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THE *SLCO* (FORMER *SLC21*) SUPERFAMILY OF TRANSPORTERS

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Abstract

The members of the organic anion transporting polypeptide superfamily (OATPs) are classified within the *SLCO* solute carrier family. All functionally well characterized members are predicted to have 12 transmembrane domains and are sodium-independent transport systems that mediate the transport of a broad range of endo- as well as xenobiotics. Substrates are mainly amphipathic organic anions with a molecular weight of more than 300 Da, but some of the known transported substrates are also neutral or even positively charged. Among the well characterized substrates are numerous drugs including statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antibiotics, antihistaminics, antihypertensives and anticancer drugs. Based on their amino acid sequence identities, the different OATPs cluster into families (in general with more than 40% amino acid sequence identity) and subfamilies (more than 60% amino acid identity). With the sequencing of genomes from different species and the computerized prediction of encoded proteins more than 300 OATPs can be found in the databases, however only a fraction of them have been identified in humans, rodents, and some additional species important for pharmaceutical research like the rhesus monkey (*Macaca mulatta*), the dog (*Canis lupus familiaris*) and the pig (*Sus scrofa*). These OATPs form 6 families (OATP1–OATP6) and 13 subfamilies. In this review we try to summarize what is currently known about OATPs with respect to endogenous substrates, tissue distribution, transport mechanisms, regulation of expression, structure-function relationship and mutations and polymorphisms.

Keywords

SLCO; SLC21; OATP; bile acid; bilirubin; steroid conjugates

1. Introduction

Cells continuously need to take up nutrients as well as signaling molecules and to release metabolic endproducts for disposal. Most such substances, even if very lipopophilic, are not

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able to diffuse across plasma membranes and consequently need transport proteins to cross the cell boundaries. This is exemplified by cholesterol, which takes advantage of (transport) proteins to cross plasma membranes. For example, cholesterol absorption in the small intestine is mediated, at least in part, by the Niemann-Pick 1-like 1 (NPC1L1) protein (Lecerf and de Lorgeril, 2011), which is susceptible to inhibition by the drug ezetimibe. Else, release of cholesterol from the canalicular membrane of hepatocytes into bile is facilitated by the heterodimeric ATP-binding-cassette (ABC) transporter ABCG5/ABCG8 (Hazard and Patel, 2007). Bilirubin, the metabolic endproduct of the breakdown of heme, is practically water insoluble and has for a long time been assumed to enter hepatocytes by simple diffusion. While the issue of transmembrane movement of bilirubin was controversially discussed (diffusion across lipid bilayer versus involvement of protein(s) (Ostrow et al., 1994)), several groups have now provided solid evidence for the involvement of organic anion transporting polypeptides (OATPs) in bilirubin uptake into hepatocytes (see below). From these prototypic results, it is safe to extrapolate that most substances and even highly non-polar or lipophilic compounds require transmembrane transport proteins to be moved between the extracellular space and the cytoplasm. The importance of transport proteins in the disposition of drugs is also gaining wide acceptance (Dobson et al., 2009; Fenner et al., 2012). The solute carrier superfamily (SLC) covers hundreds of proteins mediating the plasma membrane crossing of small molecules or solutes of various degrees of hydrophilicity and lipophilicity (Hediger et al., 2004). Among the SLC superfamily members, OATPs play a prominent role in transporting endo- as well as xenobiotics including numerous drugs across plasma membranes.

In recent years, considerable progress has been made in identifying endogenous substrates of OATPs, in elucidating the roles OATPs play in drug disposition and transport of toxins, as well as in the characterization of genetic variants. In this overview on the current status of OATP research, we do not attempt to summarize the so far characterized drugs and xenobiotics, which have been identified as OATP substrates as this information can be found in several recent reviews (Fahrmayr et al., 2010; Giacomini et al., 2010; Hagenbuch and Gui, 2008; Kalliokoski and Niemi, 2009; Konig, 2011; Kusuhara and Sugiyama, 2009; Roth et al., 2012).

2. Phylogenesis of OATPs

The first OATP, rat OATP1A1 (originally called Oatp) was isolated in 1994 using expression cloning (Jacquemin et al., 1994) and the first human OATP, OATP1A2 (originally called OATP) was isolated a year later by hybridization screening (Kullak-Ublick et al., 1995). In the following years several additional OATPs from humans and rodents were identified and characterized and we know today that there are eleven OATPs in humans. In 2004, an amino acid sequence based classification and nomenclature system was introduced and approved by the HUGO Gene Nomenclature Committee (Hagenbuch and Meier, 2004). This classification system allows us to name any newly identified OATP with a unique name if it is a unique member of the family or with the name of its already known orthologue. The general rules for this classification system are that proteins with more than 40 % identity belong to the same family while proteins with more than 60 % identity belong to the same subfamily (Hagenbuch and Meier, 2004). On this basis, the human and rodent OATPs form 6 families (OATP1, OATP2, OATP3, OATP4, OATP5, and OATP6) and each family can have subfamilies (e.g. OATP1A, OATP1B, OATP1C). Within these subfamilies the individual OATPs are numbered according to the chronology of their identification and if there is already an orthologue known they are given the same number. The symbols for human and rodent proteins are always given in capitals (e.g. OATP1A2). The corresponding gene symbols begin with *SLCO* for human and *Slco* for rodents and have the same family number, subfamily letter and chronological number as the protein symbol (e.g. *SLCO1A2*

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for OATP1A2, *Slco1a1* for mouse OATP1A1). In contrast to protein symbols, gene symbols are always given in italics. However, it turned out that the 40% and 60% are not absolute numbers because e.g. *X. laevis* oatp1a2 has only 48% amino acid sequence identity to human OATP1A2 but based on phylogenetic analysis clearly is an orthologue of human OATP1A2 and does not belong to the 1B or 1C subfamily. Thus, newly identified OATPs should be carefully classified before a new name is assigned. The currently approved human members of the *SLCO* superfamily are summarized in Table 1. In the transporter classification database maintained by Milton Saier OATPs are found in the "The Organo Anion Transporter (OAT) Family" 2.A.60 (Saier et al., 1999).

Compared to the 52 members of the OATP superfamily reported in 2004, today more than 300 members have been identified and/or predicted from over 40 species. Figure 1 shows the phylogenetic tree of 70 OATPs from human, monkey, dog, pig, rat and mouse. The OATP1 family is the largest with 27 members, followed by the OATP6 family. In both families gene duplications in rodents resulted in several genes/proteins for rats and mice as compared to humans, while in subfamily OATP1B a gene duplication resulted in two genes/proteins for humans and monkeys (OATP1B1 and OATP1B3 as compared to rodent OATP1B2 or OATP1B4). The OATP3 family has the most conserved members with amino acid sequence identities between 94 and 99 % while the OATP6 family is the most diverged. It is interesting to note that no OATP homologues have been found in bacteria or yeast suggesting that OATPs are specific to the animal kingdom.

3. Endogenous substrates of OATPs

Rat OATP1A1, the founding member of the *SLCO* superfamily of organic anion transporters, was isolated with an expression-cloning approach using the anion bromosulphophthalein as substrate (Hagenbuch and Meier, 2004; Jacquemin et al., 1994). Functional characterization of rat OATP1A1 in heterologous expression systems revealed that it can transport bile acids (e.g. cholate) and bile acid conjugates (e.g. taurocholate) (Eckhardt et al., 1999; Jacquemin et al., 1994) in a sodium-independent way with a preference for unconjugated over conjugated bile acids (Meier et al., 1997). Hence, bile salts can be considered the first identified endogenous OATP substrates. OATP1A2 can also transport unconjugated and conjugated bile acids (Table 2) (Kullak-Ublick et al., 1995). In addition, OATP1A2 can also transport dehydroepiandrosterone sulfate, a precursor for the synthesis of steroid hormones in many organs (Kullak-Ublick et al., 1998). Later, OATP1B1 (Abe et al., 1999), OATP1A2 and OATP4A1 (Fujiwara et al., 2001), OATP1C1 (Pizzagalli et al., 2002) and OATP3A1_v1 (Huber et al., 2007) were also found to transport thyroid hormones (Jansen et al., 2005). Additional endogenous OATP substrates are listed in Table 2.

To date, no severe human diseases related to bile salt homeostasis, to thyroid hormone biogenesis and metabolism or to steroid hormone synthesis have been linked to mutations in genes coding for various OATPs. Consequently, generation of *Slco* knockout mice was required to more directly prove and study the physiologic roles of OATPs in handling of endogenous substrates. Mammalian hepatocytes express two (humans) or three (rodents) different OATPs, which are members of the *SLCO* families 1A and 1B, respectively (Hagenbuch and Meier, 2004). The genes encoding these OATPs are clustered on human chromosome 12 and on mouse chromosome 6. Mice with a disrupted locus for *Slco1a/1b* subfamily members are vital and display no obvious disease phenotype, but have mildly elevated serum bile salt levels, supporting a role for OATPs in the hepatic uptake of bile salts (van de Steeg et al., 2010). Importantly, analysis of the bile salt pattern in the serum of these knock-out animals revealed unchanged levels of conjugated bile acids compared to the parent mouse strain but 13-fold elevated serum levels of unconjugated bile acids (van de

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Steeg et al., 2010). These findings were confirmed by another research group, which also reported elevated unconjugated bile acids but normal conjugated bile acids in mice with a disrupted *Slco1b2* gene (Csanaky et al., 2011). This latter finding is remarkable, as in general OATPs have overlapping substrate specificities (Table 2) and all rat orthologues of the mouse liver OATPs have been shown to transport bile salts in heterologous expression systems (Leuthold et al., 2009). Hence, *in vivo*, despite the coexpression of several OATPs in the same cells such as hepatocytes, a specific OATP may be required for the transport of a given substrate. If such an OATP is nonfunctional like in a knock-out mouse model or a human disease, the other OATPs do not seem to be capable in all instances to fully compensate for the loss of such transport activity. After cloning of the human hepatocellular OATPs, two groups reported that OATP1B1 and OATP1B3 could mediate the transport of unconjugated bilirubin (Briz et al., 2003; Cui et al., 2001)(Table 2). Serum analysis of the knock-out mice lacking the OATP1A/1B family members revealed hyperbilirubinemia (van de Steeg et al., 2010). These animals display more than 40-fold elevated serum levels of total bilirubin compared to wild-type mice. About 95 % of the increased bilirubin was due to bilirubin mono- and bis-glucuronide, but also unconjugated bilirubin was elevated about 2.5-fold. Hence, this observation supports the concept that hepatocellular OATPs are involved in the transport of unconjugated and conjugated bilirubin into hepatocytes. Again, mice with an inactivated *Slco1b2* gene also have a mild hyperbilirubinemia (Csanaky et al., 2011; Zaher et al., 2008) suggesting that in mice, OATP1B2 plays a major role in bilirubin handling. The impact of the thyroid hormone transporter OATP1C1 on the disposition of thyroid hormones has lately been studied in knock-out mice. These animals have no alterations in their serum levels of thyroid hormones and their metabolites, but display reduced thyroxin levels and altered expression of deiodinases in their brains (Mayerl et al., 2012). These examples illustrate that knock-out mice are a powerful tool in the identification of endogenous or physiologic substrates of OATPs as well as in the explanation of human diseases with unknown etiology.

4. Tissue distribution

The expression of OATPs has been studied both at the mRNA and the protein level. In general, OATPs have been detected in essentially every organ in epithelial or endothelial cells. Some OATPs have a restricted expression and are therefore assumed to be organ specific, while others are expressed ubiquitously. Examples for such a restricted expression are the two human transporters OATP1B1 and OATP1B3 that are considered to be liver-specific (Roth et al., 2012) or the brain-specific OATP1C1 characterized in the rat (Sugiyama et al., 2003). Examples of ubiquitously expressed OATPs are the human OATP2A1, OATP3A1 and OATP4A1 whose mRNA was found in essentially all the tissues analyzed (Roth et al., 2012).

In humans, the OATP1 family has four members, OATP1A2, OATP1B1, OATP1B3 and OATP1C1 (Figure 1). Messenger RNA for *SLCO1A2* encoding OATP1A2 has been detected in numerous tissues including brain, kidney, liver, lung, testes, placenta and prostate (Roth et al., 2012). At the protein level, OATP1A2 has been shown to be expressed in endothelial cells of the blood-brain barrier (Bronger et al., 2005; Gao et al., 2000; Lee et al., 2005), at the brush-border side in the distal nephron (Lee et al., 2005), in cholangiocytes (Lee et al., 2005), in the pars plana of the ciliary body epithelium (Gao et al., 2005), and in syncytiotrophoblasts (Loubiere et al., 2010) (Figure 2). As already mentioned above, OATP1B1 and OATP1B3 are considered to be liver specific transporters (Roth et al., 2012). Under normal conditions they are expressed at the sinusoidal membrane of human hepatocytes with OATP1B3 expression being stronger around the central vein than around the portal vein (Konig et al., 2000a). In a recent study protein expression of OATP1B1 and OATP1B3 was measured using a multiplex UPLC-MRM MS method and the results

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demonstrated that both proteins were found in equal amounts in membrane fractions isolated from human hepatocytes (Ji et al., 2012). *SLCO1B3* mRNA and OATP1B3 protein expression was also documented in several cancers (reviewed in (Obaidat et al., 2012)) and the high level of mRNA could be due to an alternatively spliced variant (Nagai et al., 2012). The last member in the OATP1 family, OATP1C1, is expressed in glial cells throughout the hypothalamus (Alkemade et al., 2011), at the blood-brain barrier, in the choroid plexus (Roberts et al., 2008), in Leydig cells of testes (Pizzagalli et al., 2002), and in the pars plana of the ciliary epithelium (Gao et al., 2005) (Figure 2).

