

In Vitro and In Vivo Evidence of the Importance of Organic Anion Transporters (OATs) in Drug Therapy

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Abstract Organic anion transporters 1-10 (OAT1-10) and the urate transporter 1 (URAT1) belong to the SLC22A gene family and accept a huge variety of chemically unrelated endogenous and exogenous organic anions including many frequently described drugs. OAT1 and OAT3 are located in the basolateral membrane of

renal proximal tubule cells and are responsible for drug uptake from the blood into the cells. OAT4 in the apical membrane of human proximal tubule cells is related to drug exit into the lumen and to uptake of estrone sulfate and urate from the lumen into the cell. URAT1 is the major urate-absorbing transporter in the apical membrane and is a target for uricosuric drugs. OAT10, also located in the luminal membrane, transports nicotinate with high affinity and interacts with drugs. Major extrarenal locations of OATs include the blood–brain barrier for OAT3, the placenta for OAT4, the nasal epithelium for OAT6, and the liver for OAT2 and OAT7. For all transporters we provide information on cloning, tissue distribution, factors influencing OAT abundance, interaction with endogenous compounds and different drug classes, drug/drug interactions and, if known, single nucleotide polymorphisms.

Keywords Organic anion transporter · Drug/drug interaction · Kidney · Proximal tubule · Single nucleotide polymorphisms · Species differences · Gender differences · Tissue localization · ACE inhibitors · Antibiotics · Antidiabetics · Antineoplastics · Antivirals · AT1 receptor blockers · Diuretics · Histamine receptor antagonists · NSAIDs · Statins

1 Organic Anion Transporters Within the SLC22A Gene Family

The human SCL22 family of transporters encompasses at least 22 members with an additional six structurally related but not yet assigned genes. The respective Slc22 families of rats and mice contain 21 and 23 members, respectively, and each six unassigned genes (Jacobsson et al. 2007). Substrates of the transporters encoded by these genes are organic cations, organic anions, and/or carnitine. For at least half of the gene products, transport function and substrate specificity have not been determined so far. Table 1 shows those SLC22 family members that have been functionally proven as organic anion transporters in humans, rats, and mice. Transporters for organic cations (SLC22A1-3), organic cations, and carnitine (SLC22A4, 5, and 16) as well as orphan transporters (SLC22A10, 13-15, 17-25, and unassigned gene products) are not included.

In this review, we restrict ourselves to organic anion transporters that have been functionally characterized, including human OAT1-4, OAT7, OAT10, and URAT1 (transporter symbols in capital letters for primates) as well as Oat1-3, Oat5-6, Oat8-9, and Rst/Urat1 from rodents (transporter symbols in lowercase for nonprimates). Human OAT1 to OAT4, URAT1, and OAT10 have been identified, at least at the mRNA level, in various organs and cells (Table 2). Of these transporters, OAT1, OAT3, OAT4, URAT1, and OAT10 are predominantly expressed in kidneys (Nishimura and Naito 2005; Bahn et al. 2008). There are contradictory results with respect to the presence and absence of mRNA expression of OATs in the following

Table 1 Functionally characterized organic anion transporters in humans, rats, and mice

Gene names	Chromosomal position			Protein names, aliases
	Man	Rat	Mouse	Human/rodents
SLC22A6/Slc22a6	11q12.3	1q43	19qA	OAT1/Oat1
SLC22A7/Slc22a7	6p21.1	9q12	17qB3	OAT2/Oat2, Nlt
SLC22A8/Slc22a8	11q12.3	1q43	19qA	OAT3/Oat3, Roct
SLC22A9/Slc22a9	11q12.3	1q43	–	OAT7, UST3/Oat8, Ust1
SLC22A11/–	11q13.1	–	–	OAT4/–
SLC22A12/Slc22a12	11q13.1	1q43	19qA	URAT1/Rst
SLC22A13	3p21.2	8q32	9qF3	OAT10/ORCTL3/Oct11
–/Slc22a19	–	1q43	19qA	–/Oat5
–/Slc22a20	–	1q43	19qA	–/Oat6

Data are adapted from Jacobsson et al. (2007)

human tissues: adrenal gland, epididymis, heart, liver, lung, skeletal muscle, stomach, testis, and thyroid gland. The reported discrepancies might be the result of different methods for mRNA preparation, the quality of the mRNA, the usage of different primer sets, and other experimental procedures that determine the detection limit of mRNA expression.

Within the kidneys of various species, organic anion transporters are expressed in proximal tubules and, for rodent Oat3, also in connecting tubules and collecting ducts (see Fig. 1). In proximal tubules of all species, OAT1/Oat1 and OAT3/Oat3 are localized in the basolateral membrane and take up organic anions and anionic drugs from the blood into the tubule cell. OAT2 is present in the basolateral membrane in humans, but in the apical membrane in rodents. The transport mode of OAT2/Oat2 is still unclear. The transporters OAT4, OAT10, and URAT1/Urut1 are located in the apical membrane of proximal tubules. OAT4 operates in uptake and release mode for organic anions. URAT1 is involved in urate absorption from the filtrate, and OAT10 in the absorption of nicotinate. Also indicated in Fig. 1 are sex differences occurring in rats and mice, but potentially not in other species. Gender and species differences cloud a straightforward cross-species comparison of renal handling of organic anions and drugs.

