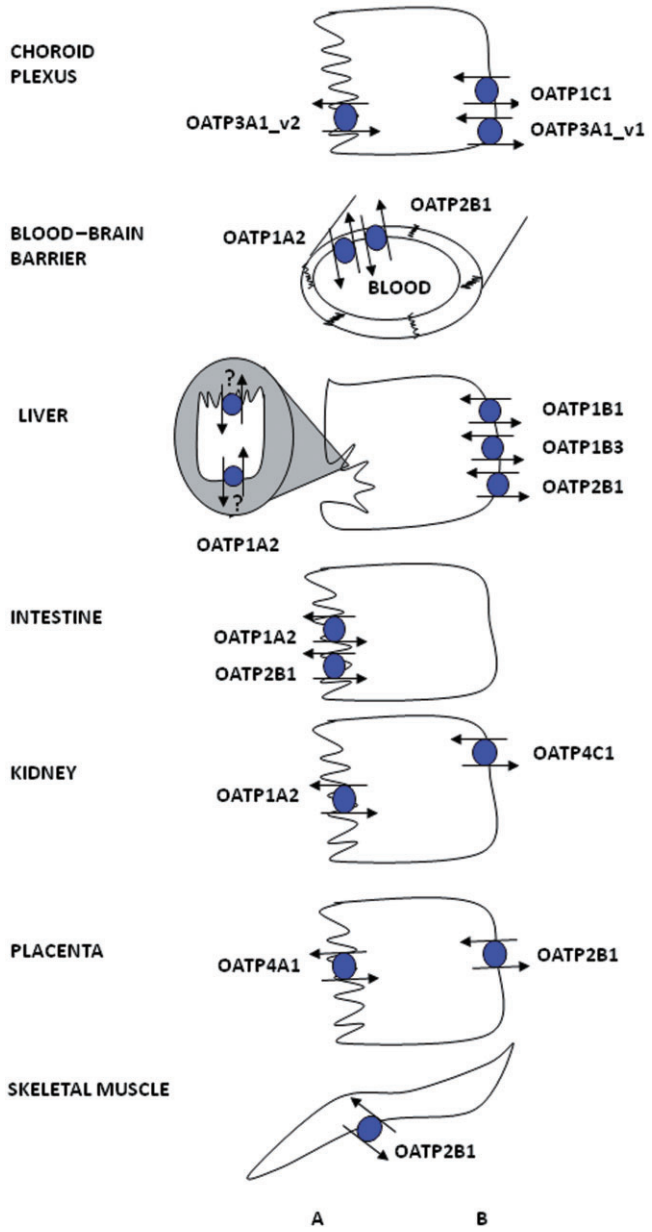

Figure 1

Expression of OATPs in selected human epithelial cells. For more details, see the text. OATP1A2 expression in cholangiocytes has been demonstrated, but it has not yet been localized to a distinct cell membrane. (A) apical; (B) basolateral.

thelium surrounding ductal epithelial cells in human mammary gland (Pizzagalli *et al.*, 2003), in vascular endothelial cells in the heart (Grube *et al.*, 2006b), in skeletal muscle (Knauer *et al.*, 2010) and at the luminal membrane of the endothelial cells of the blood–brain barrier (Bronger *et al.*, 2005).

OATP3A1 mRNA levels are highest in testes, brain and heart followed by lung, spleen, peripheral blood leukocytes and thyroid gland (Adachi *et al.*, 2003; Huber *et al.*, 2007). OATP3A1 mRNA expression has also been shown in human epidermal keratinocytes (Schiffer *et al.*, 2003). OATP3A1 has two splice variants, which have cell type-specific expression. OATP3A1_v1 was localized to the germ cells of testes, at the basolateral membrane of the choroid plexus and in neuroglial cells of the grey matter in the frontal cortex, while OATP3A1_v2 was localized in the Sertoli cells of the testes, at the apical and sub-apical membrane in choroid plexus and in cell bodies and axons of the neurons in the frontal cortex (Huber *et al.*, 2007).

OATP4A1 has been detected in several tissues with the highest levels of mRNA found in the heart and placenta, followed by lung, liver, skeletal muscle, kidney and pancreas (Tamai *et al.*, 2000; Fujiwara *et al.*, 2001). OATP4A1 protein was localized to the apical membrane of syncytiotrophoblasts in the placenta (Sato *et al.*, 2003). OATP4C1 was initially thought to be a kidney-specific OATP, based on Northern blot analysis (Mikkaichi *et al.*, 2004). Based on the localization of rat Oatp4c1, it is assumed that human OATP4C1 is also localized at the basolateral membrane of proximal tubule cells. A recent microarray suggests that OATP4C1 may also be expressed in the liver, although this has not yet been verified by RT-PCR or protein analysis (Bleasby *et al.*, 2006). This microarray also contains the only determination of OATP5A1 expression to date, showing possible expression in fetal brain, prostate, skeletal muscle and thymus. OATP6A1 mRNA has been shown mainly in the testes, with low expression in spleen, brain, fetal brain and placenta (Suzuki *et al.*, 2003; Lee *et al.*, 2004).

Substrate specificity

The mechanism of OATP-mediated transport remains controversial. It is well established that transport is ATP- and sodium-independent, but the driving force for transport is still under investigation. OATPs are capable of bidirectional transport, and several studies have suggested that they work as electroneutral exchangers. Evidence suggests that individual OATPs/Oatps may exchange their substrates for intracellular bicarbonate (Satlin *et al.*, 1997; Leuthold *et al.*, 2009), glutathione (Li *et al.*, 1998; Franco and Cidlowski, 2006) or glutathione conjugates (Li *et al.*, 2000). However, it appears that there could be differences among the different OATPs/Oatps with respect to the exact transport mechanism: for example, transport mediated by OATP1B1 and OATP1B3 is not affected by glutathione (Mahagita *et al.*, 2007).

OATP-mediated transport can also be affected by pH. Several studies have shown that OATP2B1 transport activity is increased at acidic pH (Kobayashi *et al.*, 2003; Nozawa *et al.*, 2004a; Sai *et al.*, 2006; Varma *et al.*, 2011). As OATP2B1 is expressed in the small intestine, this phenomenon could result in both increased transport of substrates and a broader substrate range and thus improve OATP2B1-mediated drug absorption. However, this effect seems to be substrate dependent and can be caused by both increased affinity (decreased K_m) and increased turnover rate (V_{max}) (Nozawa *et al.*, 2004a; Leuthold *et al.*, 2009). It has been proposed that the mechanism of increased substrate affinity is caused by the protonation of a conserved histidine residue at the extracellular end of transmembrane domain 3 (Leuthold *et al.*, 2009). Transport of estrone-3-sulphate by OATP1B1 and OATP1B3 has previously been shown to be independent of the extracellular pH and of the membrane potential (Mahagita *et al.*, 2007). However, a recent report demonstrates that these two trans-

porters are influenced in different ways by both pH and the membrane potential (Martinez-Becerra *et al.*, 2011).

To determine the driving force of OATP-mediated transport, additional studies are clearly needed. By using membrane vesicles isolated from cells that overexpress individual OATPs, the exact composition of the buffers on both sides of the plasma membrane can be controlled. Based on such experiments, an exact delineation of the involved driving forces and exchange mechanisms should be possible.

Most OATPs transport a broad range of compounds. The transported substrates are summarized for family OATP1 in Table 2, for family OATP2 in Table 3 and for all the remaining OATPs in Table 4 (no substrates have yet been identified for OATP5A1 or OATP6A1). Although the majority of substrates are anions, some OATPs can also transport neutral and cationic compounds (Bossuyt *et al.*, 1996). In general, substrates are amphipathic molecules with molecular weights greater than 350 Daltons and include bile acids, conjugated steroids, thyroid hormones, linear and cyclic peptides and mushroom toxins as well as numerous drugs, including statins, sartans, antibiotics and anticancer drugs. Many of these compounds (e.g. estrone-3-sulphate, estradiol-17β-glucuronide or bromosulphophthalein) are substrates of multiple OATPs and are therefore commonly used as model substrates. However, some substrates appear to be more specific; for example, cholecystokinin-octapeptide (CCK-8) is selectively transported by OATP1B3 (Ismair *et al.*, 2001), while digoxin seems to be mainly transported by OATP4C1 (Mikkaichi *et al.*, 2004).

It has been suggested that substrates are transported through a central positively charged pore in OATPs via a rocker-switch mechanism (Meier-Abt *et al.*, 2005). A pharmacophore model developed for OATP1B1 based on published apparent K_m values of OATP substrates suggests that substrates contain two hydrogen bond acceptors, one hydrogen bond donor and two hydrophobic regions (Chang *et al.*, 2005). A CoMFA (comparative molecular field analysis) model calculated based on 25 competitive inhibitors suggested that the substrate binding site for estradiol-17β-glucuronide on OATP1B1 consists of a large hydrophobic region with basic residues at both ends (Gui *et al.*, 2009). However, such analyses are complicated by the indication that OATPs have multiple substrate binding sites or translocation pathways. OATP1B1 has biphasic saturation kinetics for estrone-3-sulphate, suggesting the presence of both a high-affinity, low-capacity binding site and a low-affinity, high-capacity binding site (Tamai *et al.*, 2001; Noe *et al.*, 2007; Gui and Hagenbuch, 2009). Similarly, OATP4C1 was recently shown to have distinct binding sites for estrone-3-sulphate and digoxin (Yamaguchi *et al.*, 2010). In addition, inhibition studies have shown that compounds can have stimulatory, inhibitory or no effect on OATP-mediated transport, depending on the model substrate used (Gui *et al.*, 2008; Roth *et al.*, 2011a,b).

Regulation of expression

Expression of OATPs is largely controlled by transcriptional regulation. Constitutive OATP1B1 expression in hepatocytes appears to be dependent on HNF1α (Jung and Kullak-Ublick, 2003; Furihata *et al.*, 2007), while OATP1B3 is likely regulated by HNF3β (Vavricka *et al.*, 2004). There is also evidence that additional signals may be involved in OATP1B expression, including Stat5 (Wood *et al.*, 2005) and transcription factors activated by hepatocyte growth factor (Le Vee *et al.*, 2009), IFN-γ (Le Vee *et al.*, 2011) and IL-1β (Le Vee *et al.*, 2008). The mechanisms for regulating OATP expression are likely to vary by tissue type. For example, OATP1A2 expression is up-regulated in response to increased bile acid levels (Kullak-Ublick *et al.*, 1997a), which would affect expression levels in the small intestine and liver. In breast carcinoma tissues and cell lines, however, OATP1A2 expression is significantly associated with the steroid and xenobiotic receptor (SXR) expression (Miki *et al.*, 2006).

Regulation of OATPs can also occur at the protein level. As most OATPs contain a PDZ consensus sequence (Wang *et al.*, 2005a), and the carboxy-terminus of OATP1A2 has been shown to interact with PDZ proteins (Kato *et al.*, 2004), membrane localization of OATPs may be due to interactions with PDZ proteins. A recent study with rat Oatp1a1 demonstrated that in addition to the interaction with PDZ proteins, phosphorylation affected membrane expression (Choi *et al.*, 2011). It has also been shown that activation of PKC leads to the phosphorylation of OATP2B1 and a reduced V_{max} for substrates, suggesting that the protein is internalized upon phosphorylation (Kock *et al.*, 2010).

Transporter structure

Human OATPs range in size from 643 to 724 amino acids, with the exception of the as yet uncharacterized OATP5A1, which contains 848 amino acids. OATPs are predicted to contain 12 transmembrane domains, with both termini located intracellularly. Although hydropathy models predict either a 10- or 12-domain topology, the 12-transmembrane domain model was confirmed for rat Oatp1a1 (Wang *et al.*, 2008). The second and fifth extracellular loops contain multiple predicted and/or confirmed N-glycosylation sites, although the exact location varies by protein. The large fifth extracellular loop contains many conserved cysteines, which have been shown to be involved in disulphide bonds and are important for the surface expression of OATP2B1 (Hanggi *et al.*, 2006). Similar to most other mammalian transport proteins, there is no crystal structure available for any of the OATPs so far. Therefore, homology modelling has been used to construct putative three-dimensional models of OATPs; this aids in the generation of theoretical predictions that can then be tested experimentally (Meier-Abt *et al.*, 2005; Gui and Hagenbuch, 2008; Glaeser *et al.*, 2010). Based on such models, several conserved positively charged amino acids that line the putative substrate pore were studied, and amino acids R57, K361 and R580 in OATP1B1 (Weaver and Hagenbuch, 2010) and K41, R580 and K361 in OATP1B3 (Glaeser *et al.*, 2010; Mandery *et al.*, 2011) were shown to be important for substrate transport. These amino acids are highlighted in the predicted three-dimensional structure of OATP1B1 shown in Figure 2A. Additional experiments using chimeras between OATP1B1 and OATP1B3 identified transmembrane domains 8 and 9 for OATP1B1 (Miyagawa *et al.*, 2009) and transmembrane domain 10 for both OATP1B1 (Gui and Hagenbuch, 2009) and OATP1B3 (Gui and Hagenbuch, 2008) to be important for substrate transport and expression.

Table 2

Substrates of human OATP1 family

Substrates	K_m (μM)	References
OATP1A2		
Acebutolol		Kato *et al.* (2009)
APD-ajmalinium		Bossuyt *et al.* (1996); van Montfoort *et al.* (1999)
Atenolol		Kato *et al.* (2009)
Atrasentan		Katz *et al.* (2006)
Bamet-R2	24	Briz *et al.* (2002)
Bamet-UD2	14	Briz *et al.* (2002)
Bilirubin		Briz *et al.* (2003)
BQ-123		Kullak-Ublick *et al.* (2001)
Bromosulphophthalein	20	Kullak-Ublick *et al.* (1995)
Celiprolol	20.5	Kato *et al.* (2009)
Chlorambucil-taurocholate		Kullak-Ublick *et al.* (1997b)
Cholate	93	Kullak-Ublick *et al.* (1995); Meier *et al.* (1997)
Ciprofloxacin		Maeda *et al.* (2007)
CRC220		Meier *et al.* (1997)
Darunavir		Hartkoorn *et al.* (2010)
Dehydroepiandrosterone-3-sulphate	7	Kullak-Ublick *et al.* (1998)
Deltorphin II	330	Gao *et al.* (2000)
[D-penicillamine^{2,5}]enkephalin	202	Gao *et al.* (2000)
Enoxacin		Maeda *et al.* (2007)
Epicatechin gallate	10	Roth *et al.* (2011b)
Epigallocatechin gallate	19	Roth *et al.* (2011b)
Erythromycin		Franke *et al.* (2008)
Estradiol-17β-glucuronide		Meier *et al.* (1997); Kullak-Ublick *et al.* (2001); Briz *et al.* (2003)
Estrone-3-sulphate	16	Lee *et al.* (2005)
Fexofenadine	6	Cvetkovic *et al.* (1999)
Gatifloxacin		Maeda *et al.* (2007)
Gd-B20790		Pascolo *et al.* (1999)
Glycocholate		Kullak-Ublick *et al.* (1995; 2001); Meier *et al.* (1997)
Hydroxyurea		Walker *et al.* (2011)
Imatinib		Hu *et al.* (2008)
Labetalol		Kato *et al.* (2009)
Levofloxacin	136	Maeda *et al.* (2007)
Lomefloxacin		Maeda *et al.* (2007)
Lopinavir		Hartkoorn *et al.* (2010)
Methotrexate	457	Badagnani *et al.* (2006)
Microcystin	20	Fischer *et al.* (2005)
N-methylquinidine	26	van Montfoort *et al.* (1999)
N-methylquinine	5	van Montfoort *et al.* (1999); Kullak-Ublick *et al.* (2001)
Nadolol		Kato *et al.* (2009)
Norfloxacin		Maeda *et al.* (2007)
Ouabain	5 500	Bossuyt *et al.* (1996)
Pitavastatin	3	Fujino *et al.* (2005)
PGE_2		Kullak-Ublick *et al.* (2001)
Reverse triiodothyronine (rT3)		Fujiwara *et al.* (2001)
Rocuronium		van Montfoort *et al.* (1999)

Table 2

Continued

Substrates	K_m (μM)	References
Rosuvastatin	3	Ho *et al.* (2006)
Saquinavir	36	Su *et al.* (2004)
Sotalol		Kato *et al.* (2009)
Talinolol	714	Shirasaka *et al.* (2010)
Taurocholate	60	Kullak-Ublick *et al.* (1995)
Taurochenodeoxycholate		Kullak-Ublick *et al.* (1995)
Tauroursodeoxycholate	19	Kullak-Ublick *et al.* (1995)
Thyroxine (T4)	8	Fujiwara *et al.* (2001)
Tebipenem pivoxil	41	Kato *et al.* (2010)
TR-14035		Tsuda-Tsukimoto *et al.* (2006)
Triiodothyronine (T3)	7	Fujiwara *et al.* (2001)
Unoprostone metabolite	93	Gao *et al.* (2005)
OATP1B1		
ACU154		Takada *et al.* (2004)
Arsenic (arsenite, arsenate)		Lu *et al.* (2006)
Atorvastatin	10	Lau *et al.* (2007)
Atrasentan		Katz *et al.* (2006)
Bamet-R2	10	Briz *et al.* (2002)
Bamet-UD2	10	Briz *et al.* (2002)
Benzylpenicillin		Tamai *et al.* (2000)
BDE47	0.31	Pacyniak *et al.* (2010)
BDE99	0.91	Pacyniak *et al.* (2010)
BDE153	1.91	Pacyniak *et al.* (2010)
Bilirubin	0.01	Briz *et al.* (2003)
Bisglucuronosyl bilirubin	0.3	Cui *et al.* (2001)
BNP1350		Oostendorp *et al.* (2009)
Bosentan	44	Treiber *et al.* (2007)
BQ-123		Kullak-Ublick *et al.* (2001)
Bromosulphophthalein	0.1–0.3	Cui *et al.* (2001); Kullak-Ublick *et al.* (2001)
Caspofungin		Sandhu *et al.* (2005)
Cefazolin	20 800	Nakakariya *et al.* (2008)
Cefditoren	3 450	Nakakariya *et al.* (2008)
Cefoperazone	4 840	Nakakariya *et al.* (2008)
Cerivastatin	4	Shitara *et al.* (2003)
CDCA-NBD	1.5	Yamaguchi *et al.* (2006)
Cholate	11	Cui *et al.* (2001)
Cholyl-glycylamido-fluorescein (CGamF)	7.9	Annaert *et al.* (2010)
[D-Ala2, D-Leu5]enkephalin		Nozawa *et al.* (2003)
Darunavir		Hartkoorn *et al.* (2010)
Dehydroepiandrosterone-3-sulphate	22	Abe *et al.* (1999; 2001); Hsiang *et al.* (1999); Cui *et al.* (2001); Kullak-Ublick *et al.* (2001)
Demethylphalloin	17	Meier-Abt *et al.* (2004)
[D-penicillamine^{2,5}]enkephalin		Abe *et al.* (2001)
Eltrombopag		Takeuchi *et al.* (2011)
Enalapril	262	Liu *et al.* (2006)