The prostaglandin transporter, OATP2A1, is one of the ubiquitously expressed OATPs. *SLCO2A1* mRNA has been detected in almost every tissue tested (Roth et al., 2012). At the protein level, human OATP2A1 has been shown to be expressed in retinal epithelial cells and in epithelial and endothelial cell layers of different eye tissues including the ciliary body (Kraft et al., 2010) (Figure 2), in the endometrium (Kang et al., 2005), in neurons, astrocytes, and microglia (Choi et al., 2008), as well as in the parietal cells of the gastric corpus and the pyloric glands of the antrum (Mandery et al., 2010). The second transporter in the OATP2 family, OATP2B1 encoded by the *SLCO2B1 gene,* is also abundantly expressed in multiple organs at the mRNA level (Tamai et al., 2000). At the protein level OATP2B1 was detected at the sinusoidal membrane of hepatocytes (Kullak-Ublick et al., 2001), at the basolateral membrane of syncytiotrophoblasts (St Pierre et al., 2002), at the brush-border membrane in the small intestine (Kobayashi et al., 2003), in keratinocytes (Schiffer et al., 2003), in the mammary gland (Pizzagalli et al., 2003), at the luminal membrane of endothelial cells of the blood-brain barrier (Bronger et al., 2005), in the pars plicata and pars plana of the ciliary body (Gao et al., 2005; Kraft et al., 2010), in endothelial cells in the heart (Grube et al., 2006b), in human platelets (Niessen et al., 2009), and in the skeletal muscle (Knauer et al., 2010) (Figure 2).

SLCO3A1 mRNA levels were found in numerous tissues with highest levels in testes, brain, heart and lung (Huber et al., 2007). At the protein level, OATP3A1 is localized in the ciliary body epithelium (Gao et al., 2005), testes, in the choroid plexus, in neurons in the frontal cortex (Huber et al., 2007) and at the plasma membrane of epithelial cells of the lactiferous ducts in normal breast tissue (Kindla et al., 2011). In testes and in the brain two splice variants were shown to be expressed in a cell type-specific pattern (Huber et al., 2007). In testes, OATP3A1_v1 is expressed in germ cells while OATP3A1_v2 is expressed in Sertoli cells. In the choroid plexus variant 1 is expressed at the basolateral membrane while variant 2 is expressed at the apical and sub-apical membrane. In the frontal cortex, OATP3A1_v1 is localized in neuroglial cells of the grey matter and OATP3A1_v2 in cell bodies and axons of the neurons (Huber et al., 2007) (Figure 2).

SLCO4A1 mRNA was found in numerous tissues including the heart, placenta, lung, liver, skeletal muscle, kidney and pancreas (Fujiwara et al., 2001; Tamai et al., 2000). At the protein level OATP4A1 was detected in the ciliary body epithelium (Gao et al., 2005) and in syncytiotrophoblasts (Loubiere et al., 2010; Sato et al., 2003) (Figure 2). Based on northern blot analysis, OATP4C1 was predicted to be a kidney-specific transporter (Mikkaichi et al., 2004) but the human protein has not been localized yet. In addition, microarray studies suggest that mRNA from the *SLCO4C1* gene is also detectable in the liver (Bleasby et al., 2006).

SLCO5A1 mRNA was reported in fetal brain, prostate, skeletal muscle and thymus (Bleasby et al., 2006). At the protein level, OATP5A1 was detected at the plasma membrane of epithelial cells of the lactiferous ducts in normal breast tissue (Kindla et al., 2011).

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The expression of *SLCO6A1* mRNA was detected in testes, spleen, brain and placenta (Lee et al., 2004; Suzuki et al., 2003). The expression of the different OATPs in various tumors has recently been summarized (Obaidat et al., 2012).

5. Transport Mechanisms of OATPs

The mechanism(s) by which OATPs transport is(are) not fully understood, but OATPs are believed to act as organic anion exchangers (Hagenbuch and Gui, 2008). In 1997 bicarbonate was identified as the first counterion in experiments with rat OATP1A1 expressed in HeLa cells (Satlin et al., 1997). Additional experiments demonstrated that reduced glutathione and glutathione conjugates could act as counter ions. Transport of taurocholate and leukotriene C_4 mediated by rat OATP1A1 was trans-stimulated by glutathione (Li et al., 1998), while taurocholate transport by rat OATP1A4, but not by rat OATP1A1, was also trans-stimulated by the efflux of a conjugate of glutathione (Li et al., 2000), suggesting that no general transport mechanism exists for OATPs. OATP1B3 mediated cotransport of glutathione (Briz et al., 2006) could not be confirmed (Mahagita et al., 2007) and such a transport mechanism would be hard to reconcile for the uptake of organic anions into hepatocytes given the rather steep in-to-out glutathione gradient across the hepatocyte plasma membrane.

Uptake by various OATPs has been shown to be stimulated by a low extracellular pH, such as for example transport mediated by OATP2B1, which in expressed among other organs in the small intestine (Kobayashi et al., 2003). The influence of extracellular pH was tested with 13 different OATPs, out of which 12 were stimulated by a low extracellular pH. This stimulation was found to be due to a lowered K_m value at pH 6.5 compared to pH 7.4 demonstrating increased affinity of the transport process at low pH. Mutagenesis of a highly conserved histidine in the third transmembrane domain to a glutamine abolished the pH dependency of rat OATP1A1. In contrast, replacing the glutamine found at this conserved position in the pH-insensitive OATB1C1 with a histidine rendered OATP1C1 pH sensitive (Leuthold et al., 2009). Hence, an acidic microclimate like in the intestine or lowering the pH in the microclimate adjacent to OATPs by an active Na^+/H^+-exchanger could stimulate their transport compared to uptake at neutral pH.

In addition to this modulation of transport at low pH, i.e. at higher proton concentrations, a similar modulation of OATP mediated substrate uptake by another substrate has also been observed. This was first reported for rat OATP1A4, where estradiol-17β-glucuronide stimulated transport of taurocholate but not of digoxin (Sugiyama et al., 2002). A similar stimulation has also been observed for OATP2B1, where prostaglandins A1 and A2 stimulated the transport of dehydroepiandrosteron sulfate (Pizzagalli et al., 2003). Interestingly, OATP2B1-mediated transport of dehydroepiandrosterone and estrone-3-sulfate was stimulated at low progesterone concentrations, while at higher concentrations of progesterone as modulator transport activity returned to control values (Grube et al., 2006a). In the same study, testosterone and mifepristone inhibited rather than stimulated transport activity of OATP2B1. Dietary and herbal components have also been documented to stimulate OATP-mediated transport, such as rutin, which stimulated OATP1B1-mediated dehydroepiandrosterone sulfate uptake (Wang et al., 2005) and green tea extracts or the green tea epigallocatechin gallate, which stimulated OATP1B3-mediated uptake of estrone-3-sulfate (Roth et al., 2011). Finally, OATP1B3, but not OATP1B1-mediated transport of estradiol-17β-glucuronide was stimulated by clotrimazole (Gui et al., 2008). However, such a stimulation was not observed for estrone-3-sulfate transport, which was not affected by clotimazole or for fluo-3 transport, which was inhibited. Several additional drugs tested in this study did not stimulate either OATP1B1 or OATP1B3. These results clearly show that OATPs have more than one substrate binding site, which may or may not interact

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with each other. This has been formally demonstrated with kinetic experiments that revealed a high and a low affinity component for estrone-3-sulfate uptake for OATP1B1 (Gui and Hagenbuch, 2009; Noe et al., 2007; Tamai et al., 2001). In summary, the transport mechanism of OATPs is complex, may vary for the same transporter for different substrates and clearly more work is needed to elucidate it in detail.

Understanding the exact transport mechanisms of OATPs is highly relevant as depending on the transport mechanism, OATPs may or may not be able to concentrate a substrate within cells over the respective extracellular concentration, like for example drugs in hepatocytes. For illustration, the concentration of the antidiabetic drug glibenclamide is 50 times higher in rat livers than in plasma (Kellner et al., 1969). While glibenclamide has been shown to be transported by OATP2B1 (Fuchikami et al., 2006), for OATP1B1 and OATP1B3 only inhibition by glibenclamide, but not direct uptake, has been demonstrated (Bednarczyk, 2010). We would like to emphasize that although such inhibition indicates that glibenclamide could be a substrate of OATP1B1 and/or OATT1B3 it does not necessarily imply that it is a substrate. This has recently been worked out for the liver function test marker indocyanine green, which is a potent inhibitor of all three hepatocellular OATPs and of the sodium taurocholate cotransporting polypeptide NTCP, but is only transported by NTCP and OATP1B3 (de Graaf et al., 2011).

6. Regulation of expression and modulation of function

Regulation of OATP expression has been documented at the transcriptional as well as at the post-translational level. Early studies demonstrated that expression of the liver specific OATP1B1 and OATP1B3 was controlled by the liver enriched hepatocyte nuclear factor 1α (HNF1α) (Jung et al., 2001). In hepatocellular carcinoma (HCC), expression of OATP1B3 was shown to be decreased while expression of OATP1B1 was normal at the mRNA level or slightly decreased at the protein level (Cui et al., 2003; Vavricka et al., 2004). It was also shown that HNF3β, which was overexpressed in HCC, could repress transcriptional expression of OATP1B3 but not of OATP1B1, potentially explaining the selective down-regulation of OATP1B3 in HCC (Vavricka et al., 2004). It is interesting to note that in ovarian cancer, but not in healthy ovarian tissue, expression of the liver specific OATP1B1 and OATP1B3 was reported (Svoboda et al., 2011). In addition several transcription factors in the family of the nuclear receptors have been shown to regulate OATP expression. Studies in breast carcinoma and breast cancer cell lines demonstrated a positive correlation between human PXR and OATP1A2 expression (Miki et al., 2006). This correlation was confirmed and a direct effect of PXR activity on OATP1A2 expression could be demonstrated (Meyer zu Schwabedissen et al., 2008). The same study also confirmed that the *SLCO1A2* promoter could be activated by the constitutive androstane receptor (CAR) (Meyer zu Schwabedissen et al., 2008). Using isolated human hepatocytes it was shown that treatment with the prototypic activator of the aryl hydrocarbon receptor (AhR) 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and with the CAR activator phenobarbital resulted in a decreased expression of OATP1B3 and OATP2B1 (Jigorel et al., 2006). The promoter of human *SLCO4C1* was also activated via AhR by 3-methylcholanthrene and by fluvastatin (Suzuki et al., 2011). Oltipraz, which activates NFE2-related factor 2 (Nrf2), also down-regulated OATP1B3, while the PXR agonist rifampicin led to an increase of OATP1B1 (Suzuki et al., 2011). Furthermore, OATP1B1 was shown to be regulated by the liver receptor α (LXRα) and by the farnesoid X receptor (FXR) (Meyer Zu Schwabedissen et al., 2010) and earlier it was also shown that OATP1B3 is under the control of FXR (Jung et al., 2002). In addition to these studies there are many other reports that show that OATP expression is influenced by different growth factors, cytokines and chemicals. Hepatocyte growth factor (HGF) down-regulated *SLCO1B1* and *SLCO2B1* mRNA and protein while mRNA for *SLCO1B3* was not affected (Le Vee et al., 2009). Similarly, down-regulation of

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SLCO1B1, *SLCO1B3* and *SLCO2B1* mRNA as well as OATP1B1 at the protein level was shown by interleukin 1β (Le Vee et al., 2008).

Post-translational regulation was demonstrated for OATP2B1. Protein kinase C activation by a phorbol ester resulted in increased phosphorylation of OATP2B1 with a decrease in maximal transport rate suggesting a rapid internalization of the transporter (Kock et al., 2010).

All these regulations at the transcriptional and post-translational levels could lead to increased or decreased OATP-mediated uptake. However, as outlined above, modulation of OATP-mediated transport could also be due to direct effects of substances, e.g. by acting from the cis-side either as inhibitors or as stimulators of substrate transport. Furthermore, several of these modulators have been shown to act in a substrate-dependent way, making predictions of potential interactions more complicated. For example, rifampicin at 10 μM had no effect on OATP1B1-mediated uptake of bromosulfophthalein (BSP) (Vavricka et al., 2002) but inhibited estradiol-17β-glucuronide uptake by 90 % (Tirona et al., 2003). In another study, 100 μM gemfibrozil inhibited OATP1B1-mediated uptake of taurocholate, fluvastatin and simvastatin by about 60 % but had no effect on the uptake of estrone-3-sulfate or troglitazone-sulfate (Noe et al., 2007). Clotrimazole, epigallocatechin gallate, diclofenac and ibuprofen are among the chemicals that have been shown to have stimulatory, inhibitory or no effects on OATP-mediated transport in a substrate-dependent way (Gui et al., 2008; Kindla et al., 2011; Roth et al., 2011). Thus, because the molecular mechanisms of these modulations are not known yet it is crucial to test more than just a single OATP substrate when screening for potential interactions, e.g. to predict pharmacokinetic interactions during drug development.

7. Structure function relationship

Based on hydrophobicity analyses, experimental data available from rat OATP1A1 (Jacquemin et al., 1994; Wang et al., 2008) and homology modeling, OATPs are 12 transmembrane domain proteins with the amino- and the C-terminal ends located at the cytoplasmic side of the membrane (Figure 3A). Because so far no crystal structure data are available, homology modeling was used to predict a putative three-dimensional model (Figure 3B). Furthermore, several groups have used chimeric approaches combined with site-directed mutagenesis and homology modeling to investigate what regions or what amino acids would be important for OATP function. Based on such studies it became clear that cysteine residues in the large extracellular loop 5 are involved in disulfide bonds and are required for proper surface expression of OATP2B1 (Hanggi et al., 2006) (Figure 3A). Transmembrane domains 1, 8, 9 and 10 as well as extracellular loop 6 have been shown to be important for OATP1B1 and OATP1B3 substrate transport (Degorter et al., 2012; Gui and Hagenbuch, 2008, 2009; Miyagawa et al., 2009). Furthermore, site-directed mutagenesis of conserved positively charged amino acids identified several residues in transmembrane domains 1, 7 and 10 that affect substrate transport in OATP1B1 and OATP1B3 (Glaeser et al., 2010; Mandery et al., 2011; Weaver and Hagenbuch, 2010). A recent study demonstrated that when the three amino acids A45, L545 and T615 in OATP1B1 were replaced to their corresponding residues in OATP1B3, OATP1B1 was able to transport the OATP1B3-selective substrate cholecystokinin-8 (CCK-8) (Degorter et al., 2012), suggesting that these amino acids are indeed involved in substrate recognition or transport by OATP1B3. These studies are important because they will help to eventually understand the molecular mechanisms of the broad substrate specificity of OATPs and potentially allow predicting and thus preventing drug-drug interactions at the OATP levels.