2 Organic Anion Transporter 1 (OAT1/Oat1; Gene name SLC22A6/Slc22a6)

2.1 Cloning, Structure

The organic anion transporter 1 was cloned from man (Reid et al. 1998; Cihlar et al. 1999; Hosoyamada et al. 1999; Lu et al. 1999; Race et al. 1999), monkey (Tahara et al. 2005b), pig (Hagos et al. 2002), rabbit (Bahn et al. 2002), rat (Sekine et al. 1997; Sweet et al. 1997), and mouse (Lopez-Nieto et al. 1997). Initially used aliases were PAHT for human (Lu et al. 1999), ROAT1 for human and rat (Sweet et al.

Table 2 Expression of human organic anion transporter mRNAs in various tissues

Organ/tissue	OAT1	OAT2	OAT3	OAT4	URAT1	OAT10
Adipose	+	—	—		+	
Adrenal gland	—, +	+	—	—	—, +	+
Bladder	+	+	—	—	—	
Bone marrow	—	+	—	—	—	+
Brain (total)	+	+	+	—	—	+
Cerebellum	+	+	+	—	+	
Hippocampus	+	+	+	—	+	
Hypothalamus	+	+	+	—	—	
Pons	+	+	+	—	—	
Temporal cortex	—	+	—	—	—	
Cervix	—	+	—	—	—	
Choroid plexus	+					
Colon	—	—, +	—, +	—	—	+
Duodenum	—	+	—	—	—	
Epididymis	+	+				
Heart	—, +	+	—	—	—, +	+
Ileum	—	+	—	—	+	
Jejunum	—	+	—	—	—, +	+
Kidney	+	+	+	+	+	+
Liver	—, +	+	—, +	—, +	—	+
Lung	—, +	+	—	—	—, +	+
Mammary gland	+	+	+	—	—	
Ovary	—	+	—	—	—	
Pancreas	—	+	—	—	—	+
Peripheral leukocytes	—	+	—	—	—, +	
Pituitary	+	+	—	—	+	
Placenta	—	+	—	+	—, +	+
Prostate	—	+	—	—	—, +	+
Retina (eye)	+	+	+	—	—	
Salivary gland	+	+	—	—	—, +	+
Sertoli cells	—	+	—			
Skeletal muscle	—, +	+	—	—	—, +	—, +
Skin	—	+	—	—	—	
Spinal cord	+	+	+	—	—	+
Spleen	+	—	+	—	—	+
Stomach	—, +	+	—	—	—	+
Testis	—, +	+	—	—	+	+
Thymus	+	+	—	—	—	+
Thyroid gland	—, +	+	—	—	—	+
Trachea	+	+	+	—	—	+
Uterus	+	+	+	—	—	+

+, mRNA was found in the respective tissue; —, no mRNA was found or amount of mRNA was below detection limit; blank, not tested for mRNA expression. Data are derived from: Lopez-Nieto et al. (1997), Race et al. (1999), Hosoyamada et al. (1999), Lu et al. (1999), Cihlar et al. (1999), Sun et al. (2001), Alebouyeh et al. (2003), Nishimura and Naito (2005), Bleasby et al. (2006) and Hilgendorf et al. (2007)

1997; Reid et al. 1998), and NKT for mouse (Lopez-Nieto et al. 1997) organic anion transporter 1, respectively. Transporters cloned from winter flounder (fROAT; Wolff et al. 1997) and *Caenorhabditis elegans* (ceOAT1; George et al.

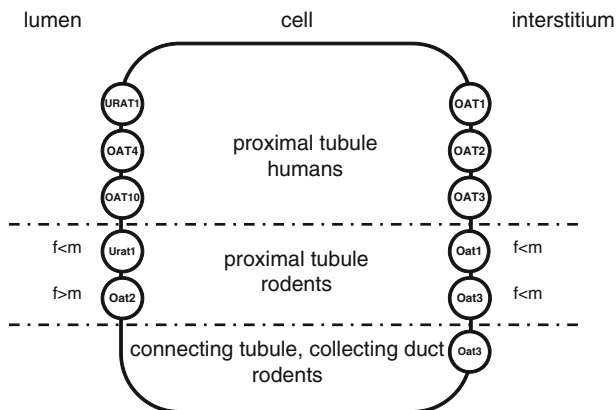


Fig. 1 Cellular localization of organic anion transporters in renal tubule cells and species and gender differences. $f > m$, transporter expression in female rodents is higher than in male rodents; $f < m$, transporter expression in female rodents is lower than in male rodents

1999) may not be homologues of OAT1, and are not discussed further in this review.

The human OAT1 protein is composed of 563 (long isoform; OAT1-1) or 550 (predominantly expressed shorter isoform; OAT1-2) amino acids (Hosoyamada et al. 1999). Two further splice variants, OAT1-3 and OAT1-4, were found to be nonfunctional (Bahn et al. 2000, 2004). Rat and mouse Oat1 have 551 and 546 amino acids, respectively (Sweet et al. 1997; Lopez-Nieto et al. 1997). Secondary structure prediction revealed twelve putative transmembrane helices with intracellularly located *N*- and *C*-termini, a large extracellular loop between helices 1 and 2, and a large intracellular loop between helices 6 and 7 (overview in: Burckhardt and Wolff 2000; Koepsell and Endou 2004). This predicted topology was verified for the hOAT1 (Hong et al. 2007). Four of the five potential *N*-glycosylation sites within the large extracellular loop of human and mouse OAT1 are glycosylated for proper targeting of OAT1 to the plasma membrane and its function (Tanaka et al. 2004). The *in vivo* use of predicted phosphorylation sites for protein kinases A and C, casein kinase II, and tyrosine kinase (overview in Burckhardt and Wolff 2000) in the regulation of OAT1 activity is not yet clear.