Table 2

Continued

Substrates	K_m (μM)	References
Estradiol-17β-glucuronide	4–24	Abe *et al.* (1999); Tamai *et al.* (2000; 2001); Konig *et al.* (2000b); Cui *et al.* (2001); Kullak-Ublick *et al.* (2001); Nakai *et al.* (2001); Hirano *et al.* (2004)
Estrone-3-sulphate	0.5 12.5	Hirano *et al.* (2004) Cui *et al.* (2001)
	0.09 and 5.4	Tamai *et al.* (2001)
	0.23 and 45	Noe *et al.* (2007)
Ezetimibe glucuronide		Oswald *et al.* (2008)
Fluorescein		Gui *et al.* (2010)
Fluorescein methotrexate	3.8	Gui *et al.* (2010)
Fluvastatin	1.4–3.5	Kopplow *et al.* (2005); Noe *et al.* (2007)
Gimatecan		Oostendorp *et al.* (2009)
Glycocholate		Kullak-Ublick *et al.* (2001)
Glycoursodeoxycholate		Maeda *et al.* (2006b)
Hydroxyurea		Walker *et al.* (2011)
Leukotriene C4		Abe *et al.* (1999)
Leukotriene E4		Abe *et al.* (1999)
Lopinavir		Hartkoorn *et al.* (2010)
Mesalazine	55	Konig (2011)
Methotrexate		Abe *et al.* (2001)
Microcystein	7	Fischer *et al.* (2005)
Monoglyucuronosyl bilirubin	0.1	Cui *et al.* (2001)
Mycophenolic acid-7-O-glucuronide		Picard *et al.* (2010)
Nafcillin	1 110	Nakakariya *et al.* (2008)
Olmesartan	13–43	Nakagomi-Hagihara *et al.* (2006); Yamada *et al.* (2007)
Phalloidin	17–39	Fehrenbach *et al.* (2003); Meier-Abt *et al.* (2004)
Pitavastatin	3–4	Hirano *et al.* (2004); Fujino *et al.* (2005)
Pravastatin	14–34	Hsiang *et al.* (1999); Nakai *et al.* (2001); Sasaki *et al.* (2002)
PG E_2		Abe *et al.* (1999); Tamai *et al.* (2000); Kullak-Ublick *et al.* (2001)
Rifampicin	2–13	Vavricka *et al.* (2002); Tirona *et al.* (2003)
Ro 48-5033	60	Treiber *et al.* (2007)
Rosuvastatin	9	Ho *et al.* (2006)
S-8921G	1.93	Sakamoto *et al.* (2008)
Saquinavir		Hartkoorn *et al.* (2010)
Simvastatin acid		Pasanen *et al.* (2006)
SN-38		Nozawa *et al.* (2005)
Taurocholate	10–34	Abe *et al.* (1999; 2001); Hsiang *et al.* (1999); Cui *et al.* (2001); Kullak-Ublick *et al.* (2001)
Tauroursodeoxycholate	7.5	Maeda *et al.* (2006b)
Temocapril		Maeda *et al.* (2006a)
Thromboxane B2		Abe *et al.* (1999)
Thyroxine (T4)	3	Abe *et al.* (1999)
Torasemide	6.2	Vormfelde *et al.* (2008); Werner *et al.* (2008)
TR-14035	7.5	Tsuda-Tsukimoto *et al.* (2006)
Triiodothyronine (T3)	3	Abe *et al.* (1999)
Troglitazone sulphate		Nozawa *et al.* (2004b)
Valsartan	1.4	Yamashiro *et al.* (2006)

Table 2

Continued

Substrates	K_m (μM)	References
OATP1B3		
Amanitin	4	Letschert *et al.* (2006)
Atrasentan		Katz *et al.* (2006)
Benzylpenicillin (Penicillin G)		Letschert *et al.* (2006)
BDE47	0.41	Pacyniak *et al.* (2010)
BDE99	0.70	Pacyniak *et al.* (2010)
BDE153	1.66	Pacyniak *et al.* (2010)
Bilirubin	0.04	Briz *et al.* (2003)
Bosentan	141	Treiber *et al.* (2007)
BQ-123		Kullak-Ublick *et al.* (2001)
Bromosulphophthalein	0.4–6	Kullak-Ublick *et al.* (2001)
Cefadroxil	4150	Nakakariya *et al.* (2008)
Cefazolin	3890	Nakakariya *et al.* (2008)
Cefditoren	5870	Nakakariya *et al.* (2008)
Cefmetazole	706	Nakakariya *et al.* (2008)
Cefoperazone	1950	Nakakariya *et al.* (2008)
Cephalexin	1190	Nakakariya *et al.* (2008)
CDCA-NBD	0.5	Yamaguchi *et al.* (2006)
Cholate	42	Briz *et al.* (2006)
Cholecystokinin octapeptide (CCK-8)	4–11	Ismair *et al.* (2001); Hirano *et al.* (2004)
Cholyl-glycylamido-fluorescein (CGamF)	2.2	Annaert *et al.* (2010)
Dehydroepiandrosterone-3-sulphate		Konig *et al.* (2000a); Cui *et al.* (2001); Kullak-Ublick *et al.* (2001)
Deltorphin II		Kullak-Ublick *et al.* (2001)
Demethylphalloin	8	Meier-Abt *et al.* (2004)
Diclofenac		Kindla *et al.* (2011)
Digoxin		Kullak-Ublick *et al.* (2001)
Docetaxel		Smith *et al.* (2005)
[D-penicillamine^{2,5}]enkephalin		Kullak-Ublick *et al.* (2001)
Enalapril		Liu *et al.* (2006)
Epicatechin gallate	34	Roth *et al.* (2011b)
Epigallocatechin gallate	13	Roth *et al.* (2011b)
Erythromycin		Franke *et al.* (2008)
Estradiol-17β-glucuronide	5–25	Konig *et al.* (2000a); Cui *et al.* (2001); Hirano *et al.* (2004)
Estrone-3-sulphate		Kullak-Ublick *et al.* (2001); Nozawa *et al.* (2004b); Nozawa *et al.* (2005)
Fexofenadine	108	Shimizu *et al.* (2005)
Fluorescein		Gui *et al.* (2010)
Fluorescein methotrexate	7.9	Gui *et al.* (2010)
Fluo-3, pentoammonium salt	6.8	Baldes *et al.* (2006)
Flutax-2		Gui *et al.* (2010)
Fluvastatin	7	Kopplow *et al.* (2005)
Glutathione	4500	Briz *et al.* (2006)
Glycocholate	43	Kullak-Ublick *et al.* (2001); Briz *et al.* (2006)
Glycoursodeoxycholate	24.7	Maeda *et al.* (2006b)
Hydroxyurea		Walker *et al.* (2011)

Table 2

Continued

Substrates	K_m (μM)	References
Imatinib		Hu *et al.* (2008)
Leukotriene C4		Konig *et al.* (2000a); Kullak-Ublick *et al.* (2001)
Mesalazine	77	Konig (2011)
Methotrexate	25–39	Abe *et al.* (2001)
Microcystin	1.2–9	Fischer *et al.* (2005); Komatsu *et al.* (2007)
Monoglyucuronosyl bilirubin	0.5	Cui *et al.* (2001)
Mycophenolic acid-7-O-glucuronide	114	Picard *et al.* (2010)
Nafcillin	73	Nakakariya *et al.* (2008)
Olmesartan	44–72	Nakagomi-Hagihara *et al.* (2006); Yamada *et al.* (2007)
Ouabain		Kullak-Ublick *et al.* (2001)
Paclitaxel	7	Smith *et al.* (2005)
Phalloidin	8	Meier-Abt *et al.* (2004)
Pitavastatin	3–4	Hirano *et al.* (2004); Fujino *et al.* (2005)
Rifampicin	2	Vavricka *et al.* (2002); Tirona *et al.* (2003)
Ro 48–5033	166	Treiber *et al.* (2007)
Rosuvastatin	10	Ho *et al.* (2007)
S-8921G	1.88	Sakamoto *et al.* (2008)
Saquinavir		Hartkoorn *et al.* (2010)
Taurocholate	6–112	Abe *et al.* (2001); Kullak-Ublick *et al.* (2001); Letschert *et al.* (2004); Briz *et al.* (2006)
Taurochenodeoxycholate		Briz *et al.* (2006)
Taurodeoxycholate		Briz *et al.* (2006)
Tauroursodeoxycholate	16	Maeda *et al.* (2006b)
Telmisartan	1	Ishiguro *et al.* (2006)
Thyroxine (T4)		Kullak-Ublick *et al.* (2001)
TR-14035	5.3	Tsuda-Tsukimoto *et al.* (2006)
Triiodothyronine (T3)	6	Abe *et al.* (2001); Kullak-Ublick *et al.* (2001)
Valsartan	18	Yamashiro *et al.* (2006)
OATP1C1		
Bromosulphophthalein		Pizzagalli *et al.* (2002)
Estradiol-17β-glucuronide		Pizzagalli *et al.* (2002)
Estrone-3-sulphate		Pizzagalli *et al.* (2002)
Thyroxine (T4)	0.09	Pizzagalli *et al.* (2002)
Triiodothyronine (T3)		Pizzagalli *et al.* (2002)
Reverse triiodothyronine (rT3)	0.128	Pizzagalli *et al.* (2002)
Thyroxine sulphate (T4S)		van der Deure *et al.* (2008)

If available, apparent affinity (K_m) values are listed. This table is an updated and extended version of a similar table published in Hagenbuch and Gui (2008).

ACU154: metabolite of PKI166, an epidermal growth factor receptor kinase inhibitor; Bamet-R2: *cis*-diammine-chloro-cholylglycinate-platinum(II); Bamet-UD2: *cis*-diammine-bisursodeoxycholate-platinum(II); BDE47: 2,2′,4,4′-Tetrabromodiphenyl ether; BDE99: 2,2′,4,4′,5-pentabromodiphenyl ether; BDE153: 2,2′,4,4′,5,5′-hexabromodiphenyl ether; BQ-123: cyclic pentapeptide endothelin receptor antagonist; CDCA-NBD: chenodeoxycholyl-(Nε-NBD)-lysine; CRC220: peptidomimetic thrombin inhibitor; Flutax-2: paclitaxel, Oregon Green® 488 conjugate; Gd-B20790: gadolonium-18-((3-(2-carboxylbutyl)-2,4,6-triiodophenyl)amino)-3,6,9-tris(carboxymethyl)-11,18-dioxo-3,6,9,12-tetrazaoctadecanoic acid; Ro 48–5033: Bosentan metabolite; SN-38: 7-ethyl-10-hydroxycamptothecin (active metabolite of irinotecan); S-8921G: methyl 1-(3,4-dimethoxyphenyl)-(3-ethylvaleryl)-4-hydroxy-6,7,8-trimethoxy-2-naphthoate glucuronide (inhibitor of the ilial apical sodium-dependent bile acid transporter); TR-14035: α4β1/α4β7 integrin dual antagonist.

Table 3

Substrates of human OATP2 family

Substrates	K_m (μM)	References
OATP2A1		
Latanoprost acid	5.4	Kraft *et al.* (2010)
PGH_2	0.4	Chi and Schuster (2010)
PGE_1	0.07	Kanai *et al.* (1995)
PGE_2	0.09	Kanai *et al.* (1995)
$PGF_{2\alpha}$	0.1	Kanai *et al.* (1995)
Thromboxane B_2	0.4	Kanai *et al.* (1995)
OATP2B1		
Aliskiren	72	Vaidyanathan *et al.* (2008)
Atorvastatin	0.2	Grube *et al.* (2006b)
Benzylpenicillin		Tamai *et al.* (2000)
BDE47	0.81	Pacyniak *et al.* (2010)
BDE99	0.87	Pacyniak *et al.* (2010)
BDE153	0.65	Pacyniak *et al.* (2010)
Bosentan	202	Treiber *et al.* (2007)
Bromosulphophthalein	0.7	Kullak-Ublick *et al.* (2001)
CP-671,305	4	Kalgutkar *et al.* (2007)
Dehydroepiandrosterone-3-sulphate	9	Pizzagalli *et al.* (2003)
Eltrombopag		Takeuchi *et al.* (2011)
Estrone-3-sulphate	5–21	Tamai *et al.* (2001); Pizzagalli *et al.* (2003); Nozawa *et al.* (2004a); Hirano *et al.* (2006); Grube *et al.* (2006a)
Ezetimibe glucuronide		Oswald *et al.* (2008)
Fexofenadine		Nozawa *et al.* (2004a)
Fluvastatin	0.7	Kopplow *et al.* (2005); Noe *et al.* (2007)
Glibenclamide	6	Satoh *et al.* (2005)
Latanoprost acid		Kraft *et al.* (2010)
M17055	4.5	Nishimura *et al.* (2007)
Mesalazine	189	Konig (2011)
Montelukast		Mougey *et al.* (2009)
Pravastatin	2	Nozawa *et al.* (2004a)
Pitavastatin	1.2	Hirano *et al.* (2006)
Pregnenolone sulphate		Grube *et al.* (2006a)
PGE_2		Tamai *et al.* (2000)
Rosuvastatin	2	Ho *et al.* (2006)
Talinolol	629	Shirasaka *et al.* (2010)
Taurocholate	72	Kobayashi *et al.* (2003)
Tebipenem pivoxil		Kato *et al.* (2010)
Thyroxine (T4)	0.77	Leuthold *et al.* (2009)
Unoprostone metabolite	91	Gao *et al.* (2005)

If available, apparent affinity (K_m) values are listed. This table is an updated and extended version of a similar table published in Hagenbuch and Gui (2008).
BDE47: 2,2′,4,4′-Tetrabromodiphenyl ether; BDE99: 2,2′,4,4′,5-pentabromodiphenyl ether; BDE153: 2,2′,4,4′,5,5′-hexabromodiphenyl ether; CP-671,305: (+)-2-[4-((2-(benzol[1,3]dioxol-5-yloxy)-pyridine-3-carbonyl]-amino)-methyl)-3-fluoro-phenoxy]-propionic acid; M17055: 7-chloro-2,3-dihydro-1-(2-methylbenzoyl)-4(1*H*)-quinolinone 4-oxime-O-sulphonic acid.

Table 4

Substrates of human OATP families 3–6

Substrates	K_m (μM)	References
OATP3A1_v1		
Benzylpenicillin		Tamai *et al.* (2000)
BQ-123		Huber *et al.* (2007)
Deltorphin		Huber *et al.* (2007)
Estrone-3-sulphate		Tamai *et al.* (2000)
PGE_1	0.05–0.1	Adachi *et al.* (2003); Huber *et al.* (2007)
PGE_2	0.06–0.2	Tamai *et al.* (2000); Adachi *et al.* (2003); Huber *et al.* (2007)
$PGF_{2\alpha}$		Adachi *et al.* (2003)
Thyroxine (T4)		Huber *et al.* (2007)
Vasopressin		Huber *et al.* (2007)
OATP3A1_v2		
Arachidonic acid		Huber *et al.* (2007)
BQ-123		Huber *et al.* (2007)
PGE_1	0.2	Huber *et al.* (2007)
PGE_2	0.4	Huber *et al.* (2007)
Thyroxine (T4)		Huber *et al.* (2007)
Vasopressin		Huber *et al.* (2007)
OATP4A1		
Benzylpenicillin		Tamai *et al.* (2000)
Estradiol-17β-glucuronide		Tamai *et al.* (2000)
Estrone-3-sulphate		Tamai *et al.* (2000)
Thyroxine (T4)		Fujiwara *et al.* (2001)
PGE_2		Tamai *et al.* (2000)
Triiodothyronine (T3)	1	Fujiwara *et al.* (2001)
Reverse triiodothyronine (rT3)		Fujiwara *et al.* (2001)
Taurocholate	15	Fujiwara *et al.* (2001)
Unoprostone metabolite		Gao *et al.* (2005)
OATP4C1		
cAMP		Mikkaichi *et al.* (2004)
Digoxin	8	Mikkaichi *et al.* (2004)
Estrone-3-sulphate	27	Yamaguchi *et al.* (2010)
Methotrexate		Mikkaichi *et al.* (2004)
Ouabain	0.4	Mikkaichi *et al.* (2004)
Sitagliptin		Chu *et al.* (2007)
Thyroxine (T4)		Mikkaichi *et al.* (2004)
Triiodothyronine (T3)	6	Mikkaichi *et al.* (2004)

If available, apparent affinity (K_m) values are listed.
BQ-123: cyclic pentapeptide endothelin receptor antagonist.

However, to identify the individual amino acids that are involved in substrate translocation, additional experiments such as cysteine scanning mutagenesis and eventually crystallography or NMR studies are needed. Because there is evidence that different substrates are handled slightly differently by at least OATP1B1 and OATP1B3 (Gui *et al.*, 2008; Roth *et al.*, 2011a,b), such experiments will have to be performed for multiple model substrates.

Pathology and clinical significance

There are only a few links between disease states and altered function of OATPs; however, there have been many studies showing associations between altered OATP expression levels and disease states, and documenting effects of different alleles and single-nucleotide polymorphisms (SNPs) in OATPs on drug disposition.