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8. Mutations and Polymorphisms of OATPs

So far, few pathophysiologic conditions related to mutations in *SLCO* genes have been reported. Mesolemia-synosteses syndrome (OMIM600383) is a rare disease and includes mesomelic limb shortening and acral synosthoses (Isidor et al., 2009). This syndrome has been linked to a disturbance in sulfate metabolism and/or homoestasis (Dawson, 2011). Cytogenetic analysis of 5 patients from four families with this disease identified a submicroscopic microdeletion on chromosome 8q13 (Isidor et al., 2010). This deletion spans the two genes *SULF1* (heparin sulphate 6-O-endosulfatase 1) and *SLCO5A1* (OATP5A1). OATP5A1 is expressed in adult heart and in fetal brain and heart (Isidor et al., 2010), but its function has not been characterized so far. As in all patients deletions spanned both the *SULF1* and the *SLCO5A1* gene, the contribution of missing or malfunctioning OATP5A1 remains to be worked out, in particular as in a single healthy individual a partial deletion of *SLCO5A1* was reported (de Smith et al., 2007). Rotor syndrome is a rare, benign syndrome presenting with conjugated and unconjugated hyperbilirubinemia in conjunction with coproporphyrinuria and a massively altered BSP clearance (Strassburg, 2010). Its inheritance is autosomal recessive. A recent investigation of individuals with Rotor syndrome from eight different families revealed mutations in the *SLCO1B1* and *SLCO1B3* genes, rendering the respective OATPs non-functional (van de Steeg et al., 2012). Mice with a disrupted *Slco1a/1b* locus also presented with unconjugated and conjugated hyperbilirubinemia. (van de Steeg et al., 2012). A study with healthy volunteers associated elevated conjugated and unconjugated bilirubin with the *15 allele of *SLCO1B1*, which is known to display reduced transport activity of the corresponding protein (Zhang et al., 2007). A study investigating the effect of the p.V174A variant of OATP1B1 on thyroid and estrogen metabolite levels in serum found total bilirubin, estrone-3-sulfate and thyroxine sulphate levels to be higher in individuals with the p.174A variant (van der Deure et al., 2008a). A genome-wide association study associated *SLCO1B3* variants with elevated total and unconjugated serum bilirubin (Sanna et al., 2009), while a meta-analysis of three studies associated a *SLCO1B1* variant with elevated serum bilirubin (Johnson et al., 2009). The finding of the latter study was recently confirmed in an independent genome-wide association study (Bielinski et al., 2011). Hence, there is now ample genetic evidence for a role of OATP1B1 and OATP1B3 in hepatocellular uptake of unconjugated and conjugated bilirubin. Finally, serum levels of reverse triiodothyronine have also been reported to be elevated in carriers of the OAPT1A2 p.172D variant (van der Deure et al., 2010).

A genome-wide association study in a cohort of individuals with progressive supranuclear palsy found a suggestive association with *SLCO1A2* in addition to other loci (Hoglinger et al., 2011). Additionally, a genome-wide association study of Crohn's diseases in an Ashekenazi Jewish population found a variant of the *SLCO6A1* to be disease associated (Kenny et al., 2012).

While evidence for the involvement of *SLCO* genes in the pathogenesis of diseases is starting to emerge, a multitude of studies have investigated the role of *SLCO* variants on drug disposition with a particular focus on pharmacokinetics of drugs. Many reviews have covered the role of genetic *SLCO* variants on pharmacokinetics of drugs (Fahrmayr et al., 2010; Franke et al., 2010; Kerb, 2006; Konig, 2011; Niemi et al., 2011; Sissung et al., 2010; Stieger and Meier, 2011; Zair et al., 2008). Understanding the impact of *SLCO* pharmacogenomics is not only relevant for understanding alterations in pharmacokinetics of drugs in patients with different *SLCO* genotypes (Kalliokoski and Niemi, 2009), but also contributes to an understanding of adverse drug reactions. This is exemplified in the case of *SLCO1B1*, which in an elegant genome-wide association study was associated with simvastatin-induced myotoxicity (Link et al., 2008). This and other studies have been the

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basis to suggest a dosing regimen for statins, which takes the *SLCO1B1* genotype into account (Niemi, 2010).

9. Conclusion and Outlook

Since the cloning of the first OATP, the *SLCO* family members have made it to center stage in drug development (Giacomini et al., 2010) and in the understanding of drug disposition (Fenner et al., 2012). While the progress in developing tools for understanding the role of OATPs in handling of endo- and xenobiotics has been enormous, knowledge on their molecular transport mechanisms and on their structure is clearly lagging behind. Both areas are however highly relevant for developing better models to predict their impact in physiology and pathophysiology as well as in drug disposition. In addition, OATPs are increasingly recognized as important transporters in cancer therapy (Obaidat et al., 2012) and in understanding clearance tests like e.g. liver function tests (Stieger et al., 2012).

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References

Abe T, Kakyo M, Tokui T, Nakagomi R, Nishio T, Nakai D, Nomura H, Unno M, Suzuki M, Naitoh T, Matsuno S, Yawo H. Identification of a novel gene family encoding human liver-specific organic anion transporter LST-1. J Biol Chem. 1999; 274:17159–17163. [PubMed: 10358072]

Abe T, Unno M, Onogawa T, Tokui T, Kondo TN, Nakagomi R, Adachi H, Fujiwara K, Okabe M, Suzuki T, Nunoki K, Sato E, Kakyo M, Nishio T, Sugita J, Asano N, Tanemoto M, Seki M, Date F, Ono K, Kondo Y, Shiiba K, Suzuki M, Ohtani H, Shimosegawa T, Iinuma K, Nagura H, Ito S, Matsuno S. LST-2, a human liver-specific organic anion transporter, determines methotrexate sensitivity in gastrointestinal cancers. Gastroenterology. 2001; 120 (7):1689–1699. [PubMed: 11375950]

Adachi H, Suzuki T, Abe M, Asano N, Mizutamari H, Tanemoto M, Nishio T, Onogawa T, Toyohara T, Kasai S, Satoh F, Suzuki M, Tokui T, Unno M, Shimosegawa T, Matsuno S, Ito S, Abe T. Molecular characterization of human and rat organic anion transporter OATP-D. Am J Physiol Renal Physiol. 2003; 285 (6):F1188–1197. [PubMed: 14631946]

Alkemade A, Friesema EC, Kalsbeek A, Swaab DF, Visser TJ, Fliers E. Expression of thyroid hormone transporters in the human hypothalamus. J Clin Endocrinol Metab. 2011; 96 (6):E967–971. [PubMed: 21508134]

Bednarczyk D. Fluorescence-based assays for the assessment of drug interaction with the human transporters OATP1B1 and OATP1B3. Anal Biochem. 2010; 405 (1):50–58. [PubMed: 20540932]

Bielinski SJ, Chai HS, Pathak J, Talwalkar JA, Limburg PJ, Gullerud RE, Sicotte H, Klee EW, Ross JL, Kocher JP, Kullo IJ, Heit JA, Petersen GM, de Andrade M, Chute CG. Mayo Genome Consortia: a genotype-phenotype resource for genome-wide association studies with an application to the analysis of circulating bilirubin levels. Mayo Clin Proc. 2011; 86 (7):606–614. [PubMed: 21646302]

Bleasby K, Castle JC, Roberts CJ, Cheng C, Bailey WJ, Sina JF, Kulkarni AV, Hafey MJ, Evers R, Johnson JM, Ulrich RG, Slatter JG. Expression profiles of 50 xenobiotic transporter genes in humans and pre-clinical species: a resource for investigations into drug disposition. Xenobiotica. 2006; 36 (10–11):963–988. [PubMed: 17118916]

Bossuyt X, Muller M, Hagenbuch B, Meier PJ. Polyspecific drug and steroid clearance by an organic anion transporter of mammalian liver. J Pharmacol Exp Ther. 1996a; 276 (3):891–896. [PubMed: 8786566]

Bossuyt X, Muller M, Meier PJ. Multispecific amphipathic substrate transport by an organic anion transporter of human liver. J Hepatol. 1996b; 25 (5):733–738. [PubMed: 8938553]

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Briz O, Romero MR, Martinez-Becerra P, Macias RI, Perez MJ, Jimenez F, San Martin FG, Marin JJ. OATP8/1B3-mediated cotransport of bile acids and glutathione: an export pathway for organic anions from hepatocytes? J Biol Chem. 2006; 281 (41):30326–30335. [PubMed: 16877380]

Briz O, Serrano MA, MacIas RI, Gonzalez-Gallego J, Marin JJ. 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. 2003; 371 (Pt 3):897–905. [PubMed: 12568656]

Bronger H, Konig J, Kopplow K, Steiner HH, Ahmadi R, Herold-Mende C, Keppler D, Nies AT. ABCC drug efflux pumps and organic anion uptake transporters in human gliomas and the blood-tumor barrier. Cancer Res. 2005; 65 (24):11419–11428. [PubMed: 16357150]

Cattori V, Hagenbuch B, Hagenbuch N, Stieger B, Ha R, Winterhalter KE, Meier PJ. Identification of organic anion transporting polypeptide 4 (Oatp4) as a major full-length isoform of the liver-specific transporter-1 (rlst-1) in rat liver. FEBS Lett. 2000; 474 (2–3):242–245. [PubMed: 10838093]

Cattori V, van Montfoort JE, Stieger B, Landmann L, Meijer DK, Winterhalter KH, Meier PJ, Hagenbuch B. Localization of organic anion transporting polypeptide 4 (Oatp4) in rat liver and comparison of its substrate specificity with Oatp1, Oatp2 and Oatp3. Pflugers Arch. 2001; 443 (2): 188–195. [PubMed: 11713643]

Choi K, Zhuang H, Crain B, Dore S. Expression and localization of prostaglandin transporter in Alzheimer disease brains and age-matched controls. J Neuroimmunol. 2008; 195 (1–2):81–87. [PubMed: 18353443]

Csanaky IL, Lu H, Zhang Y, Ogura K, Choudhuri S, Klaassen CD. Organic anion-transporting polypeptide 1b2 (Oatp1b2) is important for the hepatic uptake of unconjugated bile acids: Studies in Oatp1b2-null mice. Hepatology. 2011; 53 (1):272–281. [PubMed: 20949553]

Cui Y, Konig J, Leier I, Buchholz U, Keppler D. Hepatic uptake of bilirubin and its conjugates by the human organic anion transporter SLC21A6. J Biol Chem. 2001; 276 (13):9626–9630. [PubMed: 11134001]

Cui Y, Konig J, Nies AT, Pfannschmidt M, Hergt M, Franke WW, Alt W, Moll R, Keppler D. Detection of the human organic anion transporters SLC21A6 (OATP2) and SLC21A8 (OATP8) in liver and hepatocellular carcinoma. Lab Invest. 2003; 83 (4):527–538. [PubMed: 12695556]

Dawson PA. Sulfate in fetal development. Semin Cell Dev Biol. 2011; 22 (6):653–659. [PubMed: 21419855]

de Graaf W, Hausler S, Heger M, van Ginhoven TM, van Cappellen G, Bennink RJ, Kullak-Ublick GA, Hesselmann R, van Gulik TM, Stieger B. Transporters involved in the hepatic uptake of (99m)Tc-mebrofenin and indocyanine green. J Hepatol. 2011; 54 (4):738–745. [PubMed: 21163547]

de Smith AJ, Tsalenko A, Sampas N, Scheffer A, Yamada NA, Tsang P, Ben-Dor A, Yakhini Z, Ellis RJ, Bruhn L, Laderman S, Froguel P, Blakemore AI. Array CGH analysis of copy number variation identifies 1284 new genes variant in healthy white males: implications for association studies of complex diseases. Hum Mol Genet. 2007; 16 (23):2783–2794. [PubMed: 17666407]

Degorter MK, Ho RH, Leake BF, Tirona RG, Kim RB. Interaction of Three Regiospecific Amino Acid Residues Is Required for OATP1B1 Gain of OATP1B3 Substrate Specificity. Mol Pharm. 2012; 9 (4):986–995. [PubMed: 22352740]

Dobson PD, Lanthaler K, Oliver SG, Kell DB. Implications of the dominant role of transporters in drug uptake by cells. Curr Top Med Chem. 2009; 9 (2):163–181. [PubMed: 19200003]

Eckhardt U, Schroeder A, Stieger B, Hochli M, Landmann L, Tynes R, Meier PJ, Hagenbuch B. Polyspecific substrate uptake by the hepatic organic anion transporter Oatp1 in stably transfected CHO cells. Am J Physiol. 1999; 276 (4 Pt 1):G1037–1042. [PubMed: 10198348]

Fahrmayr C, Fromm MF, Konig J. Hepatic OATP and OCT uptake transporters: their role for drug-drug interactions and pharmacogenetic aspects. Drug Metab Rev. 2010; 42 (3):380–401. [PubMed: 20100011]

Fenner KS, Jones HM, Ullah M, Kempshall S, Dickins M, Lai Y, Morgan P, Barton HA. The evolution of the OATP hepatic uptake transport protein family in DMPK sciences: from obscure

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liver transporters to key determinants of hepatobiliary clearance. Xenobiotica. 2012; 42 (1):28–45. [PubMed: 22077101]

Franke RM, Gardner ER, Sparreboom A. Pharmacogenetics of drug transporters. Curr Pharm Des. 2010; 16 (2):220–230. [PubMed: 19835554]