2.2 Tissue Distribution of mRNA

OAT1/Oat1 transcripts are expressed abundantly in the kidneys of humans (Lopez-Nieto et al. 1997; Cihlar et al. 1999; Hosoyamada et al. 1999; Lu et al. 1999; Race et al. 1999; Sun et al. 2001; Nishimura and Naito 2005; Bleasby et al. 2006), monkeys (Tahara et al. 2005b; Bleasby et al. 2006), sheep (Wood et al. 2005), pigs (Hagos et al. 2002), dogs (Bleasby et al. 2006), rabbits (Bahn et al. 2002), rats

(Sekine et al. 1997; Sweet et al. 1997; Bleasby et al. 2006), and mice (Lopez-Nieto et al. 1997; Bleasby et al. 2006). In human (Motohashi et al. 2002) and rat (Leazer and Klaassen 2003; Augustine et al. 2005) renal cortex, the mRNA for OAT1 was second most abundant, following that of OAT3. In other studies on human kidney, OAT1 mRNA was equal to or slightly higher than that of OAT3 (Sakurai et al. 2004; Hilgendorf et al. 2007).

Table 3 shows that messenger RNA for OAT1/Oat1 was also detected in brain (human: Cihlar et al. 1999; Race et al. 1999; rat: Sekine et al. 1997; mouse: Lopez-Nieto et al. 1997), including mouse choroid plexus (Sweet et al. 2002). Microarray analyses on human brain tissues revealed a low mRNA expression in temporal cortex, hypothalamus, hippocampus, and cerebellum, as well as in retina (Bleasby et al. 2006). Further organs and tissues expressing low levels of OAT1/Oat1 mRNA included liver, stomach, pancreas, salivary glands, urinary bladder, skeletal muscle, and mammary glands; also some blood cells, that is, leukocytes, neutrophils, and mononuclear cells expressed OAT1 mRNA to a limited extent (Bleasby et al. 2006; for an overview see Table 2). In general, OAT1/Oat1 expression was much higher

Table 3 Cross-species mapping of OAT1/Oat1 with respect to mRNA and protein expression

OAT1/Oat1 Organ/tissue	Human		Rat		Mouse	
	mRNA	Protein	mRNA	Protein	mRNA	Protein
Adrenal gland	-, +			Zona fasc.		
Brain (total)	+		-		+	Neurons
Brain cerebellum	+				+	
Brain hippocampus	+	+			+	
Brain hypothalamus	+					
Brain pons	+					
Brain temporal cortex	-					
Choroid plexus	+	Membrane cytoplasm	+		+	
Heart	-, +		-		-	
Ileum	-		-			
Jeenum	-		-			
Kidney	+	S2/S3 bl	+	S2 bl	+	S1/S2 bl
Liver	-, +		-		-	
Lung	-, +		-		-	
Placenta	-, +				-	
Retina (eye)	+		-			
Sertoli cells	-		-			
Skeletal muscle	-, +		-			
Spleen	-		-		-	
Stomach	-, +				-	
Testis	-, +		+			

+, mRNA was found in the respective tissue; -, no mRNA was found or the amount of mRNA was below detection limit; blank, not tested. bl, basolateral membrane; S1, S2, S3, segments of proximal tubules; zona fasc., zona fasciculata. Data are collected from: Lopez-Nieto et al. (1997), Sekine et al. (1997), Hosoyamada et al. (1999), Tojo et al. (1999), Kojima et al. (2002), Motohashi et al. (2002), Sweet et al. (2002), Alebouyeh et al. (2003), Beéry et al. (2003), Bahn et al. (2005), Nishimura and Naito (2005) and Tahara et al. (2005b)

in the kidneys than in other organs (Lopez-Nieto et al. 1997; Sekine et al. 1997; Cihlar et al. 1999; Hosoyamada et al. 1999; Lu et al. 1999; Race et al. 1999; Sun et al. 2001; Buist et al. 2002; Buist and Klaassen 2004; Nishimura and Naito 2005; Bleasby et al. 2006). OAT1/Oat1 may thus be regarded as a transporter specific to kidneys.

2.3 Immunolocalization of OAT1/Oat1 Protein

Immunocytochemistry revealed that human and monkey OAT1 as well as rat and mouse Oat1 are located at the basolateral membrane of renal proximal tubular cells (Hosoyamada et al. 1999; Tojo et al. 1999; Nakajima et al. 2000; Enomoto et al. 2002c; Kojima et al. 2002; Motohashi et al. 2002; Ljubojevic et al. 2004; Bahn et al. 2005; Tahara et al. 2005b; Villar et al. 2005; Brandoni et al. 2006a, b; Kwon et al. 2007; Di Giusto et al. 2008, 2009). OAT1/Oat1 is restricted to proximal tubules, in contrast to OAT3/Oat3, which is located in almost all nephron segments (see Sect. 4.3).

In the brain, OAT1 was immunostained in the cytoplasm and the cell membranes of human choroid plexus cells (Alebouyeh et al. 2003). A GFP-Oat1 fusion protein was directed to the apical side of rat choroid plexus cells (Pritchard et al. 1999). Using antibodies, however, Nagata et al. (2002) found Oat3, but not Oat1, in rat choroid plexus. Mouse Oat1, but not Oat3, was found in cortex cerebri and hippocampus where the antibodies stained neurons and their axons (Bahn et al. 2005). In rat adrenal gland, Oat1 was localized to the outer zona fasciculata (Beéry et al. 2003). Taken together, data on immunolocalization of OAT1 in brain and other tissues are scarce and require further experimentation.