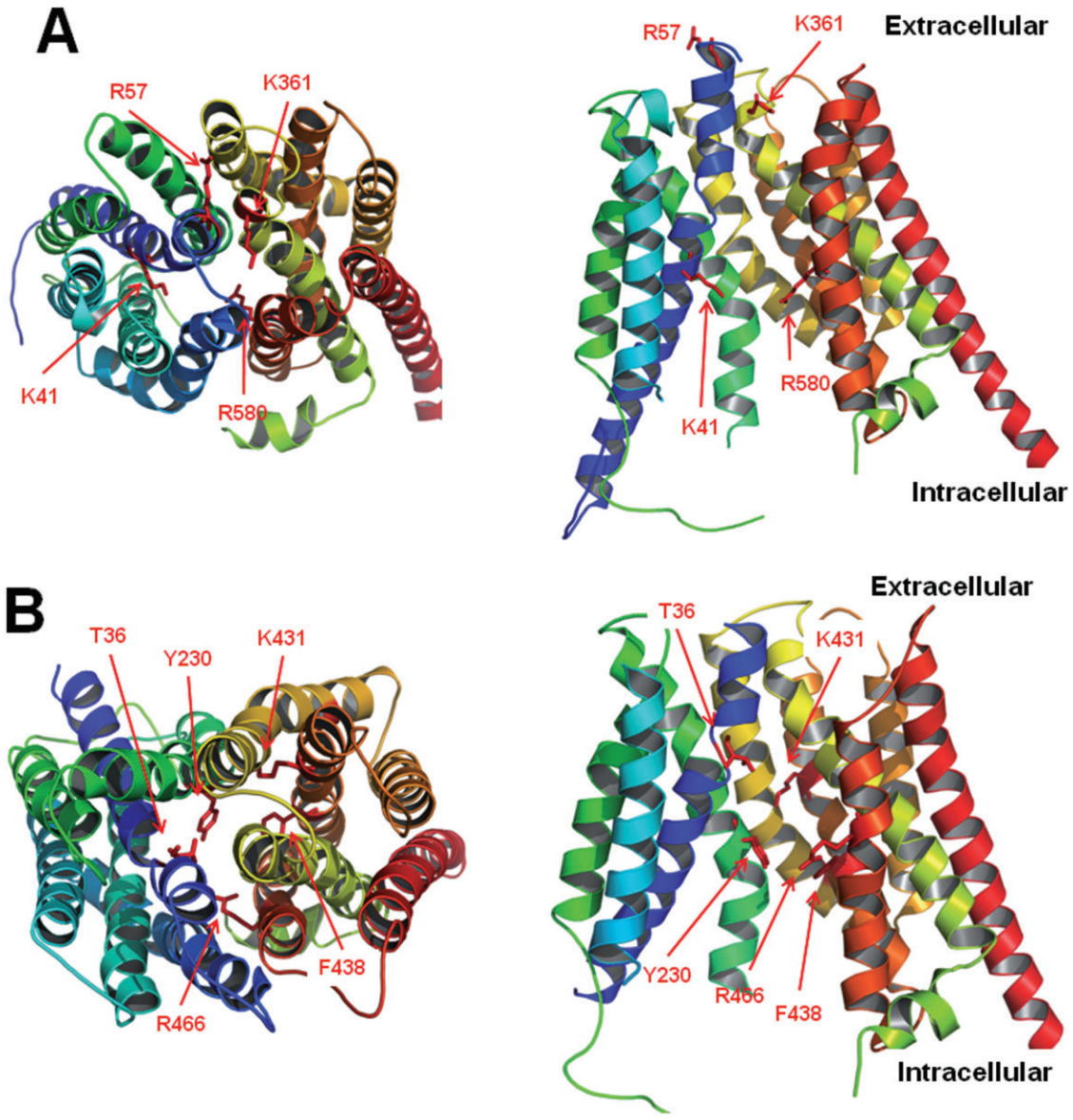

Figure 2

Homology models of members of the *SLCO* (OATP1B1) and the *SCL22A* (OAT1) families. The models were generated using Phyre[2] (Kelley and Sternberg, 2009) and are based on the *E. coli* glycerol-3-phosphate transporter. (A) OATP1B1 is shown viewed from the extracellular side (left) and from within the lipid bilayer (right). For clarity, transmembrane domains 2 and 4 are omitted in the right panel. Amino acids mentioned in the text are indicated. (B) OAT1 is shown viewed from the extracellular side (left) and from within the lipid bilayer (right). For clarity, transmembrane domains 2 and 4 are omitted in the right panel. The indicated amino acids were identified as important for the function of OAT1 and face the putative aqueous pore (Hong *et al.*, 2004; Perry *et al.*, 2006; Rizwan *et al.*, 2007).

Neonates with the OATP1B1 polymorphism N130D (found in OATP1B1*1b and *15) are at a higher risk for developing severe hyperbilirubinaemia (Huang *et al.*, 2004; Buyukkale *et al.*, 2011). Adults with the OATP1b1*15 haplotypes also have higher serum bilirubin levels (Ieiri *et al.*, 2004), though there is no associated pathology. However, OATP expression is often altered in disease states. Cholestasis results in decreased mRNA levels of OATP1A2, OATP1B1 and OATP1B3 in whole livers (Keitel *et al.*, 2005; Chen *et al.*, 2008; Congiu *et al.*, 2009). Placental expression of OATP1A2 mRNA is increased in patients with intrahepatic cholestatis of pregnancy (Cui *et al.*, 2009). OATP1B1 is also reduced in patients with severe versus mild viral hepatitis (Oswald *et al.*, 2001). Inflammatory bowel disease is associated with higher OATP2B1 and OATP4A1 levels in ileum and colon (Wojtal *et al.*, 2009), and OATP4A1 is also up-regulated in polycystic ovarian syndrome (Plaza *et al.*, 2010).

Of particular interest are several SNPs in OATP1B1, which have demonstrated the importance of this transporter in the disposition of certain drugs. The N130D allele, found in both OATP1B1*1b and *15, is associated with altered pharmacokinetics of pravastatin and pitavastatin (Nishizato *et al.*, 2003;

Mwinyi *et al.*, 2004; Niemi *et al.*, 2004; Chung *et al.*, 2005; Wen and Xiong, 2010). The V174A allele, which is found in both OATP1B1*5 and OATP1B1*15, is associated with an attenuated cholesterol lowering effect of multiple statins (Tachibana-Iimori *et al.*, 2004) as well as with an increased systemic exposure of the anti-diabetic nateglinide (Zhang *et al.*, 2006) and the HIV protease inhibitor lopinavir (Hartkoorn *et al.*, 2010). However, the V174 allele is unrelated to the pharmacokinetics of rosiglitazone and pioglitazone (Kalliokoski *et al.*, 2008), torasemide (Werner *et al.*, 2008), mycophenolic acid (Miura *et al.*, 2007) or telmisartan (Miura *et al.*, 2009). Polymorphisms in other OATPs, while less studied, can also affect drug pharmacokinetics. It has recently been shown that OATP1A2 polymorphisms are associated with imatinib clearance (Yamakawa *et al.*, 2011), and polymorphisms in OATP2B1 are associated with the pharmacokinetics of fexofenadine (Akamine *et al.*, 2010). Functional OATP polymorphisms are reviewed in detail by Kalliokoski and Niemi (2009) and Konig (2011).

Many cancer tissues and cell lines have altered expression of OATPs. For example, the normally liver-exclusive OATP1B3 is also expressed in gastric, colon and pancreatic cancers (Abe *et al.*, 2001; Lee *et al.*, 2008), as well as cancers of the lung (Monks *et al.*, 2007), breast (Muto *et al.*, 2007) and prostate (Hamada *et al.*, 2008), whereas it has a reduced expression in hepatocellular carcinomas (Kinoshita and Miyata, 2002; Cui *et al.*, 2003; Vavricka *et al.*, 2004). Similarly, most of the other OATPs have been shown to have altered expression in different types of cancers. Because OATPs are known to transport hormones and their conjugates, which are thought to play a role in the enhanced proliferation or chemo-resistance of some cancers, the overexpression of OATPs may provide a survival benefit to these cells. The role of OATPs in cancer is discussed further in the reviews by Obaidat *et al.* (2012) and Wlcek *et al.* (2011).

One of the primary pathologies caused by OATPs is likely to be adverse drug–drug or drug–food interactions. Treatment with cyclosporine, an inhibitor of OATP-mediated transport, is associated with increased plasma concentrations of statins (Neuvonen *et al.*, 2006). Cyclosporine also increases the plasma concentration of bosentan, as does rifampicin, both of which inhibit OATP-mediated bosentan uptake at clinically relevant concentrations (Treiber *et al.*, 2007; van Giersbergen *et al.*, 2007). Both rifamycin SV and rifampicin reduce bromosulphophthalein (BSP) elimination in humans and inhibit *in vitro* uptake of BSP by OATP1A2, OATP1B1, OATP1B3 and OATP2B1 (Vavricka *et al.*, 2002). Macrolide antibiotics also inhibit uptake of BSP and pravastatin by OATP1B1 and OATP1B3 *in vitro* (Seithel *et al.*, 2007). In addition, cyclosporine, saquinavir, indinavir and rifamycin SV inhibit uptake of estradiol-17β-glucuronide by OATP1B1 with potencies that correlate with the incidence of hyperbilirubinaemia associated with those four drugs (Campbell *et al.*, 2004).

There are also reports on potential drug–food interactions occurring at OATPs, particularly for OATP1A2 and OATP2B1, which are expressed at the luminal membrane of enterocytes. Fruit juices decrease the oral bioavailability of fexofenadine in humans (Dresser *et al.*, 2002; 2005; Glaeser *et al.*, 2007). It has been shown that fexofenadine is a substrate of OATP1A2, and that uptake of fexofenadine by OATP1A2 is inhibited by naringin, a component of grapefruit (Bailey *et al.*, 2007). In addition, many flavonoids affect OATP-mediated uptake of the model substrates estrone-3-sulphate, estradiol-17β-glucuronide and dehydroepiandrosterone-3-sulphate (DHEAS), suggesting that possible drug–food interactions could occur especially in patients taking 'healthy' dietary supplements in addition to their prescribed medications (Wang *et al.*, 2005b; Roth *et al.*, 2011b).

OATs

Organic anion transporters (OATs in humans, Oats in rodents) are another family of multispecific transporters and are encoded by the *SLC22/Slc22* gene superfamily. They mediate the transport of a diverse range of low molecular weight substrates including steroid hormone conjugates, biogenic amines, various drugs and toxins.

Tissue distribution

Documented protein expression for OATs is summarized in Figure 3. Organic anion transporters are expressed in membranes of different tissues throughout the body. OAT1 was the first identified human OAT (Reid *et al.*, 1998), with mRNA expression at highest levels in the kidney, followed by skeletal muscle, brain and placenta (Hosoyamada *et al.*, 1999). At the protein level, OAT1 is expressed at the basolateral membrane of proximal tubules (Hosoyamada *et al.*, 1999; Motohashi *et al.*, 2002; Ljubojevic *et al.*, 2007) and in the plasma membrane of skeletal muscle cells (Takeda *et al.*, 2004). Membrane localization of human OAT1 in the choroid plexus has not yet been investigated, but Oat1 expression has been localized to the apical membrane of mouse and rat choroid plexus (Pritchard *et al.*, 1999; Alebouyeh *et al.*, 2003; Sykes *et al.*, 2004). OAT2 mRNA has the highest expression levels in the liver with lower levels also seen in kidney (Sekine *et al.*, 1998; Sun *et al.*, 2001; Hilgendorf *et al.*, 2007). Protein expression of OAT2 has been identified at the basolateral membrane of proximal tubules (Enomoto *et al.*, 2002b), and it is assumed to be expressed at the basolateral membrane of human hepatocytes based on findings in rodents. OAT3 mRNA has highest expression levels in the kidney with lower levels in brain (Cha *et al.*, 2001; Hilgendorf *et al.*, 2007). OAT3 mRNA expression has also been shown in adrenal tissue and the human adrenal cell line NCI-H295R, and functional studies suggest the protein is expressed (Asif *et al.*, 2005). OAT3 protein has been localized to the basolateral membrane of proximal tubules in the kidney (Cha *et al.*, 2001). OAT4 mRNA is expressed in kidney and placenta (Cha *et al.*, 2000; Bleasby *et al.*, 2006), with protein identified at the apical membrane of renal proximal tubules (Babu *et al.*, 2002; Ekaratanawong *et al.*, 2004) and at the basolateral membrane of syncytiotrophoblasts in the placenta (Ugele *et al.*, 2003). Similarly to OAT3, OAT4 mRNA expression and function has also been shown in adrenal tissue and the human adrenal cell line NCI-H295R (Asif *et al.*, 2005). Little is known about human OAT5, although Northern blot analysis demonstrates mRNA expression in the liver (Sun *et al.*, 2001). The recently characterized OAT7 has been shown to be exclusively expressed in adult and fetal liver, where its expression has been localized to the basolateral membrane of hepatocytes

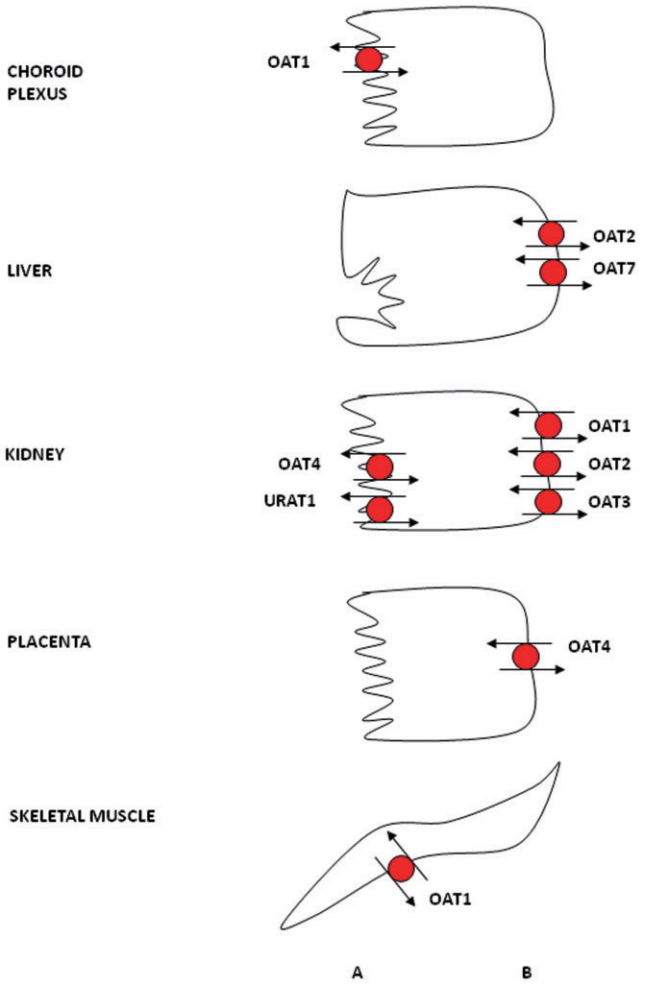

Figure 3

Expression of OATs in different human epithelia. For more details, see the text. OAT1 localization in the choroid plexus and OAT2 localization in the liver is inferred from rodent data. (A) apical; (B) basolateral.

(Shin *et al.*, 2007). OAT10 mRNA has been shown to have highest expression levels in the kidney followed by brain, heart, small intestine and colon (Nishiwaki *et al.*, 1998; Bahn *et al.*, 2008). URAT1, which was previously named the renal-specific transporter 'RST', has mRNA expression in both adult and fetal kidney (Enomoto *et al.*, 2002a); more recently, mRNA was also identified in vascular smooth muscle cells (Price *et al.*, 2006). Using immunohistochemistry, URAT1 protein has been localized to the apical membrane of renal proximal tubules (Enomoto *et al.*, 2002a).

Substrate specificity

The first cloning of human OAT1 was reported in 1998 (Reid *et al.*, 1998). Additional reports in 1999 described the initial functional characterization of human OAT1 as a multispecific organic anion-dicarboxylate exchanger (Cihlar *et al.*, 1999; Hosoyamada *et al.*, 1999; Lu *et al.*, 1999; Race *et al.*, 1999). The best characterized OATs, OAT1 and OAT3, have been

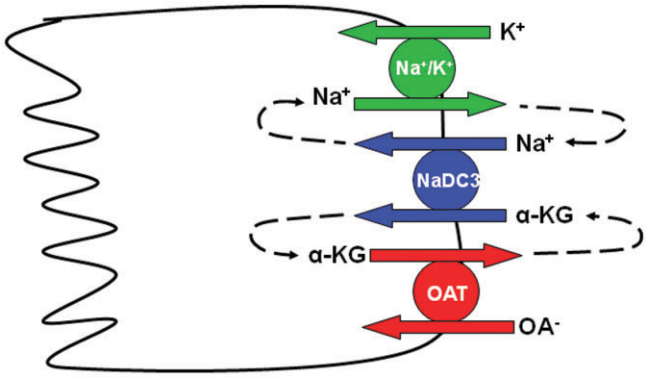

Figure 4

Cartoon of tertiary active transport mechanism for OAT-mediated uptake of organic anions. The primary active Na^+/K^+-ATPase generates the sodium gradient that is used by the secondary active Na^+-dicarboxylate cotransporter (NaDC3) to maintain a high intracellular concentration of α-ketoglutarate, which is used to drive uptake of other organic anions by OAT1 and OAT3.

shown to transport organic anions against a negative membrane potential in exchange for the counter ion α-ketoglutarate. The α-ketoglutarate gradient is maintained by the secondary active sodium-dicarboxylate co-transporter, which utilizes the sodium gradient maintained by the primary active Na^+/K^+ ATPase (see Figure 4). Therefore, transport of these OATs has been termed 'tertiary active.' Unlike OAT1 and OAT3, human OAT7 exhibits a unique exchange mechanism using short chain fatty acids such as butyrate as counter ions for the transport of sulphate conjugates (Shin *et al.*, 2007). OAT1 is primarily known for its high affinity transport of p-aminohippurate (PAH) from renal tubule cells with apparent affinity (K_m) values reported in the low micromolar range (Hosoyamada *et al.*, 1999). OAT3 can also transport PAH but with slightly lower affinity than OAT1 (Cha *et al.*, 2001). Aside from PAH, OAT1 has been shown to transport prostaglandins, α-ketoglutarate, NSAIDs, antivirals and anticancer drugs. The uricosuric drug, probenecid, is a potent inhibitor of OAT1 transport (Sweet *et al.*, 1997; Cihlar *et al.*, 1999; Hosoyamada *et al.*, 1999; Lu *et al.*, 1999; Race *et al.*, 1999). A more comprehensive review of all OAT substrates and inhibitors can be found in tables of recently published reviews by VanWert *et al.* (2010) and Burckhardt and Burckhardt (2011).

Regulation of expression

Transcriptional regulation of OATs has been studied by several groups and multiple transcription factors have been implicated. HNF-1α and/or HNF-1β have been shown to affect expression of human OAT1 (Saji *et al.*, 2008), OAT3 (Kikuchi *et al.*, 2006) and URAT1 (Kikuchi *et al.*, 2007), while HNF-4α seems to be involved in human OAT2 expression (Popowski *et al.*, 2005). In addition, for both OAT3 (Kikuchi *et al.*, 2006) and URAT1 (Kikuchi *et al.*, 2007), epigenetic mechanisms of regulation have been identified. At the protein level, PKC activation results in internalization and thus functional inhibition of human OAT1 in frog oocytes,

HEK293 cells and Cos-7 cells (Wolff *et al.*, 2003; Zhang *et al.*, 2008). Activation of PKA resulted in stimulation of PAH uptake into opossum kidney cells, indicating that OAT1 could be stimulated by agents that activate PKA (Sauvant *et al.*, 2001; 2002); however, these effects seem to depend on the agents used to stimulate the kinase (Sauvant *et al.*, 2006). Additional studies are needed to investigate what consequences and effects drugs that inhibit or stimulate activation of protein kinases have on human OATs (VanWert *et al.*, 2010).