Friesema EC, Docter R, Moerings EP, Stieger B, Hagenbuch B, Meier PJ, Krenning EP, Hennemann G, Visser TJ. Identification of thyroid hormone transporters. Biochem Biophys Res Commun. 1999; 254 (2):497–501. [PubMed: 9918867]

Fuchikami H, Satoh H, Tsujimoto M, Ohdo S, Ohtani H, Sawada Y. Effects of herbal extracts on the function of human organic anion-transporting polypeptide OATP-B. Drug Metab Dispos. 2006; 34 (4):577–582. [PubMed: 16415120]

Fujiwara K, Adachi H, Nishio T, Unno M, Tokui T, Okabe M, Onogawa T, Suzuki T, Asano N, Tanemoto M, Seki M, Shiiba K, Suzuki M, Kondo Y, Nunoki K, Shimosegawa T, Iinuma K, Ito S, Matsuno S, Abe T. Identification of thyroid hormone transporters in humans: different molecules are involved in a tissue-specific manner. Endocrinology. 2001; 142:2005–2012. [PubMed: 11316767]

Gao B, Hagenbuch B, Kullak-Ublick GA, Benke D, Aguzzi A, Meier PJ. Organic anion-transporting polypeptides mediate transport of opioid peptides across blood-brain barrier. J Pharmacol Exp Ther. 2000; 294:73–79. [PubMed: 10871297]

Gao B, Huber RD, Wenzel A, Vavricka SR, Ismair MG, Reme C, Meier PJ. Localization of organic anion transporting polypeptides in the rat and human ciliary body epithelium. Exp Eye Res. 2005; 80 (1):61–72. [PubMed: 15652527]

Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X, Dahlin A, Evers R, Fischer V, Hillgren KM, Hoffmaster KA, Ishikawa T, Keppler D, Kim RB, Lee CA, Niemi M, Polli JW, Sugiyama Y, Swaan PW, Ware JA, Wright SH, Yee SW, Zamek-Gliszczynski MJ, Zhang L. Membrane transporters in drug development. Nat Rev Drug Discov. 2010; 9 (3):215–236. [PubMed: 20190787]

Glaeser H, Mandery K, Sticht H, Fromm MF, Konig J. Relevance of conserved lysine and arginine residues in transmembrane helices for the transport activity of organic anion transporting polypeptide 1B3. Br J Pharmacol. 2010; 159 (3):698–708. [PubMed: 20100277]

Grube M, Kock K, Karner S, Reuther S, Ritter CA, Jedlitschky G, Kroemer HK. Modification of OATP2B1-mediated transport by steroid hormones. Mol Pharmacol. 2006a; 70 (5):1735–1741. [PubMed: 16908597]

Grube M, Kock K, Oswald S, Draber K, Meissner K, Eckel L, Bohm M, Felix SB, Vogelgesang S, Jedlitschky G, Siegmund W, Warzok R, Kroemer HK. Organic anion transporting polypeptide 2B1 is a high-affinity transporter for atorvastatin and is expressed in the human heart. Clin Pharmacol Ther. 2006b; 80 (6):607–620. [PubMed: 17178262]

Gui C, Hagenbuch B. Amino acid residues in transmembrane domain 10 of organic anion transporting polypeptide 1B3 are critical for cholecystokinin octapeptide transport. Biochemistry. 2008; 47 (35):9090–9097. [PubMed: 18690707]

Gui C, Hagenbuch B. Role of transmembrane domain 10 for the function of organic anion transporting polypeptide 1B1. Protein Sci. 2009; 18 (11):2298–2306. [PubMed: 19760661]

Gui C, Miao Y, Thompson L, Wahlgren B, Mock M, Stieger B, Hagenbuch B. Effect of pregnane X receptor ligands on transport mediated by human OATP1B1 and OATP1B3. Eur J Pharmacol. 2008; 584 (1):57–65. [PubMed: 18321482]

Hagenbuch B, Gui C. Xenobiotic transporters of the human organic anion transporting polypeptides (OATP) family. Xenobiotica. 2008; 38 (7–8):778–801. [PubMed: 18668430]

Hagenbuch B, Meier PJ. Organic anion transporting polypeptides of the OATP/*SLC21* family: Phylogenetic classification as OATP/*SLCO* superfamily, new nomenclature and molecular/functional properties. Pflugers Arch. 2004; 447:653–665. [PubMed: 14579113]

Hanggi E, Grundschober AF, Leuthold S, Meier PJ, St-Pierre MV. Functional analysis of the extracellular cysteine residues in the human organic anion transporting polypeptide, OATP2B1. Mol Pharmacol. 2006; 70 (3):806–817. [PubMed: 16754786]

Hazard SE, Patel SB. Sterolins ABCG5 and ABCG8: regulators of whole body dietary sterols. Pflugers Arch. 2007; 453 (5):745–752. [PubMed: 16440216]

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Hediger MA, Romero MF, Peng JB, Rolfs A, Takanaga H, Bruford EA. The ABCs of solute carriers: physiological, pathological and therapeutic implications of human membrane transport proteinsIntroduction. Pflugers Arch. 2004; 447 (5):465–468. [PubMed: 14624363]

Hirano M, Maeda K, Shitara Y, Sugiyama Y. Contribution of OATP2 (OATP1B1) and OATP8 (OATP1B3) to the hepatic uptake of pitavastatin in humans. J Pharmacol Exp Ther. 2004; 311 (1): 139–146. [PubMed: 15159445]

Hirano M, Maeda K, Shitara Y, Sugiyama Y. Drug-drug interaction between pitavastatin and various drugs via OATP1B1. Drug Metab Dispos. 2006; 34 (7):1229–1236. [PubMed: 16595711]

Hoglinger GU, Melhem NM, Dickson DW, Sleiman PM, Wang LS, Klei L, Rademakers R, de Silva R, Litvan I, Riley DE, van Swieten JC, Heutink P, Wszolek ZK, Uitti RJ, Vandrovcova J, Hurtig HI, Gross RG, Maetzler W, Goldwurm S, Tolosa E, Borroni B, Pastor P, Cantwell LB, Han MR, Dillman A, van der Brug MP, Gibbs JR, Cookson MR, Hernandez DG, Singleton AB, Farrer MJ, Yu CE, Golbe LI, Revesz T, Hardy J, Lees AJ, Devlin B, Hakonarson H, Muller U, Schellenberg GD. Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. Nat Genet. 2011; 43 (7):699–705. [PubMed: 21685912]

Hsiang B, Zhu Y, Wang Z, Wu Y, Sasseville V, Yang WP, Kirchgessner TG. 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. 1999; 274:37161–37168. [PubMed: 10601278]

Huber RD, Gao B, Sidler Pfandler MA, Zhang-Fu W, Leuthold S, Hagenbuch B, Folkers G, Meier PJ, Stieger B. Characterization of two splice variants of human organic anion transporting polypeptide 3A1 isolated from human brain. Am J Physiol Cell Physiol. 2007; 292 (2):C795–806. [PubMed: 16971491]

Ishizuka H, Konno K, Naganuma H, Nishimura K, Kouzuki H, Suzuki H, Stieger B, Meier PJ, Sugiyama Y. Transport of temocaprilat into rat hepatocytes: role of organic anion transporting polypeptide. J Pharmacol Exp Ther. 1998; 287 (1):37–42. [PubMed: 9765319]

Isidor B, Hamel A, Plasschaert F, Claus L, Mercier JM, Mortier GR, Leroy JG, Verloes A, David A. Mesomelic dysplasia with acral synostoses Verloes-David-Pfeiffer type: follow-up study documents progressive clinical course. Am J Med Genet A. 2009; 149A (10):2220–2225. [PubMed: 19725128]

Isidor B, Pichon O, Redon R, Day-Salvatore D, Hamel A, Siwicka KA, Bitner-Glindzicz M, Heymann D, Kjellen L, Kraus C, Leroy JG, Mortier GR, Rauch A, Verloes A, David A, Le Caignec C. Mesomelia-synostoses syndrome results from deletion of SULF1 and SLCO5A1 genes at 8q13. Am J Hum Genet. 2010; 87 (1):95–100. [PubMed: 20602915]

Ismair MG, Stieger B, Cattori V, Hagenbuch B, Fried M, Meier PJ, Kullak-Ublick GA. Hepatic uptake of cholecystokinin octapeptide by organic anion-transporting polypeptides OATP4 and OATP8 of rat and human liver. Gastroenterology. 2001; 121 (5):1185–1190. [PubMed: 11677211]

Jacquemin E, Hagenbuch B, Stieger B, Wolkoff AW, Meier PJ. Expression cloning of a rat liver Na(+)-independent organic anion transporter. Proc Natl Acad Sci U S A. 1994; 91 (1):133–137. [PubMed: 8278353]

Jansen J, Friesema EC, Milici C, Visser TJ. Thyroid hormone transporters in health and disease. Thyroid. 2005; 15 (8):757–768. [PubMed: 16131319]

Ji C, Tschantz WR, Pfeifer ND, Ullah M, Sadagopan N. Development of a multiplex UPLC-MRM MS method for quantification of human membrane transport proteins OATP1B1, OATP1B3 and OATP2B1 in in vitro systems and tissues. Anal Chim Acta. 2012; 717:67–76. [PubMed: 22304817]

Jigorel E, Le Vee M, Boursier-Neyret C, Parmentier Y, Fardel O. Differential regulation of sinusoidal and canalicular hepatic drug transporter expression by xenobiotics activating drug-sensing receptors in primary human hepatocytes. Drug Metab Dispos. 2006; 34 (10):1756–1763. [PubMed: 16837569]

Johnson AD, Kavousi M, Smith AV, Chen MH, Dehghan A, Aspelund T, Lin JP, van Duijn CM, Harris TB, Cupples LA, Uitterlinden AG, Launer L, Hofman A, Rivadeneira F, Stricker B, Yang Q, O'Donnell CJ, Gudnason V, Witteman JC. Genome-wide association meta-analysis for total serum bilirubin levels. Hum Mol Genet. 2009; 18 (14):2700–2710. [PubMed: 19414484]

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Jung D, Hagenbuch B, Gresh L, Pontoglio M, Meier PJ, Kullak Ublick GA. Characterization of the human OATP-C (SLC21A6) gene promoter and regulation of liver-specific OATP genes by hepatocyte nuclear factor 1 alpha. J Biol Chem. 2001; 276 (40):37206–37214. [PubMed: 11483603]

Jung D, Podvinec M, Meyer UA, Mangelsdorf DJ, Fried M, Meier PJ, Kullak-Ublick GA. Human organic anion transporting polypeptide 8 promoter is transactivated by the farnesoid X receptor/bile acid receptor. Gastroenterology. 2002; 122 (7):1954–1966. [PubMed: 12055601]

Kakyo M, Unno M, Tokui T, Nakagomi R, Nishio T, Iwasashi H, Nakai D, Seki M, Suzuki M, Naitoh T, Matsuno S, Yawo H, Abe T. Molecular characterization and functional regulation of a novel rat liver-specific organic anion transporter rlst-1. Gastroenterology. 1999; 117 (4):770–775. [PubMed: 10500057]

Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. Br J Pharmacol. 2009; 158 (3):693–705. [PubMed: 19785645]

Kanai N, Lu R, Satriano JA, Bao Y, Wolkoff AW, Schuster VL. Identification and characterization of a prostaglandin transporter. Science. 1995; 268 (5212):866–869. [PubMed: 7754369]

Kang J, Chapdelaine P, Parent J, Madore E, Laberge PY, Fortier MA. Expression of human prostaglandin transporter in the human endometrium across the menstrual cycle. J Clin Endocrinol Metab. 2005; 90 (4):2308–2313. [PubMed: 15657371]

Kellner HM, Christ O, Rupp W, Heptner W. Resorption, distribution and excretion after administration of 14C-labelled HB 419 in rabbits, rats and dogs. Arzneimittelforschung. 1969; 19(8 Suppl):1388–1400. [PubMed: 5394459]

Kenny EE, Pe'er I, Karban A, Ozelius L, Mitchell AA, Ng SM, Erazo M, Ostrer H, Abraham C, Abreu MT, Atzmon G, Barzilai N, Brant SR, Bressman S, Burns ER, Chowers Y, Clark LN, Darvasi A, Doheny D, Duerr RH, Eliakim R, Giladi N, Gregersen PK, Hakonarson H, Jones MR, Marder K, McGovern DP, Mulle J, Orr-Urtreger A, Proctor DD, Pulver A, Rotter JI, Silverberg MS, Ullman T, Warren ST, Waterman M, Zhang W, Bergman A, Mayer L, Katz S, Desnick RJ, Cho JH, Peter I. A genome-wide scan of ashkenazi jewish Crohn's disease suggests novel susceptibility Loci. PLoS Genet. 2012; 8 (3):e1002559. [PubMed: 22412388]

Kerb R. Implications of genetic polymorphisms in drug transporters for pharmacotherapy. Cancer Lett. 2006; 234 (1):4–33. [PubMed: 16504381]

Kindla J, Rau TT, Jung R, Fasching PA, Strick R, Stoehr R, Hartmann A, Fromm MF, Konig J. Expression and localization of the uptake transporters OATP2B1, OATP3A1 and OATP5A1 in non-malignant and malignant breast tissue. Cancer Biol Ther. 2011; 11 (6):584–591. [PubMed: 21278488]

Knauer MJ, Urquhart BL, Meyer zu Schwabedissen HE, Schwarz UI, Lemke CJ, Leake BF, Kim RB, Tirona RG. Human skeletal muscle drug transporters determine local exposure and toxicity of statins. Circ Res. 2010; 106 (2):297–306. [PubMed: 19940267]

Kobayashi D, Nozawa T, Imai K, Nezu J, Tsuji A, Tamai I. Involvement of human organic anion transporting polypeptide OATP-B (SLC21A9) in pH-dependent transport across intestinal apical membrane. J Pharmacol Exp Ther. 2003; 306:703–708. [PubMed: 12724351]