2.4 Species Differences, Age and Gender Dependence of Expression

Human OAT1 was found all along the proximal tubule (Motohashi et al. 2002). Rat Oat1 was much higher in the S2 segment than in S1 and S3 segments (Tojo et al. 1999; Enomoto et al. 2002c; Kojima et al. 2002; Ljubojevic et al. 2004; Di Giusto et al. 2008). Mouse Oat1 was high in segments S1 and S2 and very low in S3 (Bahn et al. 2005). Thus, OAT1/Oat1 expression along the proximal tubule exhibited species differences.

Renal Oat1 transcripts appeared at midgestation (Pavlova et al. 2000; Nakajima et al. 2000; Wood et al. 2005; Sweet et al. 2006; Shah et al. 2009), coinciding with proximal tubule differentiation, and gradually increased during nephron maturation. Controversial observations were made with regard to Oat1 protein expression. Whereas Nakajima et al. (2000) observed Oat1 protein only in Western blots, but

not in kidney sections of rat embryonic day 20, Sweet et al. (2006) observed in a rat kidney culture model Oat1 staining at comparable embryonic days. Using fetal rat kidney slices of embryonic day 20, probenecid-sensitive PAH or fluorescein uptake was noted (Nakajima et al. 2000). Independent of the species tested, Oat1 increased after birth. Immature rabbits showed less Oat1 mRNA expression than mature animals (Groves et al. 2006). In rats, Oat1 mRNA expression started to rise at day 10 after birth, and reached a maximum in adult animals (Buist et al. 2002). In mice, Oat1 mRNA stayed low and constant until day 25 after birth, and rose thereafter up to day 40 (Buist and Klaassen 2004). These observations indicate an immature excretory capacity of the fetal and neonatal kidney due to low expression of Oat1. In addition, Oat1 mRNA was observed in the fetal brain of rats and man (Pavlova et al. 2000; Bleasby et al. 2006), but not in rat and human fetal liver and lung (Bleasby et al. 2006).

Gender differences in Oat1 mRNA expression were observed in adult rats and mice. From approximately day 30 after birth on, mRNA for rat Oat1 fell slightly in female rats, whereas it further increased in male animals (Buist et al. 2002). Gonadectomy in male rats abolished the gender difference in Oat1 expression, suggesting a regulatory function of testosterone (Buist et al. 2003). Other investigators did not find an influence of testosterone on Oat1 mRNA expression in rats (Urakami et al. 1999; Ji et al. 2002; Kobayashi et al. 2002a). The reason for these discrepancies is not known. In mice, Oat1 mRNA rose from day 25 on, but much more so in male than in female animals (Buist and Klaassen 2004).

Gender-dependent *protein* expression was also tested by immunocytochemistry and Western blots. In prepubertal rats, Oat1 protein expression was weak and gender-independent. In adult female rats, however, Oat1 protein was only 20% that of male rats in Western blots. Staining for OAT1 in the basolateral membranes of proximal tubules was clearly less intense in kidneys from adult female rats as compared to male rats (Ljubojevic et al. 2004). In the same study, testosterone strongly and progesterone slightly increased Oat1 expression, whereas estrogens decreased it. Thus, Oat1 is under positive control of testosterone, leading to a considerably higher expression in adult male rats as compared to adult female rats. Consequently, the renal clearance of Oat1-specific drugs should be higher in male than in female rats. In rabbits, Oat1 expression did not show gender differences (Groves et al. 2006). In pigs and man, gender differences are also absent (Sabolic and coworkers; preliminary results), suggesting that the influence of sex hormones on Oat1 expression is species-dependent.

2.5 Factors Influencing Activity and Abundance of OAT1/Oat1

The expression of the human OAT1 is under positive control of hepatocyte nuclear factors (HNFs). Transfection of HNF-1 α alone or of HNF-1 α and HNF-1 β into HEK293 cells led to the expression of human OAT1 (Saji et al. 2008). HNF-1 α knockout mice exhibited a considerably decreased amount of renal Oat1 (Maher

et al. 2006; Saji et al. 2008). HNF-4 α increased the expression of a reporter construct of the human OAT1 gene promoter (Ogasawara et al. 2007). In this work, HNF-4 α was considered essential for OAT1 expression, but not important for tissue distribution, because HNF-4 α is present in proximal tubules and hepatocytes, whereas OAT1 is not detectable in the liver.

Because proximal tubule cells are endowed with hormone receptors signaling through protein kinases it is important to consider posttranslational modification of OAT1/Oat1. Activation of the conventional protein kinase C (PKC), happening in vivo through receptors for epinephrin and angiotensin II, decreased OAT1/Oat1-mediated transport in model cells (Uwai et al. 1998; Lu et al. 1999; You et al. 2000; Wolff et al. 2003). Transport inhibition was caused by endocytic retrieval of OAT1 from the membrane by a dynamin-dependent process (Wolff et al. 2003; Zhang et al. 2008). Mutation of all potential protein kinase C sites of human OAT1 did not prevent PKC-induced reduction in transport, suggesting that a direct phosphorylation is not important (Wolff et al. 2003). Indeed, PKC activation did not lead to a phosphorylation of OAT1 (You et al. 2000). Because OAT1 interacted with caveolin-2 (Kwak et al. 2005b), caveolin itself or caveolin-associated proteins may be phosphorylated by PKC, leading to endocytosis of OAT1.

Activated through insulin, the nonconventional PKC ζ increased the transport of an Oat1 substrate in rat kidney cortex slices (Barros et al. 2009). Epidermal growth factor increased Oat1-mediated transport activity through a complicated signal cascade involving mitogen-activated kinases, phospholipase A₂-induced release of arachidonic acid, cyclooxygenase 1-dependent production of prostaglandin E₂, binding of released PGE₂ to EP₄ receptors, intracellular elevation of cAMP and, finally, activation of protein kinase A (Sauvant et al. 2002, 2003, 2004).