Transporter structure

The size of OATs ranges from 542 amino acids for human OAT3 to 563 amino acids for OAT1. Like OATPs, OATs are predicted to have 12 transmembrane domains with intracellular amino and carboxy-termini. There is a large extracellular loop between transmembrane domains 1 and 2, as well as a large intracellular loop between transmembrane domains 6 and 7. The large extracellular loop contains potential N-glycosylation sites, while the large intracellular loop and the carboxy-terminus contain putative phosphorylation sites. The extra- and intracellular locations of the different loops were experimentally supported for human OAT1 (Hong *et al.*, 2007).

As is the case for the OATPs, there is so far no crystal structure available for any of the OATs. Therefore, homology modelling has been used to predict the putative three-dimensional structure of human OAT1 on the basis of the bacterial glycerol-3-phosphate transporter and the lactose permease (Perry *et al.*, 2006). Several groups have used site-directed mutagenesis coupled with functional experiments to investigate the role of individual amino acids identified, for example, from polymorphism studies (Bleasby *et al.*, 2005; Fujita *et al.*, 2005; Erdman *et al.*, 2006; Zhou *et al.*, 2010). Some of these amino acids are highlighted in the predicted three-dimensional structure of OAT1 shown in Figure 2B. For more details, please see Burckhardt and Burckhardt (2011).

More recently, a molecular dynamics simulation was performed for OAT1 based on the homology model developed. The data indicate that during the 100 ns simulation one pair of transmembrane domains in each half of the transporter tilt, suggesting a possible involvement in the opening and closing of the transporter (Tsigelny *et al.*, 2011). However, such molecular simulation based on a homology model will most likely improve once a crystal structure is available.

Pathology and clinical significance

Knockout mice for Oat1 (Eraly *et al.*, 2006) and Oat3 (Sweet *et al.*, 2002) have been generated and are both viable and fertile. Characterization of Oat1 null mice showed decreased *in vivo* transport of Oat1 substrates such as PAH and furosemide, but not of estrone-3-sulphate, a substrate of Oat3 (Eraly *et al.*, 2006). Renal slices from Oat3 null mice demonstrated decreased transport of estrone-3-sulphate, taurocholate and PAH (Sweet *et al.*, 2002). These animal models are important tools to investigate whether Oat1 or Oat3 is primarily responsible for the transport of common drug substrates, but potential species differences must be considered when extrapolating to the human situation (Nigam *et al.*, 2007).

For both OAT1 and OAT3, a lower than average mutation rate has been described (Urban *et al.*, 2006). Although several non-synonymous polymorphisms exist for both transporters, only a few have been shown to affect the transport function (Srimaroeng *et al.*, 2008). The only member of the OAT family for which mutations have been linked to a disease is URAT1. The first characterized mutation that was shown to result in familial idiopathic hypouricaemia is a missense mutation leading to a premature stop codon (W258X). It was first reported by Enomoto *et al.* (2002a), and later additional mutations have been described in patients with hypouricaemia (Anzai *et al.*, 2007).

Because of the broad substrate specificity of OATs, drug–drug interactions are possible especially with drugs that are eliminated by OAT1 or OAT3 in the kidneys. The interaction between probenecid and methotrexate that was first described in 1978 (Aherne *et al.*, 1978a,b) can today be explained by probenecid's inhibition of OAT3- and OAT1-mediated methotrexate transport (Nozaki *et al.*, 2007). Similarly, co-administration of probenecid with furosemide and other loop diuretics can decrease the potency of these diuretics by reducing their OAT-mediated secretion in the proximal tubule (Burckhardt and Burckhardt, 2011). However, such drug–drug interactions are not always detrimental: for instance, co-administration with probenecid is used to decrease the OAT1- and OAT3-mediated renal elimination of penicillin and other β-lactam antibiotics (Burckhardt and Burckhardt, 2011).

OCTs

In addition to the OATs described above, the *SLC22A* family also contains the organic cation transporters (OCT1, OCT2 and OCT3) and the organic cation and carnitine transporters (OCT6, OCTN1 and OCTN2). Like the OATPs and OATs, OCTs are multispecific uptake transporters expressed in numerous epithelia throughout the body.

Tissue distribution

Protein expression of OCTs is summarized in Figure 5. OCT1 is usually considered to be a liver-specific transporter, along with OATP1B1 and OATP1B3. However, weak expression of OCT1 mRNA has been seen in other tissues, such as heart, skeletal muscle, kidney, brain and placenta (Gorboulev *et al.*, 1997; Zhang *et al.*, 1997). In the liver, OCT1 protein is localized to the basolateral membrane of hepatocytes (Nies *et al.*, 2008). Furthermore, OCT1 protein was localized to the luminal membrane of lung epithelial cells (Lips *et al.*, 2005). Although rodent Oct1 protein has been identified at the basolateral membrane of enterocytes and proximal tubule epithelial cells (Karbach *et al.*, 2000), *in situ* hybridization did not detect OCT1 expression in human kidney (Gorboulev *et al.*, 1997). OCT2 is generally considered to be a kidney transporter, though mRNA is expressed at low levels in other tissues such as spleen, placenta, small intestine and brain (Gorboulev *et al.*, 1997). OCT2 protein is mainly localized to the luminal membrane of the distal convoluted tubules (Gorboulev *et al.*, 1997). OCT2 has also been identified in the pyramidal cells of the cerebral cortex and hippocampus

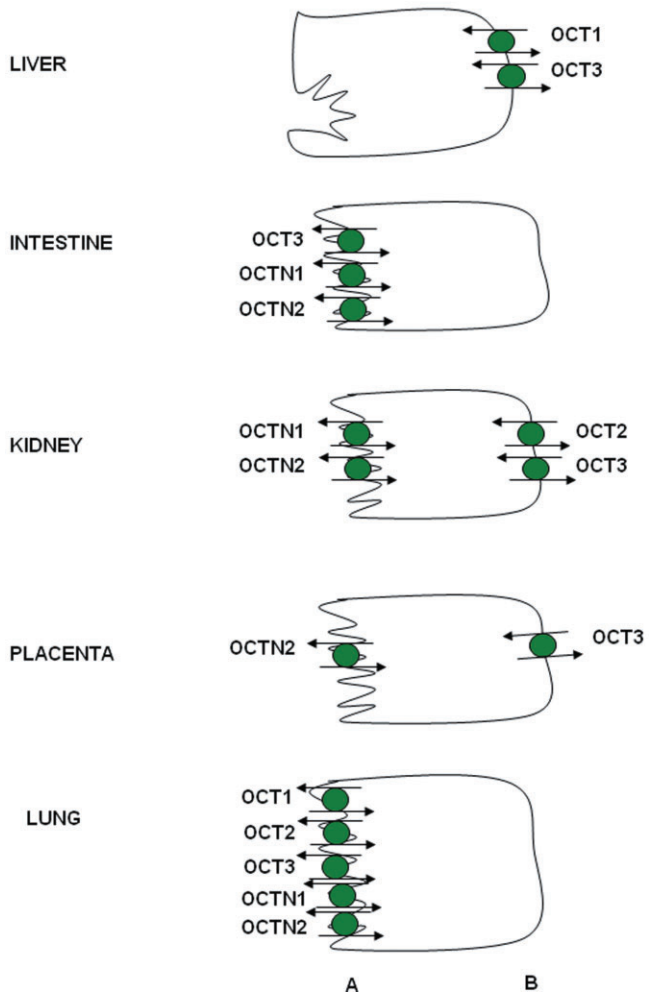

Figure 5

Expression of OCTs in human epithelial cells. For more details, see the text. Localization of OCTN1 in the kidney is concluded based on rodent data. (A) apical; (B) basolateral.

(Busch *et al.*, 1998) as well as the luminal membrane of lung epithelia (Lips *et al.*, 2005). OCT3, also known as the extraneuronal monoamine transporter (EMT), has the widest tissue distribution of the OCTs, with strong mRNA expression in liver, placenta, kidney and skeletal muscle, and weaker signals in lung, heart and brain (Wu *et al.*, 2000). OCT3 protein expression has been confirmed on the basolateral membrane of hepatocytes (Nies *et al.*, 2009), the basal membranes of trophoblasts (Sata *et al.*, 2005), the apical membrane of enterocytes (Muller *et al.*, 2005) and the luminal membrane of lung epithelial cells (Lips *et al.*, 2005).

OCTN1, which was first cloned from a human fetal liver cDNA library, is expressed at the mRNA level in fetal liver, kidney and lung (Tamai *et al.*, 1997). In adults, mRNA is strongly expressed in kidney, trachea and bone marrow, and is weakly expressed in skeletal muscle, prostate, lung, pancreas, placenta, heart, uterus, spleen and spinal cord, as well as several cancer cell lines (Tamai *et al.*, 1997). OCTN2 mRNA expression is highest in heart, placenta, skeletal muscle, kidney and pancreas, though it is also expressed in brain, lung and liver (Wu *et al.*, 1998). Within the kidney, two different transcript sizes (3.5 and 4.0 kb) were detected for OCTN2 (Wu *et al.*, 1998). OCTN2 protein expression has been identified at the apical membrane of proximal tubules in kidney (Masuda *et al.*, 2006) and the apical membrane of syncytiotrophoblasts in placenta (Grube *et al.*, 2005). Both OCTN1 and OCTN2 are also expressed in bronchial epithelial cells, with the protein mainly localized to the apical membrane (Horvath *et al.*, 2007). OCT6 (CT2) was originally cloned from a human testis cDNA library and has been localized to Sertoli cells and epithelial cells of the epididymis (Enomoto *et al.*, 2002c). Expression of OCT6 mRNA is also seen in liver, hematopoietic cells and some cancer cell lines (Gong *et al.*, 2002).

Substrate specificity

OCT1, OCT2 and OCT3 mediate the passive facilitated diffusion of a broad range of organic cations down their electrochemical gradients. As such, transport may occur in either direction, is independent of either sodium or pH, and transport of charged substrates is always electrogenic. Although OCT transporter action is independent of pH, affinity for certain substrates does depend on their degree of ionization, leading to increased transport of those substrates at reduced pH (Barendt *et al.*, 2002). Substrates include a wide variety of structurally unrelated small organic cations, both endogenous and exogenous, including many drugs. An extensive list of OCT1-3 substrates and inhibitors is included in a recent review on the importance of organic cation transporters in drug therapy (Nies *et al.*, 2011). Among these substrates are catecholamines, monoamine neurotransmitters and several antiviral drugs.

MPP (1-methyl-4-phenylpyridinium) is a commonly used model substrate for all three transporters; TEA (tetraethylammonium) is also commonly used for OCT1 and OCT2, although it is not a good substrate for OCT3 (Grundemann *et al.*, 1998). A pharmacophore model developed for OCT1 suggests that substrates contain a positive ionizable site, a hydrophobic site and two hydrogen bond acceptor sites (Moaddel *et al.*, 2007). A splice variant of OCT1 that lacks the carboxy-terminus of the protein was found to be nonfunctional for MPP transport (Hayer *et al.*, 1999). Alternatively, a somewhat longer splice variant of OCT2 that also contains a premature stop codon is found in human kidney, producing a protein which can still transport TEA, although it is less functional for MPP or cimetidine and cannot transport guanidine (Urakami *et al.*, 2002).

OCTN1, OCTN2 and OCT6 are all cation and carnitine transporters. OCTN1 transport activity can be affected by both sodium and proton gradients, depending on the substrate transported. OCTN2 also mediates both sodium-dependent and sodium-independent uptake, depending on the substrate (Koepsell *et al.*, 2007). In addition to carnitine, TEA is also a substrate of both transporters and is frequently used as a model substrate. OCTN2 appears to have different binding sites for TEA and L-carnitine, as several mutations have been found to inhibit carnitine but not TEA transport (Seth *et al.*, 1999). OCT6 has a much more limited substrate specificity than other organic cation transporters. Carnitine transport was found to be bidirectional and not fully depen-

dent on extracellular sodium, although transport was altered by both sodium and pH (Enomoto *et al.*, 2002c).

Regulation of expression

OCT regulation appears to vary depending on transporter, species and tissue localization; therefore, it remains an area of active research. Regulation of OCTs can occur at the transcriptional or protein level. OCT1 has two response elements for HNF-4α, which interacts with them and activates transcription; this activation can be inhibited through SHP (Saborowski *et al.*, 2006). The OCT2 promoter region contains putative androgen receptor elements and steroid hormones increased both mRNA levels and activity of OCT2 in MDCK cells (Shu *et al.*, 2001). OCTN1 transcription was altered by both the RUNX1 transcription factor and TNF-α *in vitro* (Tokuhiro *et al.*, 2003).

OCT proteins contain phosphorylation sites for PKA, PKC, PKG and tyrosine kinase, and activation of these kinases can alter the activity of OCT1 and OCT2. OCT3 doesn't seem to be affected by PKA, PKC or PKG, despite several conserved target sequences; however, its activity is altered by both the MAP kinase pathway and the calcium–calmodulin pathway. PDZ family members interact with OCTN1 and OCTN2, and the interaction between PDZK1 and OCTN2 has been shown to stimulate transport (Kato *et al.*, 2005). The targeting of OCTN1 and OCTN2 to brush border membrane of enterocytes has also been shown to be regulated by PDZ domain proteins. Detailed summaries of the current knowledge of OCT regulation can be found in recent reviews by Ciarimboli and Schlatter (2005), Koepsell *et al.* (2007) and Ciarimboli (2008).

Transporter structure

The organic cation transporting proteins contain between 543 and 557 amino acids. All are predicted to contain 12 transmembrane domains with intracellular amino and carboxy-termini. A large extracellular loop between the first and second transmembrane domains contains potential N-glycosylation sites, and a large intracellular loop between transmembrane domains 6 and 7 contains multiple putative phosphorylation sites. OCT1 and OCT2 have 70% amino acid identity to each other, and approximately 50% identity with OCT3 (Gorboulev *et al.*, 1997; Zhang *et al.*, 1997; Grundemann *et al.*, 1998). OCTN1 and OCTN2, which share 77% identity with each other, and 31–37% identity with OCT1-3, also contain an ATP/GTP binding motif in the second intracellular loop (Tamai *et al.*, 1997; Wu *et al.*, 1998). OCT6, also called CT2, has 36%, 38% and 37% identity to OAT1, OCT1 and OCTN2 respectively (Enomoto *et al.*, 2002c).

As has been done for the OATPs and OATs, homology modelling has been used to predict the putative three-dimensional structure of OCT1 (Popp *et al.*, 2005). According to this model, substrates seem to interact with OCT1 within a region rather than at a single binding site (Koepsell, 2011). Additional experiments demonstrated that five amino acids in the substrate binding region can interact with both extracellular and intracellular substrates and are thus likely part of the translocation pathway (Volk *et al.*, 2009; Koepsell, 2011). Furthermore, rat Oct1 has been expressed in a cell-free system, purified and reconstituted into proteoliposomes for functional characterization (Keller *et al.*, 2008). Production of OCT1 in such a cell-free system could be the first step towards the crystallization of this important drug transporter.

Pathology and clinical significance

OCT1, OCT2 and OCT3 knockout mice have been generated and have no obvious phenotype (Jonker *et al.*, 2001; 2003; Zwart *et al.*, 2001). Similarly, no known polymorphisms in OCTs are associated with human pathologies. OCT1 has 18 SNPs that alter amino acids – six have reduced transport activity and one has increased activity (Kerb *et al.*, 2002). OCT2 has ten variants: with the exception of a premature stop codon, all are functionally active, though substrate selectivity and the ability to transport may be slightly altered (Koepsell *et al.*, 2007). Five non-synonymous polymorphisms have been identified in OCT3, three of which show reduced transport activity (Sakata *et al.*, 2010). As with the OATPs, it seems that the greatest risk of pathology associated with the organic cation transporters is that of adverse drug–drug interactions. OCT1 polymorphisms have been associated with altered pharmacokinetics of the antidiabetic metformin and the tyrosine kinase inhibitor imatinib, while a wide range of drugs have been implicated in potential drug–drug interactions as reviewed by Fahrmayr *et al.* (2010).

OCTN proteins, however, have been directly indicated in pathologies. Mutations in the gene cluster that contains the OCTN1 and OCTN2 genes have been associated with autoimmune diseases. OCTN1 variant L503F is associated with familial and sporadic inflammatory bowel disease (Lin *et al.*, 2010). Functionally, this variant has altered substrate specificity with a significantly increased affinity for the common model substrate TEA (Urban *et al.*, 2007). Systemic carnitine deficiency, which is caused by a lack of active reabsorption of carnitine in the kidney, has been associated with multiple mutations that cause low or impaired function of OCTN2 (Lahjouji *et al.*, 2001).

Conclusion

Proteins encoded by the *SLCO* and *SLC22A* superfamilies are expressed in nearly every epithelium of the body, where they play a significant role in the absorption, distribution and elimination of drugs and other xenobiotics. Many members of these superfamilies transport a broad range of structurally diverse compounds, and several examples have been documented where transport proteins of the *SLCO* or *SLC22A* gene families were involved in adverse or intended drug–drug as well as drug–food interactions. Future studies should focus on the elucidation of the three-dimensional structure of these important drug uptake transporters because this will allow to predict and prevent such drug-related pathologies as well as to rationally design drugs targeted to individual tranpsorters. Overall, such studies will lead to a better and safer drug therapy.

Acknowledgements

BH is supported by grants from the National Institutes of Health (RR021940 and GM077336).

Disclosure statement

The authors have nothing to disclose.

References

Abe T, Kakyo M, Tokui T, Nakagomi R, Nishio T, Nakai D *et al.* (1999). Identification of a novel gene family encoding human liver-specific organic anion transporter LST-1. J Biol Chem 274: 17159–17163.

Abe T, Unno M, Onogawa T, Tokui T, Kondo TN, Nakagomi R *et al.* (2001). LST-2, a human liver-specific organic anion transporter, determines methotrexate sensitivity in gastrointestinal cancers. Gastroenterology 120: 1689–1699.

Adachi H, Suzuki T, Abe M, Asano N, Mizutamari H, Tanemoto M *et al.* (2003). Molecular characterization of human and rat organic anion transporter OATP-D. Am J Physiol Renal Physiol 285: F1188–F1197.