Kock K, Koenen A, Giese B, Fraunholz M, May K, Siegmund W, Hammer E, Volker U, Jedlitschky G, Kroemer HK, Grube M. Rapid modulation of the organic anion transporting polypeptide 2B1 (OATP2B1, SLCO2B1) function by protein kinase C-mediated internalization. J Biol Chem. 2010; 285 (15):11336–11347. [PubMed: 20159975]

Konig J. Uptake transporters of the human OATP family. Molecular characteristics, substrates, their role in drug-drug interactions, and functional consequences of polymorphisms. Handb Exp Pharmacol. 2011; 201:1–28. [PubMed: 21103967]

Konig J, Cui Y, Nies AT, Keppler D. Localization and genomic organization of a new hepatocellular organic anion transporting polypeptide. J Biol Chem. 2000a; 275:23161–23168. [PubMed: 10779507]

Konig J, Cui Y, Nies AT, Keppler D. A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane. Am J Physiol Gastrointest Liver Physiol. 2000b; 278:G156–164. [PubMed: 10644574]

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NIH-PA Author Manuscript

Kouzuki H, Suzuki H, Ito K, Ohashi R, Sugiyama Y. Contribution of organic anion transporting polypeptide to uptake of its possible substrates into rat hepatocytes. J Pharmacol Exp Ther. 1999; 288 (2):627–634. [PubMed: 9918568]

Kraft ME, Glaeser H, Mandery K, Konig J, Auge D, Fromm MF, Schlotzer-Schrehardt U, Welge-Lussen U, Kruse FE, Zolk O. The prostaglandin transporter OATP2A1 is expressed in human ocular tissues and transports the antiglaucoma prostanoid latanoprost. Invest Ophthalmol Vis Sci. 2010; 51 (5):2504–2511. [PubMed: 20019365]

Kullak-Ublick GA, Fisch T, Oswald M, Hagenbuch B, Meier PJ, Beuers U, Paumgartner G. Dehydroepiandrosterone sulfate (DHEAS): identification of a carrier protein in human liver and brain. FEBS Lett. 1998; 424 (3):173–176. [PubMed: 9539145]

Kullak-Ublick GA, Hagenbuch B, Stieger B, Schteingart CD, Hofmann AF, Wolkoff AW, Meier PJ. Molecular and functional characterization of an organic anion transporting polypeptide cloned from human liver. Gastroenterology. 1995; 109:1274–1282. [PubMed: 7557095]

Kullak-Ublick GA, Hagenbuch B, Stieger B, Wolkoff AW, Meier PJ. Functional characterization of the basolateral rat liver organic anion transporting polypeptide. Hepatology. 1994; 20 (2):411–416. [PubMed: 8045503]

Kullak-Ublick GA, Ismair MG, Stieger B, Landmann L, Huber R, Pizzagalli F, Fattinger K, Meier PJ, Hagenbuch B. Organic anion-transporting polypeptide B (OATP-B) and its functional comparison with three other OATPs of human liver. Gastroenterology. 2001; 120 (2):525–533. [PubMed: 11159893]

Kusuhara H, Sugiyama Y. In vitro-in vivo extrapolation of transporter-mediated clearance in the liver and kidney. Drug Metab Pharmacokinet. 2009; 24 (1):37–52. [PubMed: 19252335]

Le Vee M, Gripon P, Stieger B, Fardel O. Down-regulation of organic anion transporter expression in human hepatocytes exposed to the proinflammatory cytokine interleukin 1beta. Drug Metab Dispos. 2008; 36 (2):217–222. [PubMed: 17991769]

Le Vee M, Lecureur V, Moreau A, Stieger B, Fardel O. Differential regulation of drug transporter expression by hepatocyte growth factor in primary human hepatocytes. Drug Metab Dispos. 2009; 37 (11):2228–2235. [PubMed: 19661216]

Lecerf JM, de Lorgeril M. Dietary cholesterol: from physiology to cardiovascular risk. Br J Nutr. 2011; 106 (1):6–14. [PubMed: 21385506]

Lee SY, Williamson B, Caballero OL, Chen YT, Scanlan MJ, Ritter G, Jongeneel CV, Simpson AJ, Old LJ. Identification of the gonad-specific anion transporter SLCO6A1 as a cancer/testis (CT) antigen expressed in human lung cancer. Cancer Immun. 2004; 4:13. [PubMed: 15546177]

Lee W, Glaeser H, Smith LH, Roberts RL, Moeckel GW, Gervasini G, Leake BF, Kim RB. Polymorphisms in human organic anion-transporting polypeptide 1A2 (OATP1A2): implications for altered drug disposition and central nervous system drug entry. J Biol Chem. 2005; 280 (10): 9610–9617. [PubMed: 15632119]

Leuthold S, Hagenbuch B, Mohebbi N, Wagner CA, Meier PJ, Stieger B. Mechanisms of pH-gradient driven transport mediated by organic anion polypeptide transporters. Am J Physiol Cell Physiol. 2009; 296 (3):C570–582. [PubMed: 19129463]

Li L, Lee TK, Meier PJ, Ballatori N. Identification of glutathione as a driving force and leukotriene C4 as a substrate for oatp1, the hepatic sinusoidal organic solute transporter. J Biol Chem. 1998; 273 (26):16184–16191. [PubMed: 9632674]

Li L, Meier PJ, Ballatori N. Oatp2 mediates bidirectional organic solute transport: a role for intracellular glutathione. Mol Pharmacol. 2000; 58 (2):335–340. [PubMed: 10908301]

Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R. SLCO1B1 variants and statin-induced myopathy--a genomewide study. N Engl J Med. 2008; 359 (8):789–799. [PubMed: 18650507]

Loubiere LS, Vasilopoulou E, Bulmer JN, Taylor PM, Stieger B, Verrey F, McCabe CJ, Franklyn JA, Kilby MD, Chan SY. Expression of thyroid hormone transporters in the human placenta and changes associated with intrauterine growth restriction. Placenta. 2010; 31 (4):295–304. [PubMed: 20167367]

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Lu R, Kanai N, Bao Y, Schuster VL. Cloning, in vitro expression, and tissue distribution of a human prostaglandin transporter cDNA(hPGT). J Clin Invest. 1996; 98 (5):1142–1149. [PubMed: 8787677]

Maeda K, Kambara M, Tian Y, Hofmann AF, Sugiyama Y. 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. 2006; 3 (1):70–77. [PubMed: 16686371]

Mahagita C, Grassl SM, Piyachaturawat P, Ballatori N. 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. 2007; 293 (1):G271–278. [PubMed: 17412826]

Mandery K, Bujok K, Schmidt I, Wex T, Treiber G, Malfertheiner P, Rau TT, Amann KU, Brune K, Fromm MF, Glaeser H. Influence of Cyclooxygenase Inhibitors on the Function of the Prostaglandin Transporter Organic Anion-Transporting Polypeptide 2A1 Expressed in Human Gastroduodenal Mucosa. Journal of Pharmacology and Experimental Therapeutics. 2010; 332 (2): 345–351. [PubMed: 19843975]

Mandery K, Sticht H, Bujok K, Schmidt I, Fahrmayr C, Balk B, Fromm MF, Glaeser H. Functional and structural relevance of conserved positively charged lysine residues in organic anion transporting polypeptide 1B3. Mol Pharmacol. 2011; 80 (3):400–406. [PubMed: 21642393]

Masuda S, Ibaramoto K, Takeuchi A, Saito H, Hashimoto Y, Inui KI. Cloning and functional characterization of a new multispecific organic anion transporter, OAT-K2, in rat kidney. Mol Pharmacol. 1999; 55 (4):743–752. [PubMed: 10101033]

Mayerl S, Visser TJ, Darras VM, Horn S, Heuer H. Impact of oatp1c1 deficiency on thyroid hormone metabolism and action in the mouse brain. Endocrinology. 2012; 153 (3):1528–1537. [PubMed: 22294745]

Meier PJ, Eckhardt U, Schroeder A, Hagenbuch B, Stieger B. Substrate specificity of sinusoidal bile acid and organic anion uptake systems in rat and human liver. Hepatology. 1997; 26 (6):1667–1677. [PubMed: 9398014]

Meyer Zu Schwabedissen HE, Bottcher K, Chaudhry A, Kroemer HK, Schuetz EG, Kim RB. Liver X receptor alpha and farnesoid X receptor are major transcriptional regulators of OATP1B1. Hepatology. 2010; 52 (5):1797–1807. [PubMed: 20827719]

Meyer zu Schwabedissen HE, Tirona RG, Yip CS, Ho RH, Kim RB. Interplay between the nuclear receptor pregnane X receptor and the uptake transporter organic anion transporter polypeptide 1A2 selectively enhances estrogen effects in breast cancer. Cancer Res. 2008; 68 (22):9338–9347. [PubMed: 19010908]

Miki Y, Suzuki T, Kitada K, Yabuki N, Shibuya R, Moriya T, Ishida T, Ohuchi N, Blumberg B, Sasano H. Expression of the steroid and xenobiotic receptor and its possible target gene, organic anion transporting polypeptide-A, in human breast carcinoma. Cancer Res. 2006; 66 (1):535–542. [PubMed: 16397270]

Mikkaichi T, Suzuki T, Onogawa T, Tanemoto M, Mizutamari H, Okada M, Chaki T, Masuda S, Tokui T, Eto N, Abe M, Satoh F, Unno M, Hishinuma T, Inui K, Ito S, Goto J, Abe T. Isolation and characterization of a digoxin transporter and its rat homologue expressed in the kidney. Proc Natl Acad Sci U S A. 2004; 101:3569–3574. [PubMed: 14993604]

Miyagawa M, Maeda K, Aoyama A, Sugiyama Y. 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. 2009; 329 (2):551–557. [PubMed: 19244099]

Nagai M, Furihata T, Matsumoto S, Ishii S, Motohashi S, Yoshino I, Ugajin M, Miyajima A, Chiba K. Identification of a new organic anion transporting polypeptide 1B3 mRNA isoform primarily expressed in human cancerous tissues and cells. Biochem Biophys Res Commun. 2012; 418 (4): 818–823. [PubMed: 22326869]

Nakai D, Nakagomi R, Furuta Y, Tokui T, Abe T, Ikeda T, Nishimura K. Human liver-specific organic anion transporter, LST-1, mediates uptake of pravastatin by human hepatocytes. J Pharmacol Exp Ther. 2001; 297 (3):861–867. [PubMed: 11356905]

Niemi M. Transporter pharmacogenetics and statin toxicity. Clin Pharmacol Ther. 2010; 87 (1):130–133. [PubMed: 19890253]

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Niemi M, Pasanen MK, Neuvonen PJ. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. Pharmacol Rev. 2011; 63 (1):157–181. [PubMed: 21245207]

Niessen J, Jedlitschky G, Grube M, Bien S, Schwertz H, Ohtsuki S, Kawakami H, Kamiie J, Oswald S, Starke K, Strobel U, Siegmund W, Rosskopf D, Greinacher A, Terasaki T, Kroemer HK. Human platelets express organic anion-transporting peptide 2B1, an uptake transporter for atorvastatin. Drug Metab Dispos. 2009; 37 (5):1129–1137. [PubMed: 19237515]

Nishio T, Adachi H, Nakagomi R, Tokui T, Sato E, Tanemoto M, Fujiwara K, Okabe M, Onogawa T, Suzuki T, Nakai D, Shiiba K, Suzuki M, Ohtani H, Kondo Y, Unno M, Ito S, Iinuma K, Nunoki K, Matsuno S, Abe T. Molecular identification of a rat novel organic anion transporter moat1, which transports prostaglandin D(2), leukotriene C(4), and taurocholate. Biochem Biophys Res Commun. 2000; 275 (3):831–838. [PubMed: 10973807]

Noe B, Hagenbuch B, Stieger B, Meier PJ. Isolation of a multispecific organic anion and cardiac glycoside transporter from rat brain. Proc Natl Acad Sci U S A. 1997; 94 (19):10346–10350. [PubMed: 9294213]

Noe J, Portmann R, Brun ME, Funk C. Substrate-dependent drug-drug interactions between gemfibrozil, fluvastatin and other organic anion-transporting peptide (OATP) substrates on OATP1B1, OATP2B1, and OATP1B3. Drug Metab Dispos. 2007; 35 (8):1308–1314. [PubMed: 17470528]

Nozawa T, Imai K, Nezu J, Tsuji A, Tamai I. Functional characterization of pH-sensitive organic anion transporting polypeptide OATP-B in human. J Pharmacol Exp Ther. 2004; 308:438–445. [PubMed: 14610227]

Obaidat A, Roth M, Hagenbuch B. The expression and function of organic anion transporting polypeptides in normal tissues and in cancer. Annu Rev Pharmacol Toxicol. 2012; 52:135–151. [PubMed: 21854228]

Ostrow JD, Mukerjee P, Tiribelli C. Structure and binding of unconjugated bilirubin: relevance for physiological and pathophysiological function. J Lipid Res. 1994; 35 (10):1715–1737. [PubMed: 7852850]

Pizzagalli F, Hagenbuch B, Stieger B, Klenk U, Folkers G, Meier PJ. Identification of a novel human organic anion transporting polypeptide as a high affinity thyroxine transporter. Mol Endocrinol. 2002; 16 (10):2283–2296. [PubMed: 12351693]

Pizzagalli F, Varga Z, Huber RD, Folkers G, Meier PJ, St-Pierre MV. Identification of steroid sulfate transport processes in the human mammary gland. J Clin Endocrinol Metab. 2003; 88 (8):3902–3912. [PubMed: 12915686]

Reichel C, Gao B, Van Montfoort J, Cattori V, Rahner C, Hagenbuch B, Stieger B, Kamisako T, Meier PJ. Localization and function of the organic anion-transporting polypeptide Oatp2 in rat liver. Gastroenterology. 1999; 117 (3):688–695. [PubMed: 10464146]