Recent studies revealed that the expression of OATs is affected in several diseases. These diseases can be, at least in part, simulated by animal models that provided further insight into the regulation of OATs. During the progression of renal insufficiency, various uremic toxins derived from dietary proteins accumulate in the plasma of the patients (for reviews see: Vanholder et al. 2003; Enomoto and Niwa 2007) and are, if not removed by adequate dialysis, risk factors for cardiovascular and further renal diseases (Enomoto and Endou 2005; Obermayr et al. 2008; Saito 2010), as well as for neuropathies and myopathies. In addition, drug metabolism and drug transport can be impaired (Dreisbach and Lertora 2008; Dreisbach 2009), not only in the kidneys but also in the intestinal tract (Naud et al. 2007).

Several groups (Motojima et al. 2002; Deguchi et al. 2004) showed that the uremic toxins indoxyl sulfate, indole acetate, and hippurate are substrates of OAT1/Oat1. Two other compounds, aristolochic acid and ochratoxin A (OTA), induce interstitial nephritis (Pfohl-Leskowics and Manderville 2007; Debelle et al. 2008) and are substrates of Oat1 (Bakhiya et al. 2009; Jung et al. 2001; Tsuda et al. 1999). Low concentrations of OTA increased while high concentrations of OTA decreased the abundance of Oat1 in rat kidney, respectively (Zlender et al. 2009). Hyperuricemia induced by feeding rats for several days with a chow containing uric and oxonic acid (Habu et al. 2005) decreased the expression of Oat1.

OAT expression in various kidney diseases, such as renal insufficiency and nephritic syndrome, was analyzed by real-time PCR (Sakurai et al. 2004). This study showed that the level of human OAT1 mRNA was significantly lower in the kidney of patients with renal diseases than in normal controls. These findings were confirmed in the renal dysfunction models of ischemia/reperfusion (Kwon et al. 2007; Matsuzaki et al. 2007; Schneider et al. 2007; Di Giusto et al. 2008; Schneider et al. 2009) and ureter obstruction (Villar et al. 2005, 2008) where decreased Oat1 mRNA and protein levels were observed. As opposed to renal disease models, Oat1 expression was increased by mimicking hepatic diseases through acute biliary obstruction (Brandoni et al. 2003, 2006a; Torres 2008). After 3 days of bile duct ligation, however, the amount of Oat1 had normalized, but most of the protein was found in intracellular vesicles rather than in the basolateral membrane (Brandoni et al. 2006b).

Induction of fever led to increased concentrations of PGE₂ that not only down-regulated time-dependently the uptake of PAH but also diminished rat Oat1 protein (Sauvant et al. 2006). These observations led to the hypothesis that the increased plasma PGE₂ concentrations observed during fever and inflammation were due to reduced PGE₂ secretory capacity of the kidneys. In line with this hypothesis, COX-2 inhibition attenuated endotoxin-induced downregulation of organic anion transporters in rat renal cortex (Höcherl et al. 2009).

Some drugs caused a decrease in renal OAT1/Oat1 abundance. Cisplatin treatment of mice resulted in tubular damage and decreased Oat1 expression (Aleksunes et al. 2008). Gentamycin, possibly through generation of H₂O₂, decreased human OAT1 expressed in mouse proximal tubule cells (Takeda et al. 2000a). A single dose of methotrexate decreased renal abundance of Oat1 in rats (Shibayama et al. 2006). On the other hand, chronic (7 days) treatment of rats with furosemide or hydrochlorothiazide increased the abundance of Oat1 in Western blots (Kim et al. 2003).

2.6 Substrates

Under physiologic conditions, OAT1/Oat1 most probably operates as an organic anion/ α -ketoglutarate exchanger. The dicarboxylate α -ketoglutarate is a metabolite of the citric acid cycle and, in addition, is taken up into proximal tubule cells at the basolateral cell side via a sodium coupled system, NaDC3. The sodium concentration difference driving α -ketoglutarate through NaDC3 into the cell is maintained by the Na⁺, K⁺-ATPase in the basolateral membrane (Burckhardt and Burckhardt 2003; Wright and Dantzler 2004). By coupling the efflux of α -ketoglutarate to the uptake of various organic anions from the blood OAT1/Oat1 constitutes the first step in organic anion secretion (the second step being the release of organic anions across the apical cell membrane).

OAT1/Oat1 is well known for its very broad substrate specificity: following expression in *Xenopus laevis* oocytes and various cell lines (see VanWert et al.

2010) it interacted with several endogenous and a multitude of exogenous compounds/drugs/toxins of various chemical structures (since 2000 reviewed in: van Aubel et al. 2000; Sekine et al. 2000; Dresser et al. 2001; Burckhardt and Burckhardt 2003; van Montfoort et al. 2003; Lee and Kim 2004; Ho and Kim 2005; Rizwan and Burckhardt 2007; Srimaroeng et al. 2008; vanWert et al. 2010). For most compounds, inhibition of OAT1/Oat1-mediated transport was determined. Inhibition of transport indicates an interaction of the test substance with OAT1/Oat1, but does not prove its translocation by this transporter.