Aherne GW, Piall E, Marks V, Mould G, White WF (1978a). Prolongation and enhancement of serum methotrexate concentrations by probenecid. Br Med J 1: 1097–1099.

Aherne W, Piall E, Marks V (1978b). Radioimmunoassay of methotrexate: use of 75Se-labelled methotrexate. Ann Clin Biochem 15: 331–334.

Akamine Y, Miura M, Sunagawa S, Kagaya H, Yasui-Furukori N, Uno T (2010). Influence of drug-transporter polymorphisms on the pharmacokinetics of fexofenadine enantiomers. Xenobiotica 40: 782–789.

Alebouyeh M, Takeda M, Onozato ML, Tojo A, Noshiro R, Hasannejad H *et al.* (2003). Expression of human organic anion transporters in the choroid plexus and their interactions with neurotransmitter metabolites. J Pharmacol Sci 93: 430–436.

Annaert P, Ye ZW, Stieger B, Augustijns P (2010). Interaction of HIV protease inhibitors with OATP1B1, 1B3, and 2B1. Xenobiotica 40: 163–176.

Anzai N, Kanai Y, Endou H (2007). New insights into renal transport of urate. Curr Opin Rheumatol 19: 151–157.

Asif AR, Steffgen J, Metten M, Grunewald RW, Muller GA, Bahn A *et al.* (2005). Presence of organic anion transporters 3 (OAT3) and 4 (OAT4) in human adrenocortical cells. Pflugers Arch 450: 88–95.

Babu E, Takeda M, Narikawa S, Kobayashi Y, Enomoto A, Tojo A *et al.* (2002). Role of human organic anion transporter 4 in the transport of ochratoxin A. Biochim Biophys Acta 1590: 64–75.

Badagnani I, Castro RA, Taylor TR, Brett CM, Huang CC, Stryke D *et al.* (2006). Interaction of methotrexate with organic-anion transporting polypeptide 1A2 and its genetic variants. J Pharmacol Exp Ther 318: 521–529.

Bahn A, Hagos Y, Reuter S, Balen D, Brzica H, Krick W *et al.* (2008). Identification of a new urate and high affinity nicotinate transporter, hOAT10 (SLC22A13). J Biol Chem 283: 16332–16341.

Bailey DG, Dresser GK, Leake BF, Kim RB (2007). Naringin is a major and selective clinical inhibitor of organic anion-transporting polypeptide 1A2 (OATP1A2) in grapefruit juice. Clin Pharmacol Ther 81: 495–502.

Baldes C, Koenig P, Neumann D, Lenhof HP, Kohlbacher O, Lehr CM (2006). Development of a fluorescence-based assay for screening of modulators of human organic anion transporter 1B3 (OATP1B3). Eur J Pharm Biopharm 62: 39–43.

Barendt WM, Wright SH (2002). The human organic cation transporter (hOCT2) recognizes the degree of substrate ionization. J Biol Chem 277: 22491–22496.

Bleasby K, Hall LA, Perry JL, Mohrenweiser HW, Pritchard JB (2005). Functional consequences of single nucleotide polymorphisms in the human organic anion transporter hOAT1 (SLC22A6). J Pharmacol Exp Ther 314: 923–931.

Bleasby K, Castle JC, Roberts CJ, Cheng C, Bailey WJ, Sina JF *et al.* (2006). Expression profiles of 50 xenobiotic transporter genes in humans and pre-clinical species: a resource for investigations into drug disposition. Xenobiotica 36: 963–988.

Bossuyt X, Muller M, Meier PJ (1996). Multispecific amphipathic substrate transport by an organic anion transporter of human liver. J Hepatol 25: 733–738.

Briz O, Serrano MA, Rebollo N, Hagenbuch B, Meier PJ, Koepsell H *et al.* (2002). Carriers involved in targeting the cytostatic bile acid-cisplatin derivatives cis-diammine-chloro-cholylglycinate-platinum(II) and cis-diammine-bisursodeoxycholate-platinum(II) toward liver cells. Mol Pharmacol 61: 853–860.

Briz O, Serrano MA, MacIas RI, Gonzalez-Gallego J, Marin JJ (2003). Role of organic anion-transporting polypeptides, OATP-A, OATP-C and OATP-8, in the human placenta-maternal liver tandem excretory pathway for foetal bilirubin. Biochem J 371: 897–905.

Briz O, Romero MR, Martinez-Becerra P, Macias RI, Perez MJ, Jimenez F *et al.* (2006). OATP8/1B3-mediated cotransport of bile acids and glutathione: an export pathway for organic anions from hepatocytes? J Biol Chem 281: 30326–30335.

Bronger H, Konig J, Kopplow K, Steiner HH, Ahmadi R, Herold-Mende C *et al.* (2005). ABCC drug efflux pumps and organic anion uptake transporters in human gliomas and the blood-tumor barrier. Cancer Res 65: 11419–11428.

Burckhardt G, Burckhardt BC (2011). *In vitro* and *in vivo* evidence of the importance of organic anion transporters (OATs) in drug therapy. Handb Exp Pharmacol 201: 29–104.

Busch AE, Karbach U, Miska D, Gorboulev V, Akhoundova A, Volk C *et al.* (1998). Human neurons express the polyspecific cation transporter hOCT2, which translocates monoamine neurotransmitters, amantadine, and memantine. Mol Pharmacol 54: 342–352.

Buyukkale G, Turker G, Kasap M, Akpinar G, Arisoy E, Gunlemez A *et al.* (2011). Neonatal Hyperbilirubinemia and Organic Anion Transporting Polypeptide-2 Gene Mutations. Am J Perinatol 28: 619–626.

Campbell SD, de Morais SM, Xu JJ (2004). Inhibition of human organic anion transporting polypeptide OATP 1B1 as a mechanism of drug-induced hyperbilirubinemia. Chem Biol Interact 150: 179–187.

Cha SH, Sekine T, Kusuhara H, Yu E, Kim JY, Kim DK *et al.* (2000). Molecular cloning and characterization of multispecific organic anion transporter 4 expressed in the placenta. J Biol Chem 275: 4507–4512.

Cha SH, Sekine T, Fukushima JI, Kanai Y, Kobayashi Y, Goya T *et al.* (2001). Identification and characterization of human organic anion transporter 3 expressing predominantly in the kidney. Mol Pharmacol 59: 1277–1286.

Chang C, Pang KS, Swaan PW, Ekins S (2005). Comparative pharmacophore modeling of organic anion transporting polypeptides: a meta-analysis of rat Oatp1a1 and human OATP1B1. J Pharmacol Exp Ther 314: 533–541.

Chen HL, Liu YJ, Wu SH, Ni YH, Ho MC, Lai HS *et al.* (2008). Expression of hepatocyte transporters and nuclear receptors in children with early and late-stage biliary atresia. Pediatr Res 63: 667–673.

Chi Y, Schuster VL (2010). The prostaglandin transporter PGT transports PGH(2). Biochem Biophys Res Commun 395: 168–172.

Choi JH, Murray JW, Wolkoff AW (2011). PDZK1 binding and serine phosphorylation regulate subcellular trafficking of organic anion transport protein 1a1. Am J Physiol Gastrointest Liver Physiol 300: G384–G393.

Chu XY, Bleasby K, Yabut J, Cai X, Chan GH, Hafey MJ *et al.* (2007). Transport of the dipeptidyl peptidase-4 inhibitor sitagliptin by human organic anion transporter 3, organic anion transporting polypeptide 4C1, and multidrug resistance P-glycoprotein. J Pharmacol Exp Ther 321: 673–683.

Chung JY, Cho JY, Yu KS, Kim JR, Oh DS, Jung HR *et al.* (2005). Effect of OATP1B1 (SLCO1B1) variant alleles on the pharmacokinetics of pitavastatin in healthy volunteers. Clin Pharmacol Ther 78: 342–350.

Ciarimboli G (2008). Organic cation transporters. Xenobiotica 38: 936–971.

Ciarimboli G, Schlatter E (2005). Regulation of organic cation transport. Pflugers Arch 449: 423–441.

Cihlar T, Lin DC, Pritchard JB, Fuller MD, Mendel DB, Sweet DH (1999). The antiviral nucleotide analogs cidofovir and adefovir are novel substrates for human and rat renal organic anion transporter 1. Mol Pharmacol 56: 570–580.

Congiu M, Mashford ML, Slavin JL, Desmond PV (2009). Coordinate regulation of metabolic enzymes and transporters by nuclear transcription factors in human liver disease. J Gastroenterol Hepatol 24: 1038–1044.

Cui T, Liu Y, Men X, Xu Z, Wu L, Liu S *et al.* (2009). Bile acid transport correlative protein mRNA expression profile in human placenta with intrahepatic cholestasis of pregnancy. Saudi Med J 30: 1406–1410.

Cui Y, Konig J, Leier I, Buchholz U, Keppler D (2001). Hepatic uptake of bilirubin and its conjugates by the human organic anion transporter SLC21A6. J Biol Chem 276: 9626–9630.

Cui Y, Konig J, Nies AT, Pfannschmidt M, Hergt M, Franke WW *et al.* (2003). Detection of the human organic anion transporters SLC21A6 (OATP2) and SLC21A8 (OATP8) in liver and hepatocellular carcinoma. Lab Invest 83: 527–538.

Cvetkovic M, Leake B, Fromm MF, Wilkinson GR, Kim RB (1999). OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. Drug Metab Dispos 27: 866–871.

van der Deure WM, Hansen PS, Peeters RP, Kyvik KO, Friesema EC, Hegedus L *et al.* (2008). Thyroid hormone transport and metabolism by organic anion transporter 1C1 and consequences of genetic variation. Endocrinology 149: 5307–5314.

Dresser GK, Bailey DG, Leake BF, Schwarz UI, Dawson PA, Freeman DJ *et al.* (2002). Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. Clin Pharmacol Ther 71: 11–20.

Dresser GK, Kim RB, Bailey DG (2005). Effect of grapefruit juice volume on the reduction of fexofenadine bioavailability: possible role of organic anion transporting polypeptides. Clin Pharmacol Ther 77: 170–177.

Ekaratanawong S, Anzai N, Jutabha P, Miyazaki H, Noshiro R, Takeda M *et al.* (2004). Human organic anion transporter 4 is a renal apical organic anion/dicarboxylate exchanger in the proximal tubules. J Pharmacol Sci 94: 297–304.

Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH *et al.* (2002a). Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature 417: 447–452.

Enomoto A, Takeda M, Shimoda M, Narikawa S, Kobayashi Y, Yamamoto T *et al.* (2002b). Interaction of human organic anion transporters 2 and 4 with organic anion transport inhibitors. J Pharmacol Exp Ther 301: 797–802.

Enomoto A, Wempe MF, Tsuchida H, Shin HJ, Cha SH, Anzai N *et al.* (2002c). Molecular identification of a novel carnitine transporter specific to human testis. Insights into the mechanism of carnitine recognition. J Biol Chem 277: 36262–36271.

Eraly SA, Vallon V, Vaughn DA, Gangoiti JA, Richter K, Nagle M *et al.* (2006). Decreased renal organic anion secretion and plasma accumulation of endogenous organic anions in OAT1 knock-out mice. J Biol Chem 281: 5072–5083.

Erdman AR, Mangravite LM, Urban TJ, Lagpacan LL, Castro RA, de la Cruz M *et al.* (2006). The human organic anion transporter 3 (OAT3; SLC22A8): genetic variation and functional genomics. Am J Physiol Renal Physiol 290: F905–F912.

Fahrmayr C, Fromm MF, Konig J (2010). Hepatic OATP and OCT uptake transporters: their role for drug-drug interactions and pharmacogenetic aspects. Drug Metab Rev 42: 380–401.

Fehrenbach T, Cui Y, Faulstich H, Keppler D (2003). Characterization of the transport of the bicyclic peptide phalloidin by human hepatic transport proteins. Naunyn Schmiedebergs Arch Pharmacol 368: 415–420.

Fischer WJ, Altheimer S, Cattori V, Meier PJ, Dietrich DR, Hagenbuch B (2005). Organic anion transporting polypeptides expressed in liver and brain mediate uptake of microcystin. Toxicol Appl Pharmacol 203: 257–263.

Franco R, Cidlowski JA (2006). SLCO/OATP-like transport of glutathione in FasL-induced apoptosis: glutathione efflux is coupled to an organic anion exchange and is necessary for the progression of the execution phase of apoptosis. J Biol Chem 281: 29542–29557.

Franke RM, Baker SD, Mathijssen RH, Schuetz EG, Sparreboom A (2008). Influence of solute carriers on the pharmacokinetics of CYP3A4 probes. Clin Pharmacol Ther 84: 704–709.

Fujino H, Saito T, Ogawa S, Kojima J (2005). Transporter-mediated influx and efflux mechanisms of pitavastatin, a new inhibitor of HMG-CoA reductase. J Pharm Pharmacol 57: 1305–1311.

Fujita T, Brown C, Carlson EJ, Taylor T, de la Cruz M, Johns SJ *et al.* (2005). Functional analysis of polymorphisms in the organic anion transporter, SLC22A6 (OAT1). Pharmacogenet Genomics 15: 201–209.

Fujiwara K, Adachi H, Nishio T, Unno M, Tokui T, Okabe M *et al.* (2001). Identification of thyroid hormone transporters in humans: different molecules are involved in a tissue-specific manner. Endocrinology 142: 2005–2012.

Furihata T, Satoh T, Yamamoto N, Kobayashi K, Chiba K (2007). Hepatocyte nuclear factor 1 alpha is a factor responsible for the interindividual variation of OATP1B1 mRNA levels in adult Japanese livers. Pharm Res 24: 2327–2332.

Gao B, Hagenbuch B, Kullak-Ublick GA, Benke D, Aguzzi A, Meier PJ (2000). Organic anion-transporting polypeptides mediate transport of opioid peptides across blood-brain barrier. J Pharmacol Exp Ther 294: 73–79.

Gao B, Huber RD, Wenzel A, Vavricka SR, Ismair MG, Reme C *et al.* (2005). Localization of organic anion transporting polypeptides in the rat and human ciliary body epithelium. Exp Eye Res 80: 61–72.

van Giersbergen PL, Treiber A, Schneiter R, Dietrich H, Dingemanse J (2007). Inhibitory and inductive effects of rifampin on the pharmacokinetics of bosentan in healthy subjects. Clin Pharmacol Ther 81: 414–419.

Glaeser H, Bailey DG, Dresser GK, Gregor JC, Schwarz UI, McGrath JS *et al.* (2007). Intestinal drug transporter expression and the impact of grapefruit juice in humans. Clin Pharmacol Ther 81: 362–370.

Glaeser H, Mandery K, Sticht H, Fromm MF, Konig J (2010). Relevance of conserved lysine and arginine residues in transmembrane helices for the transport activity of organic anion transporting polypeptide 1B3. Br J Pharmacol 159: 698–708.

Gong S, Lu X, Xu Y, Swiderski CF, Jordan CT, Moscow JA (2002). Identification of OCT6 as a novel organic cation transporter preferentially expressed in hematopoietic cells and leukemias. Exp Hematol 30: 1162–1169.

Gorboulev V, Ulzheimer JC, Akhoundova A, Ulzheimer-Teuber I, Karbach U, Quester S *et al.* (1997). Cloning and characterization of two human polyspecific organic cation transporters. DNA Cell Biol 16: 871–881.

Grube M, Meyer Zu Schwabedissen H, Draber K, Prager D, Moritz KU, Linnemann K *et al.* (2005). Expression, localization, and function of the carnitine transporter octn2 (slc22a5) in human placenta. Drug Metab Dispos 33: 31–37.

Grube M, Kock K, Karner S, Reuther S, Ritter CA, Jedlitschky G *et al.* (2006a). Modification of OATP2B1-mediated transport by steroid hormones. Mol Pharmacol 70: 1735–1741.

Grube M, Kock K, Oswald S, Draber K, Meissner K, Eckel L *et al.* (2006b). Organic anion transporting polypeptide 2B1 is a high-affinity transporter for atorvastatin and is expressed in the human heart. Clin Pharmacol Ther 80: 607–620.

Grundemann D, Schechinger B, Rappold GA, Schomig E (1998). Molecular identification of the corticosterone-sensitive extraneuronal catecholamine transporter. Nat Neurosci 1: 349–351.

Gui C, Hagenbuch B (2008). Amino acid residues in transmembrane domain 10 of organic anion transporting polypeptide 1B3 are critical for cholecystokinin octapeptide transport. Biochemistry 47: 9090–9097.

Gui C, Hagenbuch B (2009). Role of transmembrane domain 10 for the function of organic anion transporting polypeptide 1B1. Protein Sci 18: 2298–2306.

Gui C, Miao Y, Thompson L, Wahlgren B, Mock M, Stieger B *et al.* (2008). Effect of pregnane X receptor ligands on transport mediated by human OATP1B1 and OATP1B3. Eur J Pharmacol 584: 57–65.

Gui C, Wahlgren B, Lushington GH, Hagenbuch B (2009). Identification, Ki determination and CoMFA analysis of nuclear receptor ligands as competitive inhibitors of OATP1B1-mediated estradiol-17beta-glucuronide transport. Pharmacol Res 60: 50–56.

Gui C, Obaidat A, Chaguturu R, Hagenbuch B (2010). Development of a cell-based high-throughput assay to screen for inhibitors of organic anion transporting polypeptides 1B1 and 1B3. Curr Chem Genomics 4: 1–8.

Hagenbuch B, Gui C (2008). Xenobiotic transporters of the human organic anion transporting polypeptide (OATP) family. Xenobiotica 7–8: 778–801.

Hagenbuch B, Meier PJ (2004). Organic anion transporting polypeptides of the OATP/ SLC21 family: phylogenetic classification as OATP/ SLCO superfamily, new nomenclature and molecular/functional properties. Pflugers Arch 447: 653–665.

Hamada A, Sissung T, Price DK, Danesi R, Chau CH, Sharifi N *et al.* (2008). Effect of SLCO1B3 haplotype on testosterone transport and clinical outcome in caucasian patients with androgen-independent prostatic cancer. Clin Cancer Res 14: 3312–3318.

Hanggi E, Grundschober AF, Leuthold S, Meier PJ, St-Pierre MV (2006). Functional analysis of the extracellular cysteine residues in the human organic anion transporting polypeptide, OATP2B1. Mol Pharmacol 70: 806–817.

Hartkoorn RC, Kwan WS, Shallcross V, Chaikan A, Liptrott N, Egan D *et al.* (2010). HIV protease inhibitors are substrates for OATP1A2, OATP1B1 and OATP1B3 and lopinavir plasma concentrations are influenced by SLCO1B1 polymorphisms. Pharmacogenet Genomics 20: 112–120.