Roberts LM, Woodford K, Zhou M, Black DS, Haggerty JE, Tate EH, Grindstaff KK, Mengesha W, Raman C, Zerangue N. Expression of the thyroid hormone transporters monocarboxylate transporter-8 (SLC16A2) and organic ion transporter-14 (SLCO1C1) at the blood-brain barrier. Endocrinology. 2008; 149 (12):6251–6261. [PubMed: 18687783]

Roth M, Obaidat A, Hagenbuch B. OATPs, OATs and OCTs: The organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. Br J Pharmacol. 2012; 165:1260–1287. [PubMed: 22013971]

Roth M, Timmermann BN, Hagenbuch B. Interactions of green tea catechins with organic anion-transporting polypeptides. Drug Metab Dispos. 2011; 39 (5):920–926. [PubMed: 21278283]

Saier MH Jr, Beatty JT, Goffeau A, Harley KT, Heijne WH, Huang SC, Jack DL, Jahn PS, Lew K, Liu J, Pao SS, Paulsen IT, Tseng TT, Virk PS. The major facilitator superfamily. J Mol Microbiol Biotechnol. 1999; 1 (2):257–279. [PubMed: 10943556]

Sanna S, Busonero F, Maschio A, McArdle PF, Usala G, Dei M, Lai S, Mulas A, Piras MG, Perseu L, Masala M, Marongiu M, Crisponi L, Naitza S, Galanello R, Abecasis GR, Shuldiner AR, Schlessinger D, Cao A, Uda M. Common variants in the SLCO1B3 locus are associated with bilirubin levels and unconjugated hyperbilirubinemia. Hum Mol Genet. 2009; 18 (14):2711–2718. [PubMed: 19419973]

NIH-PA Author Manuscript

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NIH-PA Author Manuscript

Satlin LM, Amin V, Wolkoff AW. Organic anion transporting polypeptide mediates organic anion/HCO3- exchange. J Biol Chem. 1997; 272 (42):26340–26345. [PubMed: 9334206]

Sato K, Sugawara J, Sato T, Mizutamari H, Suzuki T, Ito A, Mikkaichi T, Onogawa T, Tanemoto M, Unno M, Abe T, Okamura K. Expression of organic anion transporting polypeptide E (OATP-E) in human placenta. Placenta. 2003; 24 (2–3):144–148. [PubMed: 12566240]

Schiffer R, Neis M, Holler D, Rodriguez F, Geier A, Gartung C, Lammert F, Dreuw A, Zwadlo-Klarwasser G, Merk H, Jugert F, Baron JM. Active influx transport is mediated by members of the organic anion transporting polypeptide family in human epidermal keratinocytes. J Invest Dermatol. 2003; 120 (2):285–291. [PubMed: 12542534]

Sissung TM, Baum CE, Kirkland CT, Gao R, Gardner ER, Figg WD. Pharmacogenetics of membrane transporters: an update on current approaches. Mol Biotechnol. 2010; 44 (2):152–167. [PubMed: 19950006]

St Pierre MV, Hagenbuch B, Ugele B, Meier PJ, Stallmach T. Characterization of an organic anion-transporting polypeptide (OATP-B) in human placenta. J Clin Endocrinol Metab. 2002; 87 (4):1856–1863. [PubMed: 11932330]

Stieger B, Heger M, de Graaf W, Paumgartner G, van Gulik T. The emerging role of transport systems in liver function tests. Eur J Pharmacol. 2012; 675 (1–3):1–5. [PubMed: 22173125]

Stieger B, Meier PJ. Pharmacogenetics of drug transporters in the enterohepatic circulation. Pharmacogenomics. 2011; 12 (5):611–631. [PubMed: 21619426]

Strassburg CP. Hyperbilirubinemia syndromes (Gilbert-Meulengracht, Crigler-Najjar, Dubin-Johnson, and Rotor syndrome). Best Pract Res Clin Gastroenterol. 2010; 24 (5):555–571. [PubMed: 20955959]

Sugiyama D, Kusuhara H, Shitara Y, Abe T, Sugiyama Y. Effect of 17 beta-estradiol-D-17 beta-glucuronide on the rat organic anion transporting polypeptide 2-mediated transport differs depending on substrates. Drug Metab Dispos. 2002; 30 (2):220–223. [PubMed: 11792694]

Sugiyama D, Kusuhara H, Taniguchi H, Ishikawa S, Nozaki Y, Aburatani H, Sugiyama Y. Functional characterization of rat brain-specific organic anion transporter (Oatp14) at the blood-brain barrier: high affinity transporter for thyroxine. J Biol Chem. 2003; 278 (44):43489–43495. [PubMed: 12923172]

Suzuki T, Onogawa T, Asano N, Mizutamari H, Mikkaichi T, Tanemoto M, Abe M, Satoh F, Unno M, Nunoki K, Suzuki M, Hishinuma T, Goto J, Shimosegawa T, Matsuno S, Ito S, Abe T. Identification and characterization of novel rat and human gonad-specific organic anion transporters. Mol Endocrinol. 2003; 17 (7):1203–1215. [PubMed: 12677006]

Suzuki T, Toyohara T, Akiyama Y, Takeuchi Y, Mishima E, Suzuki C, Ito S, Soga T, Abe T. Transcriptional regulation of organic anion transporting polypeptide SLCO4C1 as a new therapeutic modality to prevent chronic kidney disease. J Pharm Sci. 2011; 100 (9):3696–3707. [PubMed: 21656517]

Svoboda M, Wlcek K, Taferner B, Hering S, Stieger B, Tong D, Zeillinger R, Thalhammer T, Jager W. Expression of organic anion-transporting polypeptides 1B1 and 1B3 in ovarian cancer cells: relevance for paclitaxel transport. Biomed Pharmacother. 2011; 65 (6):417–426. [PubMed: 21719246]

Takeuchi A, Masuda S, Saito H, Abe T, Inui K. Multispecific substrate recognition of kidney-specific organic anion transporters OAT-K1 and OAT-K2. J Pharmacol Exp Ther. 2001; 299 (1):261–267. [PubMed: 11561088]

Tamai I, Nezu J, Uchino H, Sai Y, Oku A, Shimane M, Tsuji A. Molecular identification and characterization of novel members of the human organic anion transporter (OATP) family. Biochem Biophys Res Commun. 2000; 273:251–260. [PubMed: 10873595]

Tamai I, Nozawa T, Koshida M, Nezu J, Sai Y, Tsuji A. Functional characterization of human organic anion transporting polypeptide B (OATP-B) in comparison with liver-specific OATP-C. Pharm Res. 2001; 18:1262–1269. [PubMed: 11683238]

Tirona RG, Leake BF, Wolkoff AW, Kim RB. Human organic anion transporting polypeptide-C (SLC21A6) is a major determinant of rifampin-mediated pregnane X receptor activation. J Pharmacol Exp Ther. 2003; 304 (1):223–228. [PubMed: 12490595]

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van de Steeg E, Stranecky V, Hartmannova H, Noskova L, Hrebicek M, Wagenaar E, van Esch A, de Waart DR, Oude Elferink RP, Kenworthy KE, Sticova E, al-Edreesi M, Knisely AS, Kmoch S, Jirsa M, Schinkel AH. Complete OATP1B1 and OATP1B3 deficiency causes human Rotor syndrome by interrupting conjugated bilirubin reuptake into the liver. J Clin Invest. 2012; 122 (2):519–528. [PubMed: 22232210]

van de Steeg E, Wagenaar E, van der Kruijssen CM, Burggraaff JE, de Waart DR, Elferink RP, Kenworthy KE, Schinkel AH. Organic anion transporting polypeptide 1a/1b-knockout mice provide insights into hepatic handling of bilirubin, bile acids, and drugs. J Clin Invest. 2010; 120 (8):2942–2952. [PubMed: 20644253]

van der Deure WM, Friesema EC, de Jong FJ, de Rijke YB, de Jong FH, Uitterlinden AG, Breteler MM, Peeters RP, Visser TJ. Organic anion transporter 1B1: an important factor in hepatic thyroid hormone and estrogen transport and metabolism. Endocrinology. 2008a; 149 (9):4695–4701. [PubMed: 18499754]

van der Deure WM, Hansen PS, Peeters RP, Kyvik KO, Friesema EC, Hegedus L, Visser TJ. Thyroid hormone transport and metabolism by organic anion transporter 1C1 and consequences of genetic variation. Endocrinology. 2008b; 149 (10):5307–5314. [PubMed: 18566113]

van der Deure WM, Peeters RP, Visser TJ. Molecular aspects of thyroid hormone transporters, including MCT8, MCT10, and OATPs, and the effects of genetic variation in these transporters. J Mol Endocrinol. 2010; 44 (1):1–11. [PubMed: 19541799]

Vavricka SR, Jung D, Fried M, Grutzner U, Meier PJ, Kullak-Ublick GA. The human organic anion transporting polypeptide 8 (SLCO1B3) gene is transcriptionally repressed by hepatocyte nuclear factor 3beta in hepatocellular carcinoma. J Hepatol. 2004; 40 (2):212–218. [PubMed: 14739090]

Vavricka SR, Van Montfoort J, Ha HR, Meier PJ, Fattinger K. Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver. Hepatology. 2002; 36 (1):164–172. [PubMed: 12085361]

Walters HC, Craddock AL, Fusegawa H, Willingham MC, Dawson PA. Expression, transport properties, and chromosomal location of organic anion transporter subtype 3. Am J Physiol Gastrointest Liver Physiol. 2000; 279 (6):G1188–1200. [PubMed: 11093941]

Wang P, Hata S, Xiao Y, Murray JW, Wolkoff AW. Topological assessment of oatp1a1: a 12-transmembrane domain integral membrane protein with three N-linked carbohydrate chains. Am J Physiol Gastrointest Liver Physiol. 2008; 294 (4):G1052–1059. [PubMed: 18308854]

Wang X, Wolkoff AW, Morris ME. Flavonoids as a novel class of human organic anion-transporting polypeptide OATP1B1 (OATP-C) modulators. Drug Metab Dispos. 2005; 33 (11):1666–1672. [PubMed: 16081670]

Weaver YM, Hagenbuch B. Several conserved positively charged amino acids in OATP1B1 are involved in binding or translocation of different substrates. J Membr Biol. 2010; 236 (3):279–290. [PubMed: 20821001]

Yamaguchi H, Sugie M, Okada M, Mikkaichi T, Toyohara T, Abe T, Goto J, Hishinuma T, Shimada M, Mano N. 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. 2010; 25 (3):314–317. [PubMed: 20610891]

Zaher H, Meyer zu Schwabedissen HE, Tirona RG, Cox ML, Obert LA, Agrawal N, Palandra J, Stock JL, Kim RB, Ware JA. Targeted disruption of murine organic anion-transporting polypeptide 1b2 (Oatp1b2/Slco1b2) significantly alters disposition of prototypical drug substrates pravastatin and rifampin. Mol Pharmacol. 2008; 74 (2):320–329. [PubMed: 18413659]

Zair ZM, Eloranta JJ, Stieger B, Kullak-Ublick GA. Pharmacogenetics of OATP (SLC21/SLCO), OAT and OCT (SLC22) and PEPT (SLC15) transporters in the intestine, liver and kidney. Pharmacogenomics. 2008; 9 (5):597–624. [PubMed: 18466105]

Zhang W, He YJ, Gan Z, Fan L, Li Q, Wang A, Liu ZQ, Deng S, Huang YF, Xu LY, Zhou HH. OATP1B1 polymorphism is a major determinant of serum bilirubin level but not associated with rifampicin-mediated bilirubin elevation. Clin Exp Pharmacol Physiol. 2007; 34 (12):1240–1244. [PubMed: 17973861]

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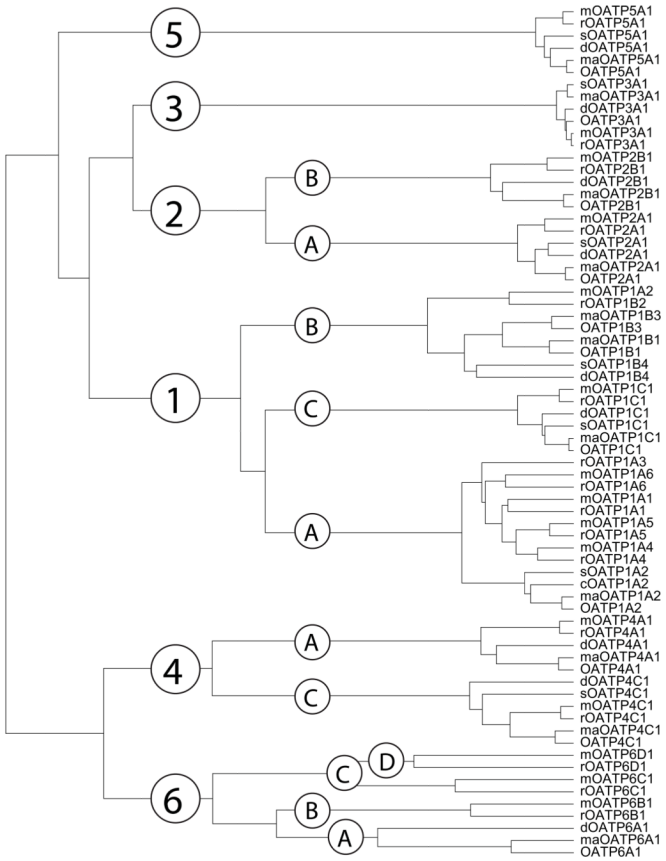

Figure 1.

Phylogenetic tree and classification of 70 members of the OATP/*SLCO* superfamily of transporters. Human (all capitalized OATP), monkey (maOATP), dog (dOATP), pig (sOATP), rat (rOATP) and mouse (mOATP) proteins are grouped into families (with more than 40% amino acid sequence identity) and subfamilies (with more than 60% amino acid sequence identity).