Radiolabeled *p*-aminohippurate (PAH) is the prototypical test anion for OAT1/Oat1. Using various expression systems, K_m values for human OAT1 were found between 3.1 and 112.7 μM with a mean of 28.5 μM (Cihlar et al. 1999; Hosoyamada et al. 1999; Cihlar and Ho 2000; Takeda et al. 2000a, 2001; Islinger et al. 2001; Ichida et al. 2003; Hong et al. 2004; Sakurai et al. 2004; Bleasby et al. 2005; Fujita et al. 2005; Srimaroeng et al. 2005a, b; Tahara et al. 2005b; Perry et al. 2006; Xu et al. 2006b; Kimura et al. 2007; Rizwan et al. 2007; Ueo et al. 2005, 2007; Uwai et al. 2007b; Windass et al. 2007; Zhang et al. 2008). The K_m values for monkey (10.1 μM ; Tahara et al. 2005b), rabbit (15.5 μM ; Bahn et al. 2002), rat (11–85.1 μM ; mean 41.6 μM from 12 publications; Sekine et al. 1997; Uwai et al. 1998, 2000a; Cihlar et al. 1999; Takeda et al. 1999; Pombrio et al. 2001; Sugiyama et al. 2001; Hasegawa et al. 2002; Nagata et al. 2002; Deguchi et al. 2004; Keller et al. 2008; Minematsu et al. 2008), and mouse Oat1 (37 and 162 μM ; Kuze et al. 1999; You et al. 2000) have also been determined.

2.6.1 Endogenous Substrates of OAT1/Oat1

Second messengers. cAMP and cGMP were transported by rat Oat1 (Sekine et al. 1997), and cGMP by human OAT1 (Cropp et al. 2008).

Citric acid cycle intermediates, dicarboxylates. Citrate weakly inhibited OAT1 (Sugawara et al. 2005). The dicarboxylate α -ketoglutarate was transported by human and rat OAT1/Oat1 (Sekine et al. 1997; Lu et al. 1999) and inhibited transport by human OAT1 (Cihlar et al. 1999; Hosoyamada et al. 1999; Lu et al. 1999; Race et al. 1999; Motojima et al. 2002; Ichida et al. 2003; Hagos et al. 2008), monkey OAT1 (Tahara et al. 2005b), rabbit Oat1 (Bahn et al. 2002), rat Oat1 (Sekine et al. 1997; Sweet et al. 1997; Uwai et al. 1998; Nakakariya et al. 2009), and mouse Oat1 (Kuze et al. 1999). Maleate inhibited rat (Shikano et al. 2004) and mouse Oat1 (Kaler et al. 2007a).

The interaction of OAT1/Oat1 with dicarboxylates depended on the length of the carbon chain separating the two negatively charged carboxyl groups with a maximum inhibition by dicarboxylates with five or six carbons (Uwai et al. 1998). Affinities, that is K_m or K_i values, have not been reported for any of the dicarboxylates. For preloading cells, α -ketoglutarate is replaced by the nonmetabolizable glutarate. This five-carbon dicarboxylate was transported by human OAT1 (K_m 6.8 or 10.7 μM ; Cihlar and Ho 2000; Rizwan et al. 2007) and mouse Oat1 (Bahn et al. 2005), and inhibited human (IC_{50} 4.9 or 38.3 μM ; Cihlar and Ho 2000; Kimura et al.

2007), rat (Uwai et al. 1998) and mouse Oat1 (IC_{50} 6.7 μ M; Kaler et al. 2007a). Preloading of cells with glutarate *trans*-stimulated OAT1-mediated uptake of test anions (Ichida et al. 2003; Bakhiya et al. 2007).

Monocarboxylates, short chain fatty acids. Hexanoate and heptanoate inhibited mouse Oat1 with much higher affinity (IC_{50} 38 and 16.7 μ M, respectively) than propionate (IC_{50} 8.18 mM), butyrate (IC_{50} 3.5 mM), and pyruvate (IC_{50} 11.9 mM; Kaler et al. 2007a). Octanoate inhibited human (IC_{50} 5.41 μ M; Jung et al. 2001) and rat Oat1 (Tsuda et al. 1999). Lactate did not inhibit at all human OAT1 (Ichida et al. 2003). Taken together, OAT1/Oat1 has a very low or no affinity for monocarboxylates with three or four carbons, but a very high affinity for monocarboxylates beyond a chain length of six carbons.

Bile salts. Cholate inhibited mouse Oat1 (Kaler et al. 2007a), and deoxycholate inhibited rat Oat1 (Chen et al. 2008). For taurocholate either a weak inhibition (Sugiyama et al. 2001; Islinger et al. 2001; Mori et al. 2004) or no inhibition (Sekine et al. 1997; Uwai et al. 1998; Chen et al. 2008) of human and rat OAT1/Oat1 was reported. Transport of taurocholate by human and rat OAT1/Oat1 was not observed (Sekine et al. 1997; Chen et al. 2008). Thereby, OAT1/Oat1 differs from OAT3/Oat3, which transports taurocholate (see Sect. 4.6.1).

Hormones, hormone derivatives. Corticosterone inhibited rat Oat1 (Beéry et al. 2003). Dehydroepiandrosterone sulfate inhibited rat Oat1, but was not transported (IC_{50} 80.9 μ M; Hasegawa et al. 2003). No transport was also found for human OAT1 (Ueo et al. 2005; Nozaki et al. 2007a). With regard to estrone-3-sulfate (ES), differing results were reported. For human OAT1, either no uptake of ES (Aslamkhan et al. 2006; Ueo et al. 2007; Chen et al. 2008) or a weak uptake (Ueo et al. 2005; Uwai et al. 2007a) was found. In addition, OAT1 was (Srimaroeng et al. 2005b) or was not (Srimaroeng et al. 2005a) inhibited by ES. Monkey OAT1 did not transport ES (Tahara et al. 2005b). Data for rat Oat1 are again ambiguous: ES was not (Sweet et al. 2003; Aslamkhan et al. 2006) or weakly transported (Hasegawa et al. 2003). Rat (IC_{50} 50.1 μ M; Hasegawa et al. 2003) and mouse Oat1 (IC_{50} 203 μ M; Kaler et al. 2007a) were inhibited by ES. The ambiguous handling of ES distinguishes OAT1/Oat1 from OAT3/Oat3 and many other OATs that clearly transport estrone sulfate (see later).