Hayer M, Bonisch H, Bruss M (1999). Molecular cloning, functional characterization and genomic organization of four alternatively spliced isoforms of the human organic cation transporter 1 (hOCT1/SLC22A1). Ann Hum Genet 63: 473–482.

Hilgendorf C, Ahlin G, Seithel A, Artursson P, Ungell AL, Karlsson J (2007). Expression of thirty-six drug transporter genes in human intestine, liver, kidney, and organotypic cell lines. Drug Metab Dispos 35: 1333–1340.

Hirano M, Maeda K, Shitara Y, Sugiyama Y (2004). Contribution of OATP2 (OATP1B1) and OATP8 (OATP1B3) to the hepatic uptake of pitavastatin in humans. J Pharmacol Exp Ther 311: 139–146.

Hirano M, Maeda K, Shitara Y, Sugiyama Y (2006). Drug-drug interaction between pitavastatin and various drugs via OATP1B1. Drug Metab Dispos 34: 1229–1236.

Ho RH, Tirona RG, Leake BF, Glaeser H, Lee W, Lemke CJ *et al.* (2006). Drug and bile acid transporters in rosuvastatin hepatic uptake: function, expression, and pharmacogenetics. Gastroenterology 130: 1793–1806.

Ho RH, Choi L, Lee W, Mayo G, Schwarz UI, Tirona RG *et al.* (2007). Effect of drug transporter genotypes on pravastatin disposition in European- and African-American participants. Pharmacogenet Genomics 17: 647–656.

Hong M, Zhou F, You G (2004). Critical amino acid residues in transmembrane domain 1 of the human organic anion transporter hOAT1. J Biol Chem 279: 31478–31482.

Hong M, Tanaka K, Pan Z, Ma J, You G (2007). Determination of the external loops and the cellular orientation of the N- and the C-termini of the human organic anion transporter hOAT1. Biochem J 401: 515–520.

Horvath G, Schmid N, Fragoso MA, Schmid A, Conner GE, Salathe M *et al.* (2007). Epithelial organic cation transporters ensure pH-dependent drug absorption in the airway. Am J Respir Cell Mol Biol 36: 53–60.

Hosoyamada M, Sekine T, Kanai Y, Endou H (1999). Molecular cloning and functional expression of a multispecific organic anion transporter from human kidney. Am J Physiol 276: F122–F128.

Hsiang B, Zhu Y, Wang Z, Wu Y, Sasseville V, Yang WP *et al.* (1999). A novel human hepatic organic anion transporting polypeptide (OATP2). Identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters. J Biol Chem 274: 37161–37168.

Hu S, Franke RM, Filipski KK, Hu C, Orwick SJ, de Bruijn EA *et al.* (2008). Interaction of imatinib with human organic ion carriers. Clin Cancer Res 14: 3141–3148.

Huang MJ, Kua KE, Teng HC, Tang KS, Weng HW, Huang CS (2004). Risk factors for severe hyperbilirubinemia in neonates. Pediatr Res 56: 682–689.

Huber RD, Gao B, Sidler Pfandler MA, Zhang-Fu W, Leuthold S, Hagenbuch B *et al.* (2007). Characterization of two splice variants of human organic anion transporting polypeptide 3A1 isolated from human brain. Am J Physiol Cell Physiol 292: C795–C806.

Ieiri I, Suzuki H, Kimura M, Takane H, Nishizato Y, Irie S *et al.* (2004). Influence of common variants in the pharmacokinetic genes (OATP-C, UGT1A1, and MRP2) on serum bilirubin levels in healthy subjects. Hepatol Res 30: 91–95.

Ishiguro N, Maeda K, Kishimoto W, Saito A, Harada A, Ebner T *et al.* (2006). Predominant contribution of OATP1B3 to the hepatic uptake of telmisartan, an angiotensin II receptor antagonist, in humans. Drug Metab Dispos 34: 1109–1115.

Ismair MG, Stieger B, Cattori V, Hagenbuch B, Fried M, Meier PJ *et al.* (2001). Hepatic uptake of cholecystokinin octapeptide by organic anion-transporting polypeptides OATP4 and OATP8 of rat and human liver. Gastroenterology 121: 1185–1190.

Jonker JW, Wagenaar E, Mol CA, Buitelaar M, Koepsell H, Smit JW *et al.* (2001). Reduced hepatic uptake and intestinal excretion of organic cations in mice with a targeted disruption of the organic cation transporter 1 (Oct1 [Slc22a1]) gene. Mol Cell Biol 21: 5471–5477.

Jonker JW, Wagenaar E, Van Eijl S, Schinkel AH (2003). Deficiency in the organic cation transporters 1 and 2 (Oct1/Oct2 [Slc22a1/Slc22a2]) in mice abolishes renal secretion of organic cations. Mol Cell Biol 23: 7902–7908.

Jung D, Kullak-Ublick GA (2003). Hepatocyte nuclear factor 1 alpha: a key mediator of the effect of bile acids on gene expression. Hepatology 37: 622–631.

Kalgutkar AS, Feng B, Nguyen HT, Frederick KS, Campbell SD, Hatch HL *et al.* (2007). Role of transporters in the disposition of the selective phosphodiesterase-4 inhibitor (+)-2-[4-({[2-(benzo[1,3] dioxol-5-yloxy)-pyridine-3-carbonyl]-amino}-methy l)-3-fluoro-phenoxy]-propionic acid in rat and human. Drug Metab Dispos 35: 2111–2118.

Kalliokoski A, Niemi M (2009). Impact of OATP transporters on pharmacokinetics. Br J Pharmacol 158: 693–705.

Kalliokoski A, Neuvonen M, Neuvonen PJ, Niemi M (2008). No significant effect of SLCO1B1 polymorphism on the pharmacokinetics of rosiglitazone and pioglitazone. Br J Clin Pharmacol 65: 78–86.

Kanai N, Lu R, Satriano JA, Bao Y, Wolkoff AW, Schuster VL (1995). Identification and characterization of a prostaglandin transporter. Science 268: 866–869.

Karbach U, Kricke J, Meyer-Wentrup F, Gorboulev V, Volk C, Loffing-Cueni D *et al.* (2000). Localization of organic cation transporters OCT1 and OCT2 in rat kidney. Am J Physiol Renal Physiol 279: F679–F687.

Kato K, Shirasaka Y, Kuraoka E, Kikuchi A, Iguchi M, Suzuki H *et al.* (2010). Intestinal absorption mechanism of tebipenem pivoxil, a novel oral carbapenem: involvement of human OATP family in apical membrane transport. Mol Pharmacol 7: 1747–1756.

Kato Y, Yoshida K, Watanabe C, Sai Y, Tsuji A (2004). Screening of the interaction between xenobiotic transporters and PDZ proteins. Pharm Res 21: 1886–1894.

Kato Y, Sai Y, Yoshida K, Watanabe C, Hirata T, Tsuji A (2005). PDZK1 directly regulates the function of organic cation/carnitine transporter OCTN2. Mol Pharmacol 67: 734–743.

Kato Y, Miyazaki T, Kano T, Sugiura T, Kubo Y, Tsuji A (2009). Involvement of influx and efflux transport systems in gastrointestinal absorption of celiprolol. J Pharm Sci 98: 2529–2539.

Katz DA, Carr R, Grimm DR, Xiong H, Holley-Shanks R, Mueller T *et al.* (2006). Organic anion transporting polypeptide 1B1 activity classified by SLCO1B1 genotype influences atrasentan pharmacokinetics. Clin Pharmacol Ther 79: 186–196.

Keitel V, Burdelski M, Warskulat U, Kuhlkamp T, Keppler D, Haussinger D *et al.* (2005). Expression and localization of hepatobiliary transport proteins in progressive familial intrahepatic cholestasis. Hepatology 41: 1160–1172.

Keller T, Schwarz D, Bernhard F, Dotsch V, Hunte C, Gorboulev V *et al.* (2008). Cell free expression and functional reconstitution of eukaryotic drug transporters. Biochemistry 47: 4552–4564.

Kelley L, Sternberg M (2009). Protein structure prediction on the Web: a case study using the Phyre server. Nat Protoc 4: 363–371.

Kerb R, Brinkmann U, Chatskaia N, Gorbunov D, Gorboulev V, Mornhinweg E *et al.* (2002). Identification of genetic variations of the human organic cation transporter hOCT1 and their functional consequences. Pharmacogenetics 12: 591–595.

Kikuchi R, Kusuhara H, Hattori N, Shiota K, Kim I, Gonzalez FJ *et al.* (2006). Regulation of the expression of human organic anion transporter 3 by hepatocyte nuclear factor 1alpha/beta and DNA methylation. Mol Pharmacol 70: 887–896.

Kikuchi R, Kusuhara H, Hattori N, Kim I, Shiota K, Gonzalez FJ *et al.* (2007). Regulation of tissue-specific expression of the human and mouse urate transporter 1 gene by hepatocyte nuclear factor 1 alpha/beta and DNA methylation. Mol Pharmacol 72: 1619–1625.

Kindla J, Muller F, Mieth M, Fromm MF, Konig J (2011). Influence of non-steroidal anti-inflammatory drugs on Organic Anion Transporting Polypeptide (OATP) 1B1- and OATP1B3-mediated drug transport. Drug Metab Dispos 39: 1047–1053.

Kinoshita M, Miyata M (2002). Underexpression of mRNA in human hepatocellular carcinoma focusing on eight loci. Hepatology 36: 433–438.

Knauer MJ, Urquhart BL, Meyer zu Schwabedissen HE, Schwarz UI, Lemke CJ, Leake BF *et al.* (2010). Human skeletal muscle drug transporters determine local exposure and toxicity of statins. Circ Res 106: 297–306.

Kobayashi D, Nozawa T, Imai K, Nezu J, Tsuji A, Tamai I (2003). Involvement of human organic anion transporting polypeptide OATP-B (SLC21A9) in pH-dependent transport across intestinal apical membrane. J Pharmacol Exp Ther 306: 703–708.

Kock K, Koenen A, Giese B, Fraunholz M, May K, Siegmund W *et al*. (2010). Rapid modulation of the organic anion transporting polypeptide 2B1 (OATP2B1, SLCO2B1) function by protein kinase C-mediated internalization. J Biol Chem 285: 11336–11347.

Koepsell H (2011). Substrate recognition and translocation by polyspecific organic cation transporters. Biol Chem 392: 95–101.

Koepsell H, Lips K, Volk C (2007). Polyspecific organic cation transporters: structure, function, physiological roles, and biopharmaceutical implications. Pharm Res 24: 1227–1251.

Komatsu M, Furukawa T, Ikeda R, Takumi S, Nong Q, Aoyama K *et al*. (2007). Involvement of mitogen-activated protein kinase signaling pathways in microcystin-LR-induced apoptosis after its selective uptake mediated by OATP1B1 and OATP1B3. Toxicol Sci 97: 407–416.

Konig J (2011). Uptake transporters of the human OATP family: molecular characteristics, substrates, their role in drug-drug interactions, and functional consequences of polymorphisms. Handb Exp Pharmacol 201: 1–28.

Konig J, Cui Y, Nies AT, Keppler D (2000a). Localization and genomic organization of a new hepatocellular organic anion transporting polypeptide. J Biol Chem 275: 23161–23168.

Konig J, Cui Y, Nies AT, Keppler D (2000b). A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane. Am J Physiol Gastrointest Liver Physiol 278: G156–G164.

Kopplow K, Letschert K, Konig J, Walter B, Keppler D (2005). Human hepatobiliary transport of organic anions analyzed by quadruple-transfected cells. Mol Pharmacol 68: 1031–1038.

Kraft ME, Glaeser H, Mandery K, Konig J, Auge D, Fromm MF *et al*. (2010). The prostaglandin transporter OATP2A1 is expressed in human ocular tissues and transports the antiglaucoma prostanoid latanoprost. Invest Ophthalmol Vis Sci 51: 2504–2511.

Kullak-Ublick GA, Hagenbuch B, Stieger B, Schteingart CD, Hofmann AF, Wolkoff AW *et al*. (1995). Molecular and functional characterization of an organic anion transporting polypeptide cloned from human liver. Gastroenterology 109: 1274–1282.

Kullak-Ublick GA, Beuers U, Fahney C, Hagenbuch B, Meier PJ, Paumgartner G (1997a). Identification and functional characterization of the promoter region of the human organic anion transporting polypeptide gene. Hepatology 26: 991–997.

Kullak-Ublick GA, Glasa J, Boker C, Oswald M, Grutzner U, Hagenbuch B *et al*. (1997b). Chlorambucil-taurocholate is transported by bile acid carriers expressed in human hepatocellular carcinomas. Gastroenterology 113: 1295–1305.

Kullak-Ublick GA, Fisch T, Oswald M, Hagenbuch B, Meier PJ, Beuers U *et al*. (1998). Dehydroepiandrosterone sulfate (DHEAS): identification of a carrier protein in human liver and brain. FEBS Lett 424: 173–176.

Kullak-Ublick GA, Ismair MG, Stieger B, Landmann L, Huber R, Pizzagalli F *et al*. (2001). Organic anion-transporting polypeptide B (OATP-B) and its functional comparison with three other OATPs of human liver. Gastroenterology 120: 525–533.

Lahjouji K, Mitchell GA, Qureshi IA (2001). Carnitine transport by organic cation transporters and systemic carnitine deficiency. Mol Genet Metab 73: 287–297.

Lamhonwah AM, Ackerley CA, Tilups A, Edwards VD, Wanders RJ, Tein I (2005). OCTN3 is a mammalian peroxisomal membrane carnitine transporter. Biochem Biophys Res Commun 338: 1966–1972.

Lau YY, Huang Y, Frassetto L, Benet LZ (2007). effect of OATP1B transporter inhibition on the pharmacokinetics of atorvastatin in healthy volunteers. Clin Pharmacol Ther 81: 194–204.

Le Vee M, Gripon P, Stieger B, Fardel O (2008). Down-regulation of organic anion transporter expression in human hepatocytes exposed to the proinflammatory cytokine interleukin 1beta. Drug Metab Dispos 36: 217–222.

Le Vee M, Lecureur V, Moreau A, Stieger B, Fardel O (2009). Differential regulation of drug transporter expression by hepatocyte growth factor in primary human hepatocytes. Drug Metab Dispos 37: 2228–2235.

Le Vee M, Jouan E, Moreau A, Fardel O (2011). Regulation of drug transporter mRNA expression by interferon-gamma in primary human hepatocytes. Fundam Clin Pharmacol 25: 99–103.

Lee SY, Williamson B, Caballero OL, Chen YT, Scanlan MJ, Ritter G *et al*. (2004). Identification of the gonad-specific anion transporter SLCO6A1 as a cancer/testis (CT) antigen expressed in human lung cancer. Cancer Immun 4: 13–21.

Lee W, Glaeser H, Smith LH, Roberts RL, Moeckel GW, Gervasini G *et al*. (2005). Polymorphisms in human organic anion-transporting polypeptide 1A2 (OATP1A2): implications for altered drug disposition and central nervous system drug entry. J Biol Chem 280: 9610–9617.

Lee W, Belkhiri A, Lockhart AC, Merchant N, Glaeser H, Harris EI *et al*. (2008). Overexpression of OATP1B3 confers apoptotic resistance in colon cancer. Cancer Res 68: 10315–10323.

Letschert K, Keppler D, Konig J (2004). Mutations in the SLCO1B3 gene affecting the substrate specificity of the hepatocellular uptake transporter OATP1B3 (OATP8). Pharmacogenetics 14: 441–452.

Letschert K, Faulstich H, Keller D, Keppler D (2006). Molecular characterization and inhibition of amanitin uptake into human hepatocytes. Toxicol Sci 91: 140–149.

Leuthold S, Hagenbuch B, Mohebbi N, Wagner CA, Meier PJ, Stieger B (2009). Mechanisms of pH-gradient driven transport mediated by organic anion polypeptide transporters. Am J Physiol Cell Physiol 296: C570–C582.

Li L, Meier PJ, Ballatori N (2000). Oatp2 mediates bidirectional organic solute transport: a role for intracellular glutathione. Mol Pharmacol 58: 335–340.

Li LQ, Lee TK, Meier PJ, Ballatori N (1998). Identification of glutathione as a driving force and leukotriene C-4 as a substrate for oatp1, the hepatic sinusoidal organic solute transporter. J Biol Chem 273: 16184–16191.

Lin Z, Nelson L, Franke A, Poritz L, Li TY, Wu R *et al*. (2010). OCTN1 variant L503F is associated with familial and sporadic inflammatory bowel disease. J Crohns Colitis 4: 132–138.

Lips KS, Volk C, Schmitt BM, Pfeil U, Arndt P, Miska D *et al*. (2005). Polyspecific cation transporters mediate luminal release of acetylcholine from bronchial epithelium. Am J Respir Cell Mol Biol 33: 79–88.

Liu L, Cui Y, Chung AY, Shitara Y, Sugiyama Y, Keppler D *et al*. (2006). Vectorial transport of enalapril by Oatp1a1/Mrp2 and OATP1B1 and OATP1B3/MRP2 in rat and human livers. J Pharmacol Exp Ther 318: 395–402.

Ljubojevic M, Balen D, Breljak D, Kusan M, Anzai N, Bahn A *et al*. (2007). Renal expression of organic anion transporter OAT2 in rats and mice is regulated by sex hormones. Am J Physiol Renal Physiol 292: F361–F372.

Lu R, Chan BS, Schuster VL (1999). Cloning of the human kidney PAH transporter: narrow substrate specificity and regulation by protein kinase C. Am J Physiol 276: F295–F303.

Lu WJ, Tamai I, Nezu J, Lai ML, Huang JD (2006). Organic anion transporting polypeptide-C mediates arsenic uptake in HEK-293 cells. J Biomed Sci 13: 525–533.

Maeda K, Ieiri I, Yasuda K, Fujino A, Fujiwara H, Otsubo K *et al.* (2006a). Effects of organic anion transporting polypeptide 1B1 haplotype on pharmacokinetics of pravastatin, valsartan, and temocapril. Clin Pharmacol Ther 79: 427–439.

Maeda K, Kambara M, Tian Y, Hofmann AF, Sugiyama Y (2006b). Uptake of ursodeoxycholate and its conjugates by human hepatocytes: role of Na(+)-taurocholate cotransporting polypeptide (NTCP), organic anion transporting polypeptide (OATP) 1B1 (OATP-C), and oatp1B3 (OATP8). Mol Pharm 3: 70–77.

Maeda T, Takahashi K, Ohtsu N, Oguma T, Ohnishi T, Atsumi R *et al.* (2007). Identification of influx transporter for the quinolone antibacterial agent levofloxacin. Mol Pharm 4: 85–94.