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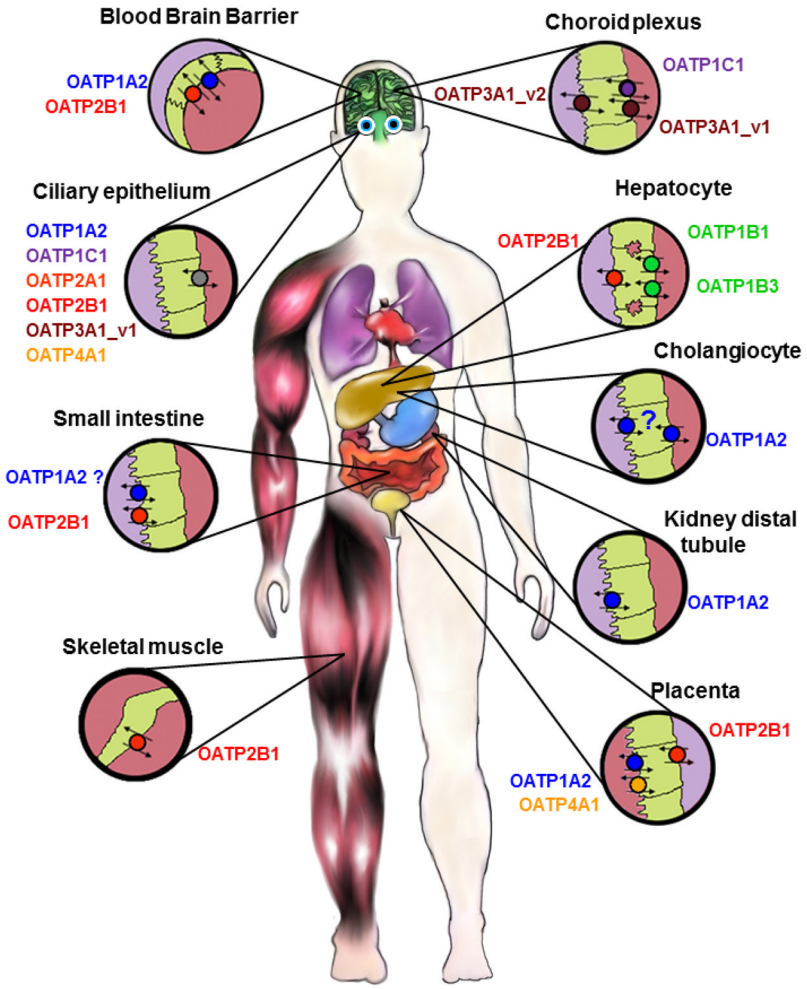

Figure 2.
Distribution of OATPs in selected human epithelial tissues. The OATPs within the same subfamily are labelled with the same color. For more details see text.

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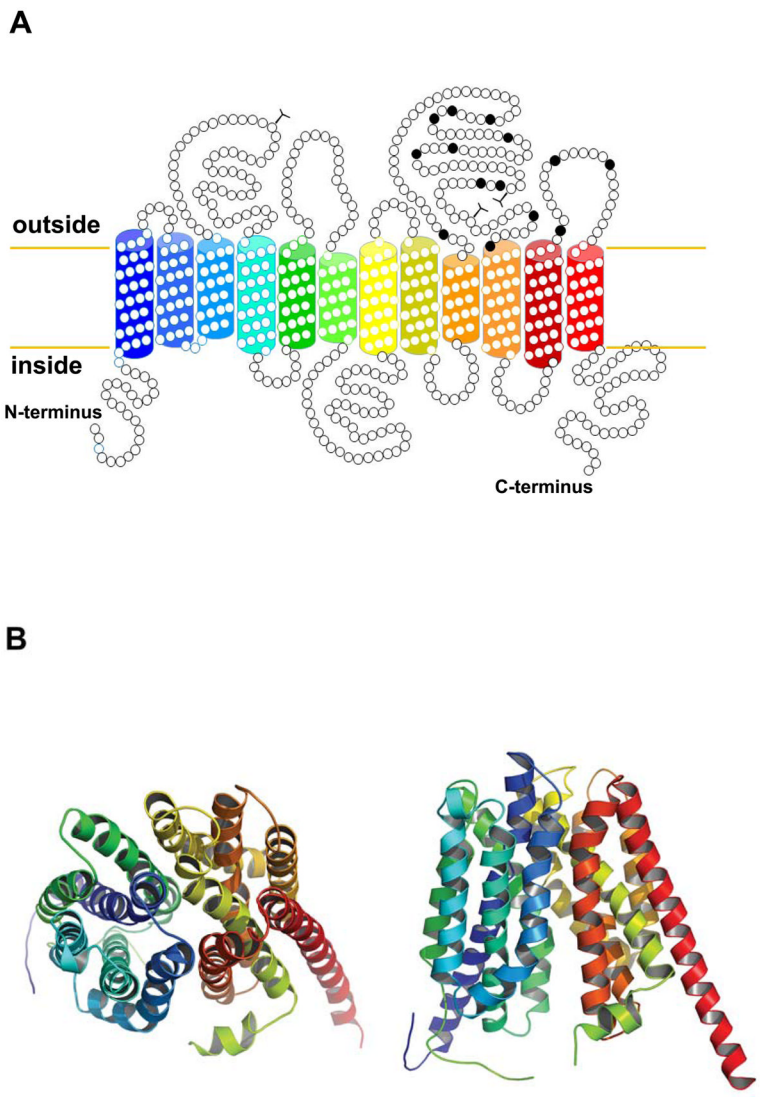

Figure 3.

Topology models for OATP1B1. A) The predicted secondary structure model for OATP1B1 is shown with 12 transmembrane domains. The extracellular conserved cysteine residues are labelled in black. B) Homology modelling was performed as described (Roth et al., 2012) based on the *E. coli* glycerol-3-phosphate transporter. OATP1B1 is shown from the extracellular side (left) and from within the lipid bilayer (right). Colors of the transmembrane domains match the colors used in the secondary structure model.

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Table 1

The human members of the organic anion transporting superfamily

New gene symbol	New protein name	Predominant substrates	Tissue distribution/subcellular expression	Link to disease	Human gene locus	Sequence Accession ID	Splice variants
SLCO1A2	OATP1A2	Bile salts, organic anions and cations	Brain (endothelial cells), kidney (apical), intestine (apical), liver (cholangiocytes), eye (ciliary body)		12p12	NM_021094 NM_134431	2
SLCO1B1	OATP1B1	Bile salts, organic anions	Liver (hepatocytes)	(Statin-induced myopathy, Rotor Syndrome)	12p	NM_6446	
SLCO1B3	OATP1B3	Bile salts, organic anions	Liver (hepatocytes)	(Unconjugated hyperbilirubinemia, Rotor syndrome)	12p12	NM_019844	
SLCO1C1	OATP1C1	T4,T3, rT3, BSP	Brain (blood-brain barrier), testis (Leydig cells)	(Hyperthyroidism)	12p12.2	NM_017435 NM_001145944 NM_001145945 NM_001145946	4
SLCO2A1	OATP2A1	Prostaglandins	Ubiquitous		3q21	NM_005630	
SLCO2B1	OATP2B1	E-3-S, DHEAS, BSP	Liver (hepatocytes), placenta, intestine (apical), eye (ciliary body)		11q13	NM_007256 NM_001145211 NM_001145212	3
SLCO3A1	OATP3A1	E-3-S, prostaglandin	Testis, heart, brain, ovary		15q26	NM_013272 NM_001145044	2
SLCO4A1	OATP4A1	Taurocholate, T3, prostaglandin	Ubiquitous		20q13.33	NM_016354	
SLCO4C1	OATP4C1	Digoxin, ouabain, thyroid hormones, methotrexate	Kidney (basolateral)		5q21.2	NM_180991	
SLCO5A1	OATP5A1				8q13.3	NM_030958 NM_001146008 NM_001146009	3
SLCO6A1	OATP6A1		Testis		5q21.1	NM_173488	

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Table 2
Endogenous substrates of organic anion transporting polypeptides

If K_m-values are available, data demonstrating transport are omitted. Endogenous concentrations are given for systemic concentration and are, due to space reasons, not necessarily found in the references given in this table. The concentrations found for many substances in plasma vary widely (in some instances more than factor of 10). In addition, many of the listed substance have a considerable binding to plasma proteins. Consequently, the values given should only be taken as approximate.

Transporter	Substrate	Affinity	Plasma concentration	Reference
Rat				
OATP1A1	cholate	54 μM	~ 3 μM	(Eckhardt et al., 1999)
	taurocholate	32 – 50 μM	~ 1 μM	(Eckhardt et al., 1999; Kullak-Ublick et al., 1994; Satlin et al., 1997)
	glycocholate	54 μM	~ 0.1 μM	(Eckhardt et al., 1999)
	taurochenodeoxycholate	7 μM	~ 0.1 μM	(Eckhardt et al., 1999)
	tauroursodeoxycholate	13 μM	~ 0.01 μM	(Eckhardt et al., 1999)
	bilirubinmonoglucuronide		~ 1 μM	(Reichel et al., 1999)
	dehydroepiandrostenone sulfate	5 μM	~ 0.1 nM	(Eckhardt et al., 1999)
	aldosterone	15 nM	~ 0.1 nM	(Bossuyt et al., 1996a)
	cortisol	13 μM	~ 0.1 μM	(Bossuyt et al., 1996a)
	estradiol-17β-glucuronide	3 – 20 μM		(Bossuyt et al., 1996a; Eckhardt et al., 1999; Ishizuka et al., 1998; Kouzuki et al., 1999)
	Estrone-3-sulfate	5 – 12 μM		(Bossuyt et al., 1996a; Eckhardt et al., 1999)
	Leukotriene C_4		~ 1 pM	(Li et al., 1998)
	diiodothyronine (T2)			(Friesema et al., 1999)
	diiodothronine sulfate (T2S)			(Friesema et al., 1999)
	prostaglandine E_2	pH 6.5	~ 1 nM	(Leuthold et al., 2009)
	triiodothyronine (T3)		~ 1 nM	(Friesema et al., 1999)
	triiodothyronine sulfate (T3S)		~ 0.1 nM	(Friesema et al., 1999)
	reverse triiodothyronine (rT3)		~ 0.01 nM	(Friesema et al., 1999)
	reverse triiodothyronine sulfate (rT3S)		~ 0.1 nM	(Friesema et al., 1999)
	thyroxine (T4)		~ 50 nM	(Friesema et al., 1999)
	thyroxine sulphate (T4S)		~ 0.05 nM	(Friesema et al., 1999)
OATP1A3	taurocholate	10–31 μM	~ 1 μM	(Masuda et al., 1999; Takeuchi et al., 2001)
	dehydroepiandrostenone sulfate	9 – 17 μM	~ 0.1 nM	(Reichel et al., 1999; Takeuchi et al., 2001)
	estradiol-17β-glucuronide	3–35 μM		(Noe et al., 1997; Takeuchi et al., 2001)
	estrone-3-sulfate	11–15 μM		Noe, 1997 #333}(Takeuchi et al., 2001)
	thyroxine (T4)	7–20 μM	~ 50 nM	Abe, 1999 #670}(Takeuchi et al., 2001)
	triiodothyronine (T3)	6–44 μM	~ 1 nM	(Abe et al., 1999; Takeuchi et al., 2001)
OATP1A4	cholate	46 μM	~ 3 μM	(Noe et al., 1997)

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Transporter	Substrate	Affinity	Plasma concentration	Reference
	taurocholate	35 – 36 μM	~ 1 μM	(Abe et al., 1999; Noe et al., 1997)
	glycocholate	40 μM	~ 0.1 μM	(Reichel et al., 1999)
	taurochenodeoxycholate	12 μM	~ 0.1 μM	(Reichel et al., 1999)
	tauroursodeoxycholate	17 μM	~ 0.01 μM	(Reichel et al., 1999)
	dehydroepiadrostenone sulfate	17 μM	~ 0.1 nM	(Reichel et al., 1999)
	estradiol-17β-glucuronide	3 μM		(Noe et al., 1997)
	estrone-3-sulfate	11 μM		(Noe et al., 1997)
	prostaglandine E_2	pH 6.5	~ 5 nM	(Leuthold et al., 2009)
	triiodothyronine (T3)	6 μM	~ 1 nM	(Abe et al., 1999)
	thyroxine (T4)	7 μM	~ 50 nM	(Abe et al., 1999)
OATP1A5	cholate	9 μM	~ 3 μM	(Walters et al., 2000)
	taurocholate	18 – 30 μM	~ 1 μM	(Abe et al., 1999; Walters et al., 2000)
	glycocholate	15 μM	~ 0.1 μM	(Walters et al., 2000)
	taurochenodeoxycholate	7 μM	~ 0.1 μM	(Walters et al., 2000)
	glycochenodeoxycholate	6 μM		(Walters et al., 2000)
	tauroursodeoxycholate	7 μM	~ 0.01 μM	(Walters et al., 2000)
	glycoursodeoxycholate	5 μM		(Walters et al., 2000)
	taurodeoxycholate	6 μM	~ 0.1 μM	(Walters et al., 2000)
	glycodeoxycholate	4 μM		(Walters et al., 2000)
	dehydroepiandrostenone sulfate	162 μM	~ 0.1 nM	(Cattori et al., 2001)
	estradiol-17β-glucuronide	39 μM		(Cattori et al., 2001)
	estrone-3-sulfate	268 μM		(Cattori et al., 2001)
	leukotriene C_4		~ 1 pM	(Cattori et al., 2001)
	prostaglandine E_2	35 μM	~ 5 nM	(Cattori et al., 2001)
	thyroxine (T4)	5 μM	~ 50 nM	(Abe et al., 1999)
	triiodothyronine (T3)	7 μM	~ 1 nM	(Abe et al., 1999)
OATP1B2	taurocholate	9 – 27 μM	~ 1 μM	(Cattori et al., 2000; Kakyo et al., 1999)
	dehydroepiadrostenone sulfate	5 μM	~ 0.1 nM	(Cattori et al., 2001)
	estradiol-17β-glucuronide	32 μM		(Cattori et al., 2001)
	estrone-3-sulfate	37 μM		(Cattori et al., 2001)
	arachidonate	96 μM	~ 10 μM	(Kanai et al., 1995)
	CCK8	15 μM	~ 1 pM	(Ismair et al., 2001)
	leukotriene C_4	7 μM	~ 1 pM	(Cattori et al., 2001)
	prostaglandine E_2	13 μM	~ 5 nM	(Cattori et al., 2001)
	triiodothyronine (T3)		~ 1 nM	(Cattori et al., 2000)
	thyroxine (T4)		~ 50 nM	(Cattori et al., 2000)
OATP1C1	taurocholate		~ 1 μM	(Sugiyama et al., 2003)
	CCK-8		~ 1 pM	(Sugiyama et al., 2003)
	estradiol-17β-glucuronide	11 μM		(Sugiyama et al., 2003)