Local hormones. Prostaglandin E_2 was transported by human OAT1 (K_m 0.97 μ M; Kimura et al. 2002), as well as by rat and mouse Oat1 (Sekine et al. 1997; Kaler et al. 2007a). In one study, no transport of PGE_2 by human OAT1 was found (Lu et al. 1999). Prostaglandin $F_{2\alpha}$ was transported by human OAT1 (K_m 0.58 μ M; Kimura et al. 2002); at odds, no inhibition of OAT1 by $PGF_{2\alpha}$ was found in another study (Lu et al. 1999). Most data suggest that OAT1/Oat1 has a very high affinity for these prostaglandins and is able to translocate them.

Purine metabolites, urate. Hypoxanthine and xanthine inhibited OAT1 (K_i 243.9 μ M for xanthine; Sugawara et al. 2005). For urate uptake by human OAT1, two differing K_m values, 197.6 μ M (Sato et al. 2008) and 943 μ M (Ichida et al. 2003) were reported. In another study (Race et al. 1999), no urate transport could be detected. With exception of a single study (Race et al. 1999), an inhibition of human OAT1 by urate was reported with IC_{50} values between 46 and 440 μ M (mean out of

four publications: 295.9 μM ; Cihlar et al. 1999; Hosoyamada et al. 1999; Motojima et al. 2002; Bahn et al. 2004; Sugawara et al. 2005). Rabbit Oat1 was inhibited by urate (Bahn et al. 2002). Rat Oat1 transported urate and was weakly or not inhibited by urate (Sekine et al. 1997; Sweet et al. 1997). Taken together, OAT1/Oat1 interacts with urate and may be involved in proximal tubular urate secretion or absorption (Hediger et al. 2005).

Acidic neurotransmitter metabolites. Several anionic neurotransmitter metabolites including 3,4-dihydroxymandelate, 3,4-dihydroxyphenylacetate, homovanillate, and 5-hydroxyindole acetate and many others inhibited human OAT1 (Alebouyeh et al. 2003) and mouse Oat1 (Bahn et al. 2005).

Mercapturic acid derivatives. The *N*-acetyl-*S*-cysteine conjugates are formed in the liver and renally excreted. *N*-acetyl-*L*-cysteine (NAC) itself only weakly interacted with rat Oat1, but some conjugates showed μmolar affinities, for example *N*-acetyl-*S*-2,4-dinitrophenyl-*L*-cysteine (DNP-NAC; IC_{50} 1.9 μM ; K_m for uptake 2 μM ; Pombrio et al. 2001). Among the many conjugates tested as inhibitors of Oat1 (Pombrio et al. 2001), NAC conjugates of mercury were found to be transported. Radiolabeled NAC-Hg (K_m 44 μM) and NAC-Hg-NAC (K_m 144 μM) were taken up into cells expressing human OAT1 (Aslamkhan et al. 2003; Zalups and Ahmad 2005). Because OAT1/Oat1 takes up mercury conjugates from the blood it contributes to the proximal tubular damage observed after mercury poisoning.

Further compounds. Oat1 knockout mice exhibited a decreased renal organic anion secretion in line with increased plasma concentrations of endogenous organic anions such as 3-hydroxyisobutyrate, 3-hydroxybutyrate, benzoate and others, indicating that these compounds are endogenous substrates of Oat1 (Eraly et al. 2006).

2.6.2 Drugs

OAT1/Oat1 was shown to interact with numerous, frequently prescribed drugs (see Table 4). For reviews see Burckhardt and Burckhardt (2003), Rizwan and Burckhardt (2007), and VanWert et al. (2010).

ACE inhibitors. Transport by human OAT1 was shown for captopril and quinaprilat (Ueo et al. 2005, 2007; Yuan et al. 2009). With rat Oat1, a K_m of 0.56 μM was determined for temocaprilat uptake (Hasegawa et al. 2003). There is, however, no systematic study on transport of ACE inhibitors in any species. Thus, the role of OAT1/Oat1 in ACE inhibitor excretion remains to be studied further.

Angiotensin II receptor I blockers (ARB). A complete list of inhibitory constants is available for human OAT1. Olmesartan (K_m 68.3 nM; IC_{50} 280 nM; Yamada et al. 2007; Sato et al. 2008) and telmisartan (IC_{50} 460 nM; Sato et al. 2008) exhibited very high affinities for OAT1, followed by losartan (IC_{50} 12 μM) and prazosartan (IC_{50} 12 μM), valsartan (IC_{50} 16 μM) and candesartan (IC_{50} 17 μM ; Sato et al. 2008). For rat Oat1, a few, and for mice no IC_{50} values are available, respectively (see Table 4).