Mahagita C, Grassl SM, Piyachaturawat P, Ballatori N (2007). Human organic anion transporter 1B1 and 1B3 function as bidirectional carriers and do not mediate GSH-bile acid cotransport. Am J Physiol Gastrointest Liver Physiol 293: G271–G278.

Mandery K, Bujok K, Schmidt I, Wex T, Treiber G, Malfertheiner P *et al.* (2010). Influence of cyclooxygenase inhibitors on the function of the prostaglandin transporter organic anion-transporting polypeptide 2A1 expressed in human gastroduodenal mucosa. J Pharmacol Exp Ther 332: 345–351.

Mandery K, Sticht H, Bujok K, Schmidt I, Fahrmayr C, Balk B *et al.* (2011). Functional and structural relevance of conserved positively charged lysine residues in organic anion transporting polypeptide 1B3. Mol Pharmacol 80: 400–406.

Martinez-Becerra P, Briz O, Romero MR, Macias RI, Perez MJ, Sancho-Mateo C *et al.* (2011). Further characterization of the electrogenicity and pH sensitivity of the human organic anion-transporting polypeptides OATP1B1 and OATP1B3. Mol Pharmacol 79: 596–607.

Masuda S, Terada T, Yonezawa A, Tanihara Y, Kishimoto K, Katsura T *et al.* (2006). Identification and functional characterization of a new human kidney-specific H+/organic cation antiporter, kidney-specific multidrug and toxin extrusion 2. J Am Soc Nephrol 17: 2127–2135.

Meier PJ, Eckhardt U, Schroeder A, Hagenbuch B, Stieger B (1997). Substrate specificity of sinusoidal bile acid and organic anion uptake systems in rat and human liver. Hepatology 26: 1667–1677.

Meier-Abt F, Faulstich H, Hagenbuch B (2004). Identification of phalloidin uptake systems of rat and human liver. Biochim Biophys Acta 1664: 64–69.

Meier-Abt F, Mokrab Y, Mizuguchi K (2005). Organic anion transporting polypeptides of the OATP/SLCO superfamily: identification of new members in nonmammalian species, comparative modeling and a potential transport mode. J Membr Biol 208: 213–227.

Michalski C, Cui Y, Nies AT, Nuessler AK, Neuhaus P, Zanger UM *et al.* (2002). A naturally occurring mutation in the SLC21A6 gene causing impaired membrane localization of the hepatocyte uptake transporter. J Biol Chem 277: 43058–43063.

Miki Y, Suzuki T, Kitada K, Yabuki N, Shibuya R, Moriya T *et al.* (2006). Expression of the steroid and xenobiotic receptor and its possible target gene, organic anion transporting polypeptide-A, in human breast carcinoma. Cancer Res 66: 535–542.

Mikkaichi T, Suzuki T, Onogawa T, Tanemoto M, Mizutamari H, Okada M *et al.* (2004). Isolation and characterization of a digoxin transporter and its rat homologue expressed in the kidney. Proc Natl Acad Sci U S A 101: 3569–3574.

Miura M, Satoh S, Inoue K, Kagaya H, Saito M, Inoue T *et al.* (2007). Influence of SLCO1B1, 1B3, 2B1 and ABCC2 genetic polymorphisms on mycophenolic acid pharmacokinetics in Japanese renal transplant recipients. Eur J Clin Pharmacol 63: 1161–1169.

Miura M, Satoh S, Inoue K, Saito M, Habuchi T, Suzuki T (2009). Telmisartan pharmacokinetics in Japanese renal transplant recipients. Clin Chim Acta 399: 83–87.

Miyagawa M, Maeda K, Aoyama A, Sugiyama Y (2009). The eighth and ninth transmembrane domains in organic anion transporting polypeptide 1B1 affect the transport kinetics of estrone-3-sulfate and estradiol-17beta-D-glucuronide. J Pharmacol Exp Ther 329: 551–557.

Moaddel R, Ravichandran S, Bighi F, Yamaguchi R, Wainer IW (2007). Pharmacophore modelling of stereoselective binding to the human organic cation transporter (hOCT1). Br J Pharmacol 151: 1305–1314.

Monks NR, Liu S, Xu Y, Yu H, Bendelow AS, Moscow JA (2007). Potent cytotoxicity of the phosphatase inhibitor microcystin LR and microcystin analogues in OATP1B1- and OATP1B3-expressing HeLa cells. Mol Cancer Ther 6: 587–598.

van Montfoort JE, Hagenbuch B, Fattinger KE, Muller M, Groothuis GM, Meijer DK *et al.* (1999). Polyspecific organic anion transporting polypeptides mediate hepatic uptake of amphipathic type II organic cations. J Pharmacol Exp Ther 291: 147–152.

Motohashi H, Sakurai Y, Saito H, Masuda S, Urakami Y, Goto M *et al.* (2002). Gene expression levels and immunolocalization of organic ion transporters in the human kidney. J Am Soc Nephrol 13: 866–874.

Mougey EB, Feng H, Castro M, Irvin CG, Lima JJ (2009). Absorption of montelukast is transporter mediated: a common variant of OATP2B1 is associated with reduced plasma concentrations and poor response. Pharmacogenet Genomics 19: 129–138.

Muller J, Lips KS, Metzner L, Neubert RH, Koepsell H, Brandsch M (2005). Drug specificity and intestinal membrane localization of human organic cation transporters (OCT). Biochem Pharmacol 70: 1851–1860.

Muto M, Onogawa T, Suzuki T, Ishida T, Rikiyama T, Katayose Y *et al.* (2007). Human liver-specific organic anion transporter-2 is a potent prognostic factor for human breast carcinoma. Cancer Sci 98: 1570–1576.

Mwinyi J, Johne A, Bauer S, Roots I, Gerloff T (2004). Evidence for inverse effects of OATP-C (SLC21A6) 5 and 1b haplotypes on pravastatin kinetics. Clin Pharmacol Ther 75: 415–421.

Nakagomi-Hagihara R, Nakai D, Kawai K, Yoshigae Y, Tokui T, Abe T *et al.* (2006). OATP1B1, OATP1B3, and mrp2 are involved in hepatobiliary transport of olmesartan, a novel angiotensin II blocker. Drug Metab Dispos 34: 862–869.

Nakai D, Nakagomi R, Furuta Y, Tokui T, Abe T, Ikeda T *et al.* (2001). Human liver-specific organic anion transporter, LST-1, mediates uptake of pravastatin by human hepatocytes. J Pharmacol Exp Ther 297: 861–867.

Nakakariya M, Shimada T, Irokawa M, Maeda T, Tamai I (2008). Identification and species similarity of OATP transporters responsible for hepatic uptake of beta-lactam antibiotics. Drug Metab Pharmacokinet 23: 347–355.

Neuvonen PJ, Niemi M, Backman JT (2006). Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther 80: 565–581.

Niemi M, Schaeffeler E, Lang T, Fromm MF, Neuvonen M, Kyrklund C *et al*. (2004). High plasma pravastatin concentrations are associated with single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide-C (OATP-C, SLCO1B1). Pharmacogenetics 14: 429–440.

Nies AT, Herrmann E, Brom M, Keppler D (2008). Vectorial transport of the plant alkaloid berberine by double-transfected cells expressing the human organic cation transporter 1 (OCT1, SLC22A1) and the efflux pump MDR1 P-glycoprotein (ABCB1). Naunyn Schmiedebergs Arch Pharmacol 376: 449–461.

Nies AT, Koepsell H, Winter S, Burk O, Klein K, Kerb R *et al*. (2009). Expression of organic cation transporters OCT1 (SLC22A1) and OCT3 (SLC22A3) is affected by genetic factors and cholestasis in human liver. Hepatology 50: 1227–1240.

Nies AT, Koepsell H, Damme K, Schwab M (2011). Organic cation transporters (OCTs, MATEs), *in vitro* and *in vivo* evidence for the importance in drug therapy. Handb Exp Pharmacol 201: 105–167.

Nigam SK, Bush KT, Bhatnagar V (2007). Drug and toxicant handling by the OAT organic anion transporters in the kidney and other tissues. Nat Clin Pract Nephrol 3: 443–448.

Nishimura T, Kubo Y, Kato Y, Sai Y, Ogihara T, Tsuji A (2007). Characterization of the uptake mechanism for a novel loop diuretic, M17055, in Caco-2 cells: involvement of organic anion transporting polypeptide (OATP)-B. Pharm Res 24: 90–98.

Nishiwaki T, Daigo Y, Tamari M, Fujii Y, Nakamura Y (1998). Molecular cloning, mapping, and characterization of two novel human genes, ORCTL3 and ORCTL4, bearing homology to organic-cation transporters. Cytogenet Cell Genet 83: 251–255.

Nishizato Y, Ieiri I, Suzuki H, Kimura M, Kawabata K, Hirota T *et al*. (2003). Polymorphisms of OATP-C (SLC21A6) and OAT3 (SLC22A8) genes: consequences for pravastatin pharmacokinetics. Clin Pharmacol Ther 73: 554–565.

Noe J, Portmann R, Brun ME, Funk C (2007). Substrate-dependent drug-drug interactions between gemfibrozil, fluvastatin and other organic anion-transporting peptide (OATP) substrates on OATP1B1, OATP2B1, and OATP1B3. Drug Metab Dispos 35: 1308–1314.

Nomura T, Lu R, Pucci ML, Schuster VL (2004). The two-step model of prostaglandin signal termination: *in vitro* reconstitution with the prostaglandin transporter and prostaglandin 15 dehydrogenase. Mol Pharmacol 65: 973–978.

Nomura T, Chang HY, Lu R, Hankin J, Murphy RC, Schuster VL (2005). Prostaglandin signaling in the renal collecting duct: release, reuptake, and oxidation in the same cell. J Biol Chem 280: 28424–28429.

Nozaki Y, Kusuhara H, Kondo T, Iwaki M, Shiroyanagi Y, Nakayama H *et al*. (2007). Species difference in the inhibitory effect of nonsteroidal anti-inflammatory drugs on the uptake of methotrexate by human kidney slices. J Pharmacol Exp Ther 322: 1162–1170.

Nozawa T, Tamai I, Sai Y, Nezu J, Tsuji A (2003). Contribution of organic anion transporting polypeptide OATP-C to hepatic elimination of the opioid pentapeptide analogue [D-Ala2, D-Leu5]-enkephalin. J Pharm Pharmacol 55: 1013–1020.

Nozawa T, Imai K, Nezu J, Tsuji A, Tamai I (2004a). Functional characterization of pH-sensitive organic anion transporting polypeptide OATP-B in human. J Pharmacol Exp Ther 308: 438–445.

Nozawa T, Sugiura S, Nakajima M, Goto A, Yokoi T, Nezu J *et al*. (2004b). Involvement of organic anion transporting polypeptides in the transport of troglitazone sulfate: implications for understanding troglitazone hepatotoxicity. Drug Metab Dispos 32: 291–294.

Nozawa T, Minami H, Sugiura S, Tsuji A, Tamai I (2005). Role of organic anion transporter OATP1B1 (OATP-C) in hepatic uptake of irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin: *in vitro* evidence and effect of single nucleotide polymorphisms. Drug Metab Dispos 33: 434–439.

Obaidat A, Roth M, Hagenbuch B (2012). The expression and function of organic anion transporting polypeptides in cancer. Annu Rev Pharmacol Toxicol 52: 135–151.

Oostendorp RL, van de Steeg E, van der Kruijssen CM, Beijnen JH, Kenworthy KE, Schinkel AH *et al*. (2009). Organic anion-transporting polypeptide 1B1 mediates transport of Gimatecan and BNP1350 and can be inhibited by several classic ATP-binding cassette (ABC) B1 and/or ABCG2 inhibitors. Drug Metab Dispos 37: 917–923.

Oswald M, Kullak-Ublick GA, Paumgartner G, Beuers U (2001). Expression of hepatic transporters OATP-C and MRP2 in primary sclerosing cholangitis. Liver 21: 247–253.

Oswald S, Konig J, Lutjohann D, Giessmann T, Kroemer HK, Rimmbach C *et al*. (2008). Disposition of ezetimibe is influenced by polymorphisms of the hepatic uptake carrier OATP1B1. Pharmacogenet Genomics 18: 559–568.

Pacyniak E, Roth M, Hagenbuch B, Guo GL (2010). Mechanism of polybrominated diphenyl ether uptake into the liver: PBDE congeners are substrates of human hepatic OATP transporters. Toxicol Sci 115: 344–353.

Pasanen MK, Neuvonen M, Neuvonen PJ, Niemi M (2006). SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. Pharmacogenet Genomics 16: 873–879.

Pascolo L, Cupelli F, Anelli PL, Lorusso V, Visigalli M, Uggeri F *et al*. (1999). Molecular mechanisms for the hepatic uptake of magnetic resonance imaging contrast agents. Biochem Biophys Res Commun 257: 746–752.

Perry JL, Dembla-Rajpal N, Hall LA, Pritchard JB (2006). A three-dimensional model of human organic anion transporter 1: aromatic amino acids required for substrate transport. J Biol Chem 281: 38071–38079.

Picard N, Yee SW, Woillard JB, Lebranchu Y, Le Meur Y, Giacomini KM *et al*. (2010). The role of organic anion-transporting polypeptides and their common genetic variants in mycophenolic acid pharmacokinetics. Clin Pharmacol Ther 87: 100–108.

Pizzagalli F, Hagenbuch B, Stieger B, Klenk U, Folkers G, Meier PJ (2002). Identification of a novel human organic anion transporting polypeptide as a high affinity thyroxine transporter. Mol Endocrinol 16: 2283–2296.

Pizzagalli F, Varga Z, Huber RD, Folkers G, Meier PJ, St-Pierre MV (2003). Identification of steroid sulfate transport processes in the human mammary gland. J Clin Endocrinol Metab 88: 3902–3912.

Plaza F, Gabler F, Romero C, Vantman D, Valladares L, Vega M (2010). The conversion of dehydroepiandrosterone into androst-5-ene-3beta,17beta-diol (androstenediol) is increased in endometria from untreated women with polycystic ovarian syndrome. Steroids 75: 810–817.

Popowski K, Eloranta JJ, Saborowski M, Fried M, Meier PJ, Kullak-Ublick GA (2005). The human organic anion transporter 2 gene is transactivated by hepatocyte nuclear factor-4 alpha and suppressed by bile acids. Mol Pharmacol 67: 1629–1638.

Popp C, Gorboulev V, Muller TD, Gorbunov D, Shatskaya N, Koepsell H (2005). Amino acids critical for substrate affinity of rat organic cation transporter 1 line the substrate binding region in a model derived from the tertiary structure of lactose permease. Mol Pharmacol 67: 1600–1611.

Price KL, Sautin YY, Long DA, Zhang L, Miyazaki H, Mu W *et al.* (2006). Human vascular smooth muscle cells express a urate transporter. J Am Soc Nephrol 17: 1791–1795.

Pritchard JB, Sweet DH, Miller DS, Walden R (1999). Mechanism of organic anion transport across the apical membrane of choroid plexus. J Biol Chem 274: 33382–33387.

Race JE, Grassl SM, Williams WJ, Holtzman EJ (1999). Molecular cloning and characterization of two novel human renal organic anion transporters (hOAT1 and hOAT3). Biochem Biophys Res Commun 255: 508–514.

Reid G, Wolff NA, Dautzenberg FM, Burckhardt G (1998). Cloning of a human renal p-aminohippurate transporter, hROAT1. Kidney Blood Press Res 21: 233–237.

Rizwan AN, Krick W, Burckhardt G (2007). The chloride dependence of the human organic anion transporter 1 (hOAT1) is blunted by mutation of a single amino acid. J Biol Chem 282: 13402–13409.

Roberts LM, Woodford K, Zhou M, Black DS, Haggerty JE, Tate EH *et al.* (2008). Expression of the thyroid hormone transporters monocarboxylate transporter-8 (SLC16A2) and organic ion transporter-14 (SLCO1C1) at the blood-brain barrier. Endocrinology 149: 6251–6261.

Roth M, Araya JJ, Timmermann BN, Hagenbuch B (2011a). Isolation of modulators of the liver specific Organic Anion Transporting Polypeptides (OATPs) 1B1 and 1B3 from Rollinia emarginata Schlecht (Annonaceae). J Pharmacol Exp Ther 339: 624–632.

Roth M, Timmermann BN, Hagenbuch B (2011b). Interactions of green tea catechins with organic anion-transporting polypeptides. Drug Metab Dispos 39: 920–926.

Saborowski M, Kullak-Ublick GA, Eloranta JJ (2006). The human organic cation transporter-1 gene is transactivated by hepatocyte nuclear factor-4alpha. J Pharmacol Exp Ther 317: 778–785.

Sai Y, Kaneko Y, Ito S, Mitsuoka K, Kato Y, Tamai I *et al.* (2006). Predominant contribution of organic anion transporting polypeptide OATP-B (OATP2B1) to apical uptake of estrone-3-sulfate by human intestinal Caco-2 cells. Drug Metab Dispos 34: 1423–1431.

Saji T, Kikuchi R, Kusuhara H, Kim I, Gonzalez FJ, Sugiyama Y (2008). Transcriptional regulation of human and mouse organic anion transporter 1 by hepatocyte nuclear factor 1 alpha/beta. J Pharmacol Exp Ther 324: 784–790.

Sakamoto S, Kusuhara H, Horie K, Takahashi K, Baba T, Ishizaki J *et al.* (2008). Identification of the transporters involved in the hepatobiliary transport and intestinal efflux of methyl 1-(3,4-dimethoxyphenyl)-3-(3-ethylvaleryl)-4-hydroxy-6,7,8-trimethoxy-2-na phthoate (S-8921) glucuronide, a pharmacologically active metabolite of S-8921. Drug Metab Dispos 36: 1553–1561.

Sakata T, Anzai N, Kimura T, Miura D, Fukutomi T, Takeda M *et al.* (2010). Functional analysis of human organic cation transporter OCT3 (SLC22A3) polymorphisms. J Pharmacol Sci 113: 263–266.

Sandhu P, Lee W, Xu X, Leake BF, Yamazaki M, Stone JA *et al.* (2005). Hepatic uptake of the novel antifungal agent caspofungin. Drug Metab Dispos 33: 676–682.

Sasaki M, Suzuki H, Ito K, Abe T, Sugiyama Y (2002). Transcellular transport of organic anions across a double-transfected Madin-Darby canine kidney II cell monolayer expressing both human organic anion-transporting polypeptide (OATP2/SLC21A6) and Multidrug resistance-associated protein 2 (MRP2/ABCC2). J Biol Chem 277: 6497–6503.