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Transporter	Substrate	Affinity	Plasma concentration	Reference
	estrone		~ 0.1 nM	(Sugiyama et al., 2003)
	estrone-3-sulfate			(Sugiyama et al., 2003)
	dehydroepiandrostenone sulfate		~ 0.1 nM	(Sugiyama et al., 2003)
	dihydrotestosterone		~ 1 nM	(Sugiyama et al., 2003)
	leukotriene C_4		~ 1 pM	(Sugiyama et al., 2003)
	leukotriene E_4			(Sugiyama et al., 2003)
	testosterone		~ 10 nM	(Sugiyama et al., 2003)
	thyroxine (T4)	180 nM	~ 50 nM	(Sugiyama et al., 2003)
	reverse triiodothyronine (rT3)		~ 0.01 nM	(Sugiyama et al., 2003)
	triiodothyronine (T3)		~ 1 nM	(Sugiyama et al., 2003)
OATP2A1	arachidonate	96 μM	~ 10 μM	(Kanai et al., 1995)
	6-keto prostaglandine $F_{1\alpha}$	8 μM	~ 1 nM	(Kanai et al., 1995)
	prostaglandine E_1	70 nM		(Kanai et al., 1995)
	prostaglandine E_2	94 nM	~ 0.1 nM	(Kanai et al., 1995)
	prostaglandine $E_{2\alpha}$	104 nM		(Kanai et al., 1995)
	thromboxane B_2	423 nM	~ 1 nM	(Kanai et al., 1995)
OATP2B1	taurocholate	18 μM	~1 μM	(Nishio et al., 2000)
	leukotriene C_4	3 μM	~ 1 pM	(Nishio et al., 2000)
	prostaglandin D_2	18 μM	~ 10 nM	(Nishio et al., 2000)
	prostaglandin E_1			(Nishio et al., 2000)
	prostaglandin E_2		~ 0.1 nM	(Nishio et al., 2000)
	thromboxane B_2		~ 1 nM	(Nishio et al., 2000)
OATP4A1	taurocholate		~ 1 μM	(Fujiwara et al., 2001)
	triiodothyronine (T3)		~ 1 nM	(Fujiwara et al., 2001)
OATP4C1	triiodothyronine/T3)	2 μM	~ 1 nM	(Mikkaichi et al., 2004)
OATP6B1	taurocholate	9 μM	~ 1 μM	(Suzuki et al., 2003)
	dehydroepiandrostenone sulfate	26 μM	~ 0.1 nM	(Suzuki et al., 2003)
	thyroxine (T4)	6 μM	~ 50 nM+	(Suzuki et al., 2003)
	triiodothyronine (T3)		~ 1 nM	(Suzuki et al., 2003)
OATP6C1	taurocholate	3 μM	~ 1 μM	(Suzuki et al., 2003)
	dehydroepiandrostenone sulfate	22 μM	~ 0.1 nM	(Suzuki et al., 2003)
	thyroxine (T4)	6 μM	~ 50 nM	(Suzuki et al., 2003)
	triiodothyronine (T3)		~ 1 nM	(Suzuki et al., 2003)
human				
OATP1A2	cholate	93 μM	~ 1 μM	(Kullak-Ublick et al., 1995)
	taurocholate	60 μM	~ 0.1 μM	(Kullak-Ublick et al., 1995)
	glycocholate		~ 0.5 μM	(Kullak-Ublick et al., 1995; Kullak-Ublick et al., 2001)
	taurochenodeoxycholate		~ 0.5 μM	(Kullak-Ublick et al., 1995)

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Transporter	Substrate	Affinity	Plasma concentration	Reference
	tauroursodeoxycholate	19	~ 0.001 μM	(Kullak-Ublick et al., 1995)
	bilirubin		~ 10 μM	(Briz et al., 2003)
	estradiol-17β-glucuronide			(Briz et al., 2003; Kullak-Ublick et al., 2001)
	estrone-3-sulfate	16 – 59	~ 2 nM	(Bossuyt et al., 1996b; Lee et al., 2005)
	dehydroepiandrostenone sulfate	7 μM	~ 5 μM	(Kullak-Ublick et al., 1998)
	prostaglandin E_2		~ 1 nM	(Kullak-Ublick et al., 2001)
	reverse triiodothyronine (rT3)		~ 0.1 nM	(Fujiwara et al., 2001)
	triiodothyronine (T3)	7 μM	~ 1 nM	(Fujiwara et al., 2001)
	triiodothyronine sulfate (T3S)		~ 0.1 nM	(van der Deure et al., 2010)
	thyroxine (T4)	8 μM	~ 100 nM	(Fujiwara et al., 2001)
	thyroxine sulfate (T4S)		~ 10 pM	(van der Deure et al., 2010)
OATP1B1	cholate	11 μM	~ 1μM	(Cui et al., 2001)
	taurocholate	10 – 34 μM	~ 0.1 μM	(Abe et al., 1999; Cui et al., 2001; Hsiang et al., 1999)
	glycocholate		~ 0.5 μM	(Kullak-Ublick et al., 2001)
	tauroursodeoxycholate	7 μM	~ 0.001 μM	(Maeda et al., 2006)
	glycoursodeoxycholate	5 μM	~ 0.1 μM	(Maeda et al., 2006)
	bilirubin	8 – 160 nM	~ 10 μM	(Briz et al., 2003; Cui et al., 2001)
	bilirubinmonoglucuronide	100 nM	~ 1 μM	(Cui et al., 2001)
	bilirubindiglucuronide	280 nM	~ 1 μM	(Cui et al., 2001)
	estradiol-17β-glucuronide	4–14 μM		(Cui et al., 2001; Hirano et al., 2004; Konig et al., 2000b; Nakai et al., 2001; Tamai et al., 2001)
	estrone-3-sulfate	458 nM – 13 μM 68 – 94 nM and 5 – 7μM	~ 2 nM	(Cui et al., 2001; Hirano et al., 2004) (Tamai et al., 2001)
	dehydroepianstrostenone sulfate	22 μM	~ 5 μM	(Cui et al., 2001)
	leukotriene C_4		~ 10 pM	(Abe et al., 1999; Kullak-Ublick et al., 2001)
	leukotriene E_4		~ 0.1 nM	(Abe et al., 1999)
	prostaglandine E_2		~ 1 nM	(Abe et al., 1999; Kullak-Ublick et al., 2001; Tamai et al., 2000)
	reverse triiodothyronine sulphate (rT3S)		~ 10 nM	(van der Deure et al., 2008a)
	triiodothyronine (T3)	3 μM	~ 1 nM	(Abe et al., 1999)
	triiodothyronine sulphate (T3S)		~ 0.1 nM	(van der Deure et al., 2008a)
	thyroxine (T4)	3 μM	~ 100 nM	(Abe et al., 1999)
	thyroxine sulphate (T4S)		~ 10 pM	(van der Deure et al., 2008a)
	thromboxane B_2		~ 0.1 nM	(Abe et al., 1999)
OATP1B3	cholate	42 μM	~ 1 μM	(Briz et al., 2006)
	taurocholate	6 – 42 μM	~ 0.1 μM	(Abe et al., 2001; Briz et al., 2006)

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Transporter	Substrate	Affinity	Plasma concentration	Reference
	glycocholate	43 μM	~ 0.5 μM	(Briz et al., 2006)
	taurochenodeoxycholate		~ 0.5 μM	(Briz et al., 2006)
	tauroursodeoxycholate	16 μM	~ 0.001 μM	(Maeda et al., 2006)
	glycoursodeoxycholate	25 μM	~ 0.1 μM	(Maeda et al., 2006)
	taurodeoxycholate		~ 0.5 μM	(Briz et al., 2006)
	bilirubin	39 nM	~ 10 μM	(Briz et al., 2003)
	bilirubinmonoglucuronide	500 nM	~ 1 μM	(Cui et al., 2001)
	CCK8	4 – 11 μM	~ 1 pM	(Hirano et al., 2004; Ismair et al., 2001)
	dehydroepiandrostenone sulfate		~ 5 μM	(Konig et al., 2000a)
	estradiol-17β-glucuronide	5 – 25 μM		(Cui et al., 2001; Hirano et al., 2004; Konig et al., 2000a)
	estrone-3-sulfate	73μM (pH 8.0) 55μM (pH 6.5)	~ 2 nM	(Leuthold et al., 2009)
	dehydroepiandrostenone sulfate	> 30 μM	~ 5 μM	(Cui et al., 2001)
	glutathione	5 μM		(Briz et al., 2006)
	leukotriene C_4		~ 10 pM	(Konig et al., 2000a; Kullak-Ublick et al., 2001)
	prostaglandine E_2		~ 1 nM	(Kullak-Ublick et al., 2001; Tamai et al., 2000)
	triiodothyronine (T3)	6 μM	~ 1 nM	(Abe et al., 2001)
	thyroxine (T4)		~ 100 nM	(Kullak-Ublick et al., 2001)
OATP1C1	taurocholate		~ 0.1 μM	(Leuthold et al., 2009)
	estradiol-17β-glucuronide			(Pizzagalli et al., 2002)
	estrone-3-sulfate		~ 2 nM	(Pizzagalli et al., 2002)
	reverse triiodothyronine (rT3)	128 nM	~ 0.1 nM	(Pizzagalli et al., 2002)
	thyroxine (T4)	90 – 120 nM	~ 100 nM	(Pizzagalli et al., 2002; van der Deure et al., 2008b)
	thyroxine sulfate (T4S)	3 μM	~ 10 pM	(van der Deure et al., 2008b)
	triiodothyronine (T3)		~ 1 nM	(Pizzagalli et al., 2002)
OATP2B1	taurocholate	72μM (pH 5.0)	~ 0.1 μM	(Nozawa et al., 2004)
	estrone-3-sulfate	5 – 21 μM	~ 2 nM	(Kullak-Ublick et al., 2001; Tamai et al., 2001) (Grube et al., 2006a; Hirano et al., 2006; Nozawa et al., 2004; Pizzagalli et al., 2003)
	dehydroepadrostenone sulfate	9 μM	~ 5 μM	(Pizzagalli et al., 2003)
	prostaglandine E_2		~ 1 nM	(Tamai et al., 2000)
	tyroxine (T4)	770 nM (pH 8.0) 310 nM (pH 6.5)	~ 100 nM	(Leuthold et al., 2009)
OATP2A1	prostaglandin D_2			(Lu et al., 1996)
	prostaglandin E_1			(Lu et al., 1996)
	prostaglandin E_2		~ 1 nM	(Kraft et al., 2010; Lu et al., 1996)

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Transporter	Substrate	Affinity	Plasma concentration	Reference
	prostaglandin $F_{2\alpha}$		~ 10 pM	(Lu et al., 1996)
	thromboxane B_2		~ 0.1 nM	(Lu et al., 1996)
OATP3A1	estrone-3-sulfate		~ 2 nM	(Tamai et al., 2000)
	prostaglandine E_1	49 nM		(Adachi et al., 2003)
	prostaglandine E_2	56 nM	~ 1 nM	(Adachi et al., 2003)
	prostaglandine F_2			(Adachi et al., 2003)
OATP3A1_v1	estrone-3-sulfate	pH 6.5	~ 2 nM	(Leuthold et al., 2009)
	prostaglandine E1	101 nM		(Huber et al., 2007)
	prostaglandine E2	218 nM	~ 1 nM	(Huber et al., 2007)
	tyroxine (T4)		~ 100 nM	
	vasopressin		~ 1 pM	(Huber et al., 2007)
OATP3A1_v2	arachidonate		~ 0.1 nM	(Huber et al., 2007)
	estrone-3-sulfate	pH 6.5	~ 2 nM	(Leuthold et al., 2009)
	prostaglandine E_1	218 nM		(Huber et al., 2007)
	prostaglandine E_2	371 nM	~ 1 nM	(Huber et al., 2007)
	tyroxine (T4)	pH 6.5	~ 100 nM	(Leuthold et al., 2009)
	vasopressin		~ 1 pM	(Huber et al., 2007)
OATP4A1	taurocholate	15 μM	~ 0.1 μM	(Fujiwara et al., 2001)
	estradiol-17β-glucuronide			(Tamai et al., 2000)
	estrone-3-sulfate		~ 2 nM	(Tamai et al., 2000)
	prostaglandine E_2		~ 1 nM	(Tamai et al., 2000)
	triiodothyronine (T3)	1 μM	~ 1 nM	(Fujiwara et al., 2001)
	reverse triiodothyronine (rT3)		~ 0.1 nM	(Fujiwara et al., 2001)
	thyroxine (T4)		~ 100 nM	(Fujiwara et al., 2001)
OATP4C1	glycoycholate		~ 0.5 μM	(Yamaguchi et al., 2010)
	chenodeoxycholate		~ 0.5 μM	(Yamaguchi et al., 2010)
	cAMP		~ 10 nM	(Mikkaichi et al., 2004)
	estrone-3-sulfate	27 μM	~ 2 nM	(Yamaguchi et al., 2010)
	triiodothyronine (T3)	6 μM	~ 1 nM	(Mikkaichi et al., 2004)
	tyroxine (T4)		~ 100 nM	(Mikkaichi et al., 2004)