Sata R, Ohtani H, Tsujimoto M, Murakami H, Koyabu N, Nakamura T *et al.* (2005). Functional analysis of organic cation transporter 3 expressed in human placenta. J Pharmacol Exp Ther 315: 888–895.

Satlin LM, Amin V, Wolkoff AW (1997). Organic anion transporting polypeptide mediates organic anion/HCO3- exchange. J Biol Chem 272: 26340–26345.

Sato K, Sugawara J, Sato T, Mizutamari H, Suzuki T, Ito A *et al.* (2003). Expression of Organic Anion Transporting Polypeptide E (OATP-E) in human placenta. Placenta 24: 144–148.

Satoh H, Yamashita F, Tsujimoto M, Murakami H, Koyabu N, Ohtani H *et al.* (2005). Citrus juices inhibit the function of human organic anion-transporting polypeptide OATP-B. Drug Metab Dispos 33: 518–523.

Sauvant C, Holzinger H, Gekle M (2001). Modulation of the basolateral and apical step of transepithelial organic anion secretion in proximal tubular opossum kidney cells. Acute effects of epidermal growth factor and mitogen-activated protein kinase. J Biol Chem 276: 14695–14703.

Sauvant C, Holzinger H, Gekle M (2002). Short-term regulation of basolateral organic anion uptake in proximal tubular OK cells: EGF acts via MAPK, PLA(2), and COX1. J Am Soc Nephrol 13: 1981–1991.

Sauvant C, Holzinger H, Gekle M (2006). Prostaglandin E2 inhibits its own renal transport by downregulation of organic anion transporters rOAT1 and rOAT3. J Am Soc Nephrol 17: 46–53.

Schiffer R, Neis M, Holler D, Rodriguez F, Geier A, Gartung C *et al.* (2003). Active influx transport is mediated by members of the organic anion transporting polypeptide family in human epidermal keratinocytes. J Invest Dermatol 120: 285–291.

Schuster VL (2002). Prostaglandin transport. Prostaglandins Other Lipid Mediat 68–69: 633–647.

Seithel A, Eberl S, Singer K, Auge D, Heinkele G, Wolf NB *et al.* (2007). The influence of macrolide antibiotics on the uptake of organic anions and drugs mediated by OATP1B1 and OATP1B3. Drug Metab Dispos 35: 779–786.

Sekine T, Cha SH, Tsuda M, Apiwattanakul N, Nakajima N, Kanai Y *et al.* (1998). Identification of multispecific organic anion transporter 2 expressed predominantly in the liver. FEBS Lett 429: 179–182.

Seth P, Wu X, Huang W, Leibach FH, Ganapathy V (1999). Mutations in novel organic cation transporter (OCTN2), an organic cation/carnitine transporter, with differential effects on the organic cation transport function and the carnitine transport function. J Biol Chem 274: 33388–33392.

Shimizu M, Fuse K, Okudaira K, Nishigaki R, Maeda K, Kusuhara H *et al.* (2005). Contribution of OATP (organic anion-transporting polypeptide) family transporters to the hepatic uptake of fexofenadine in humans. Drug Metab Dispos 33: 1477–1481.

Shin HJ, Anzai N, Enomoto A, He X, Kim K, Endou H *et al.* (2007). Novel liver-specific organic anion transporter OAT7 that operates the exchange of sulfate conjugates for short chain fatty acid butyrate. Hepatology 45: 1046–1055.

Shirasaka Y, Kuraoka E, Spahn-Langguth H, Nakanishi T, Langguth P, Tamai I (2010). Species difference in the effect of grapefruit juice on intestinal absorption of talinolol between human and rat. J Pharmacol Exp Ther 332: 181–189.

Shitara Y, Itoh T, Sato H, Li AP, Sugiyama Y (2003). Inhibition of transporter-mediated hepatic uptake as a mechanism for drug-drug interaction between cerivastatin and cyclosporin A. J Pharmacol Exp Ther 304: 610–616.

Shu Y, Bello CL, Mangravite LM, Feng B, Giacomini KM (2001). Functional characteristics and steroid hormone-mediated regulation of an organic cation transporter in Madin-Darby canine kidney cells. J Pharmacol Exp Ther 299: 392–398.

Smith NF, Acharya MR, Desai N, Figg WD, Sparreboom A (2005). Identification of OATP1B3 as a high-affinity hepatocellular transporter of paclitaxel. Cancer Biol Ther 4: 815–818.

Srimaroeng C, Perry JL, Pritchard JB (2008). Physiology, structure, and regulation of the cloned organic anion transporters. Xenobiotica 38: 889–935.

Steckelbroeck S, Nassen A, Ugele B, Ludwig M, Watzka M, Reissinger A *et al*. (2004). Steroid sulfatase (STS) expression in the human temporal lobe: enzyme activity, mRNA expression and immunohistochemistry study. J Neurochem 89: 403–417.

St-Pierre MV, Hagenbuch B, Ugele B, Meier PJ, Stallmach T (2002). Characterization of an organic anion-transporting polypeptide (OATP-B) in human placenta. J Clin Endocrinol Metab 87: 1856–1863.

Su Y, Zhang X, Sinko PJ (2004). Human organic anion-transporting polypeptide OATP-A (SLC21A3) acts in concert with P-glycoprotein and multidrug resistance protein 2 in the vectorial transport of Saquinavir in Hep G2 cells. Mol Pharm 1: 49–56.

Sun W, Wu RR, van Poelje PD, Erion MD (2001). Isolation of a family of organic anion transporters from human liver and kidney. Biochem Biophys Res Commun 283: 417–422.

Suzuki T, Onogawa T, Asano N, Mizutamari H, Mikkaichi T, Tanemoto M *et al*. (2003). Identification and characterization of novel rat and human gonad specific organic anion transporters. Mol Endocrinol 17: 1203–1215.

Sweet DH, Wolff NA, Pritchard JB (1997). Expression cloning and characterization of ROAT1. The basolateral organic anion transporter in rat kidney. J Biol Chem 272: 30088–30095.

Sweet DH, Miller DS, Pritchard JB, Fujiwara Y, Beier DR, Nigam SK (2002). Impaired organic anion transport in kidney and choroid plexus of organic anion transporter 3 (Oat3 (Slc22a8)) knockout mice. J Biol Chem 277: 26934–26943.

Sykes D, Sweet DH, Lowes S, Nigam SK, Pritchard JB, Miller DS (2004). Organic anion transport in choroid plexus from wild-type and organic anion transporter 3 (Slc22a8)-null mice. Am J Physiol Renal Physiol 286: F972–F978.

Tachibana-Iimori R, Tabara Y, Kusuhara H, Kohara K, Kawamoto R, Nakura J *et al*. (2004). Effect of genetic polymorphism of OATP-C (SLCO1B1) on lipid-lowering response to HMG-CoA reductase inhibitors. Drug Metab Pharmacokinet 19: 375–380.

Takada T, Weiss HM, Kretz O, Gross G, Sugiyama Y (2004). Hepatic transport of PKI166, an epidermal growth factor receptor kinase inhibitor of the pyrrolo-pyrimidine class, and its main metabolite, ACU154. Drug Metab Dispos 32: 1272–1278.

Takeda M, Noshiro R, Onozato ML, Tojo A, Hasannejad H, Huang XL *et al*. (2004). Evidence for a role of human organic anion transporters in the muscular side effects of HMG-CoA reductase inhibitors. Eur J Pharmacol 483: 133–138.

Takeuchi K, Sugiura T, Umeda S, Matsubara K, Horikawa M, Nakamichi N *et al*. (2011). Pharmacokinetics and hepatic uptake of eltrombopag, a novel platelet-increasing agent. Drug Metab Dispos 39: 1088–1096.

Tamai I, Yabuuchi H, Nezu J, Sai Y, Oku A, Shimane M *et al*. (1997). Cloning and characterization of a novel human pH-dependent organic cation transporter, OCTN1. FEBS Lett 419: 107–111.

Tamai I, Nezu J, Uchino H, Sai Y, Oku A, Shimane M *et al*. (2000). Molecular identification and characterization of novel members of the human organic anion transporter (OATP) family. Biochem Biophys Res Commun 273: 251–260.

Tamai I, Nozawa T, Koshida M, Nezu J, Sai Y, Tsuji A (2001). Functional characterization of human organic anion transporting polypeptide B (OATP-B) in comparison with liver-specific OATP-C. Pharm Res 18: 1262–1269.

Tirona RG, Leake BF, Wolkoff AW, Kim RB (2003). Human organic anion transporting polypeptide-C (SLC21A6) is a major determinant of rifampin-mediated pregnane X receptor activation. J Pharmacol Exp Ther 304: 223–228.

Tokuhiro S, Yamada R, Chang X, Suzuki A, Kochi Y, Sawada T *et al*. (2003). An intronic SNP in a RUNX1 binding site of SLC22A4, encoding an organic cation transporter, is associated with rheumatoid arthritis. Nat Genet 35: 341–348.

Treiber A, Schneiter R, Hausler S, Stieger B (2007). Bosentan is a substrate of human OATP1B1 and OATP1B3: inhibition of hepatic uptake as the common mechanism of its interactions with cyclosporin A, rifampicin, and sildenafil. Drug Metab Dispos 35: 1400–1407.

Tsigelny IF, Kovalskyy D, Kouznetsova VL, Balinskyi O, Sharikov Y, Bhatnagar V *et al*. (2011). Conformational changes of the multispecific transporter Organic Anion Transporter 1 (OAT1/SLC22A6) suggests a molecular mechanism for initial stages of drug and metabolite transport. Cell Biochem Biophys 61: 251–259.

Tsuda-Tsukimoto M, Maeda T, Iwanaga T, Kume T, Tamai I (2006). Characterization of hepatobiliary transport systems of a novel alpha4beta1/alpha4beta7 dual antagonist, TR-14035. Pharm Res 23: 2646–2656.

Ugele B, St-Pierre MV, Pihusch M, Bahn A, Hantschmann P (2003). Characterization and identification of steroid sulfate transporters of human placenta. Am J Physiol Endocrinol Metab 284: E390–E398.

Urakami Y, Akazawa M, Saito H, Okuda M, Inui K (2002). cDNA cloning, functional characterization, and tissue distribution of an alternatively spliced variant of organic cation transporter hOCT2 predominantly expressed in the human kidney. J Am Soc Nephrol 13: 1703–1710.

Urban TJ, Sebro R, Hurowitz EH, Leabman MK, Badagnani I, Lagpacan LL *et al*. (2006). Functional genomics of membrane transporters in human populations. Genome Res 16: 223–230.

Urban TJ, Yang C, Lagpacan LL, Brown C, Castro RA, Taylor TR *et al*. (2007). Functional effects of protein sequence polymorphisms in the organic cation/ergothioneine transporter OCTN1 (SLC22A4). Pharmacogenet Genomics 17: 773–782.

Vaidyanathan S, Camenisch G, Schuetz H, Reynolds C, Yeh CM, Bizot MN *et al*. (2008). Pharmacokinetics of the oral direct renin inhibitor aliskiren in combination with digoxin, atorvastatin, and ketoconazole in healthy subjects: the role of P-glycoprotein in the disposition of aliskiren. J Clin Pharmacol 48: 1323–1338.

VanWert AL, Gionfriddo MR, Sweet DH (2010). Organic anion transporters: discovery, pharmacology, regulation and roles in pathophysiology. Biopharm Drug Dispos 31: 1–71.

Varma MV, Rotter CJ, Chupka J, Whalen KM, Duignan DB, Feng B *et al.* (2011). pH-sensitive interaction of HMG-CoA reductase inhibitors (statins) with organic anion transporting polypeptide 2B1. Mol Pharm 8: 1303–1313.

Vavricka SR, Van Montfoort J, Ha HR, Meier PJ, Fattinger K (2002). Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver. Hepatology 36: 164–172.

Vavricka SR, Jung D, Fried M, Grutzner U, Meier PJ, Kullak-Ublick GA (2004). The human organic anion transporting polypeptide 8 (SLCO1B3) gene is transcriptionally repressed by hepatocyte nuclear factor 3beta in hepatocellular carcinoma. J Hepatol 40: 212–218.

Volk C, Gorboulev V, Kotzsch A, Muller TD, Koepsell H (2009). Five amino acids in the innermost cavity of the substrate binding cleft of organic cation transporter 1 interact with extracellular and intracellular corticosterone. Mol Pharmacol 76: 275–289.

Vormfelde SV, Toliat MR, Schirmer M, Meineke I, Nurnberg P, Brockmoller J (2008). The polymorphisms Asn130Asp and Val174Ala in OATP1B1 and the CYP2C9 allele *3 independently affect torsemide pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 83: 815–817.

Walker AL, Franke RM, Sparreboom A, Ware RE (2011). Transcellular movement of hydroxyurea is mediated by specific solute carrier transporters. Exp Hematol 39: 446–456.

Wang P, Wang JJ, Xiao Y, Murray JW, Novikoff PM, Angeletti RH *et al.* (2005a). Interaction with PDZK1 is required for expression of organic anion transporting protein 1A1 on the hepatocyte surface. J Biol Chem 280: 30143–30149.

Wang P, Hata S, Xiao Y, Murray JW, Wolkoff AW (2008). Topological assessment of oatp1a1: a 12-transmembrane domain integral membrane protein with three N-linked carbohydrate chains. Am J Physiol Gastrointest Liver Physiol 294: G1052–G1059.

Wang X, Wolkoff AW, Morris ME (2005b). Flavonoids as a novel class of human organic anion-transporting polypeptide OATP1B1 (OATP-C) modulators. Drug Metab Dispos 33: 1666–1672.

Weaver YM, Hagenbuch B (2010). Several conserved positively charged amino acids in OATP1B1 are involved in binding or translocation of different substrates. J Membr Biol 236: 279–290.

Wen J, Xiong Y (2010). OATP1B1 388A>G polymorphism and pharmacokinetics of pitavastatin in Chinese healthy volunteers. J Clin Pharm Ther 35: 99–104.

Werner D, Werner U, Meybaum A, Schmidt B, Umbreen S, Grosch A *et al.* (2008). Determinants of steady-state torasemide pharmacokinetics: impact of pharmacogenetic factors, gender and angiotensin II receptor blockers. Clin Pharmacokinet 47: 323–332.

Wlcek K, Svoboda M, Riha J, Zakaria S, Olszewski U, Dvorak Z *et al.* (2011). The analysis of organic anion transporting polypeptide (OATP) mRNA and protein patterns in primary and metastatic liver cancer. Cancer Biol Ther 11: 801–811.

Wojtal KA, Eloranta JJ, Hruz P, Gutmann H, Drewe J, Staumann A *et al.* (2009). Changes in mRNA expression levels of solute carrier transporters in inflammatory bowel disease patients. Drug Metab Dispos 37: 1871–1877.

Wolff NA, Thies K, Kuhnke N, Reid G, Friedrich B, Lang F *et al.* (2003). Protein kinase C activation downregulates human organic anion transporter 1-mediated transport through carrier internalization. J Am Soc Nephrol 14: 1959–1968.

Wood M, Ananthanarayanan M, Jones B, Wooton-Kee R, Hoffman T, Suchy FJ *et al.* (2005). Hormonal regulation of hepatic organic anion transporting polypeptides. Mol Pharmacol 68: 218–225.

Wu X, Prasad PD, Leibach FH, Ganapathy V (1998). cDNA sequence, transport function, and genomic organization of human OCTN2, a new member of the organic cation transporter family. Biochem Biophys Res Commun 246: 589–595.

Wu X, Huang W, Ganapathy ME, Wang H, Kekuda R, Conway SJ *et al.* (2000). Structure, function, and regional distribution of the organic cation transporter OCT3 in the kidney. Am J Physiol Renal Physiol 279: F449–F458.

Yamada A, Maeda K, Kamiyama E, Sugiyama D, Kondo T, Shiroyanagi Y *et al.* (2007). Multiple human isoforms of drug transporters contribute to the hepatic and renal transport of olmesartan, a selective antagonist of the angiotensin II AT1-receptor. Drug Metab Dispos 35: 2166–2176.

Yamaguchi H, Okada M, Akitaya S, Ohara H, Mikkaichi T, Ishikawa H *et al.* (2006). Transport of fluorescent chenodeoxycholic acid via the human organic anion transporters OATP1B1 and OATP1B3. J Lipid Res 47: 1196–1202.

Yamaguchi H, Sugie M, Okada M, Mikkaichi T, Toyohara T, Abe T *et al.* (2010). Transport of estrone 3-sulfate mediated by organic anion transporter OATP4C1: estrone 3-sulfate binds to the different recognition site for digoxin in OATP4C1. Drug Metab Pharmacokinet 25: 314–317.

Yamakawa Y, Hamada A, Shuto T, Yuki M, Uchida T, Kai H *et al.* (2011). Pharmacokinetic impact of SLCO1A2 polymorphisms on imatinib disposition in patients with chronic myeloid leukemia. Clin Pharmacol Ther 90: 157–163.

Yamashiro W, Maeda K, Hirouchi M, Adachi Y, Hu Z, Sugiyama Y (2006). Involvement of transporters in the hepatic uptake and biliary excretion of valsartan, a selective antagonist of the angiotensin II AT1-receptor, in humans. Drug Metab Dispos 34: 1247–1254.

Youngblood GL, Sweet DH (2004). Identification and functional assessment of the novel murine organic anion transporter Oat5 (Slc22a19) expressed in kidney. Am J Physiol Renal Physiol 287: F236–F244.

Zhang L, Dresser MJ, Gray AT, Yost SC, Terashita S, Giacomini KM (1997). Cloning and functional expression of a human liver organic cation transporter. Mol Pharmacol 51: 913–921.

Zhang Q, Hong M, Duan P, Pan Z, Ma J, You G (2008). Organic anion transporter OAT1 undergoes constitutive and protein kinase C-regulated trafficking through a dynamin- and clathrin-dependent pathway. J Biol Chem 283: 32570–32579.

Zhang W, He YJ, Han CT, Liu ZQ, Li Q, Fan L *et al.* (2006). Effect of SLCO1B1 genetic polymorphism on the pharmacokinetics of nateglinide. Br J Clin Pharmacol 62: 567–572.

Zhou F, Zhu L, Cui PH, Church WB, Murray M (2010). Functional characterization of nonsynonymous single nucleotide polymorphisms in the human organic anion transporter 4 (hOAT4). Br J Pharmacol 159: 419–427.

Zwart R, Verhaagh S, Buitelaar M, Popp-Snijders C, Barlow DP (2001). Impaired activity of the extraneuronal monoamine transporter system known as uptake-2 in Orct3/Slc22a3-deficient mice. Mol Cell Biol 21: 4188–4196.