Table 4 Drugs interacting with OAT1/Oat1

	Human		Rat		Mouse	
	Transport	Inhibition	Transport	Inhibition	Transport	Inhibition
<i>ACE inhibitors</i>						
Captopril	+	(+)				(+)
Enalaprilat						+
Lisinoprilat						-
Quinaprilat	+					
Temocaprilat			0.56			
<i>Angiotensin II receptor blockers</i>						
Candesartan		17		-		
Losartan		12				
Olmesartan	0.068	0.28				
Prasartan		12		6.47		
Telmisartan		0.46		0.316		
Valsartan		16				
<i>Diuretics</i>						
Acetazolamide	I: 75		+	1,100		
Amiloride	no I					
Bendroflumethazide						8
Bumetanide	+	+ or -; 7.6	+	5.5		
Chlorothiazide		3.78		+		
Cyclothiazide		84.3		+		
Ethacrynate		29.6		+		
Ethoxzolamide				+		
Furosemide	+	14-20	+	9.5		8.1
Hydrochlorothiazide		67.3 or -		150		
Methazolamide		438				
Torsemide		55.2				
Trichlormethiazide		19.2				
<i>Statins/fibrates</i>						
Atorvastatin		-				
Bezafibrate		+				
Fluvastatin		26.3				
Pravastatin	-	408 or -	-	1,150-1,620		
Rosuvastatin	-	-				
Simvastatin		73.6				
<i>Antibiotics</i>						
Amoxicillin				+		
Ampicillin						
Benzympenicillin		+ or -	+ or -	418-2,763		328
Carbenicillin				500		1,280
Cefaclor		1,096				
Cefadroxil		6,140		+		+ or -
Cefamandol		30	+ or -; 450			
Cefazolin	-	100-180	+	72-560		
Cefdinir	(+)	692				
Cefoperazone		210	-	298-480		
Cefoselis	-	2,601				
Cefotaxime		3,130		+ or -		
Cefotiam	-	640	+ or -	2,718		

(continued)

Table 4 (continued)

	Human		Rat		Mouse	
	Transport	Inhibition	Transport	Inhibition	Transport	Inhibition
Cefsulodin				+		
Ceftazidime				+		
Ceftibuten	+	563				
Ceftizoxime	+	3,599				
Ceftriaxone		230		840		
Cephalexin			+	2,310–6,010		
Cephaloridine	(+)	740–2,470	+	1,320–2,330		
Cephalothin		220		290–530		
Cephradine		1,600				
Cinoxacin		+		+		
Ciprofloxacin	–	–			–	–
Chloramphenicol				(+)		
Cloxacillin				+		
Doxycyclin		+				
Erythromycin				–		
Gentamycin				–		
Grepofloxacin			–	(+)		
Levofloxacin		–	–	(+)		
Minocyclin		+				
Nafcillin				+		
Nalidixate		+		+		
Norfloxacin				–		
Ofloxacin				–		
Oxytetracycline		+				
Piperacillin				+		
Streptomycin				–		
Tetracycline	(+)	+				
Ticarcillin						530
Vancomycin				–		
<i>Antivirals</i>						
Acyclovir	342	+	242	981		209
Adefovir	17.2–30.0	28–65	270			36
Amantadine				(+)		
Cidofovir	30–63	60	238			25.7
Cidofovir prodrug	309	1,100				
Didanosine			+	(+)		600
Foscarnet			–	–		
Ganciclovir	896	(+)				
Lamivudine			+			104.3
PMEDAP	+					
PMEG	+					
Stavudine			+	(+)		628
Tenofovir	22.3					81
Trifluridine			+	+		
Vidarabine				(+)		
Zalcitabine	+	1,230	+	(+)		1,479
Zidovudine	45.9	+	41.5–68			78.3

(continued)

Table 4 (continued)

	Human		Rat		Mouse	
	Transport	Inhibition	Transport	Inhibition	Transport	Inhibition
<i>Antineoplastics</i>						
Azathioprine		–				
Cisplatin						–
Imatinib	–					
6-Mercaptopurine			98			
Methotrexate	724 or –	–	0.87–14.9	+	+	901
<i>Immune suppressants</i>						
Cyclosporin A		–		–		
Mycophenolate	–	1.52–10.0				
Tacrolimus		–				
<i>Antidiabetics</i>						
Chlorpropamide				39.5		
Glibenclamide				1.6		
Metformin	–					
Nateglinide				9.2		
Sitagliptin	–	–				
Tolbutamide				55.5		
<i>Histamine receptor 2 blockers/antacidic drugs</i>						
Cimetidine	+	492	+ or –	+ or –	–	1,038
Famotidine	–	–				
Omeprazole		+				
Ranitidine	+					
<i>NSAIDs</i>						
Acetaminophen		639				
Acetylsalicylate	–	769		428		687
Aminopyrine				+		
Antipyrin		(+)				
Benzydamine				+		
Carprofen						+
Diclofenac		4.0–6.07		1.52–4.56		
Diflusinal		0.85		+		
Etodolac		50–103		–		
Flufenamate		+		+		
Flurbiprofen		1.5		+		
Ibuprofen	+ or –	1.38–8.0		3.5–4.33		4.7
Indomethacin	+	3.0–6.72		4.2–10.0		+
Ketoprofen	+ or –	0.98–4.43		0.5–6.11		
Loxoprofen		27.1				
Meclofenamate				+		
Mefenamate		0.14–0.83				
Naproxen		1.18–5.8		2.0–5.54		
Oxiphenbutazone				32		
Paracetamol				2,099		
Phenacetin		200–275		488		
Phenylbutazone		71.6		47.9		
Piroxicam		19.8–62.8		52		
Salicylate	+	280–1.573	+	341–2,110		145
Salicylurate				11		
Sulfinpyrazone				+		

(continued)

Table 4 (continued)

	Human		Rat		Mouse	
	Transport	Inhibition	Transport	Inhibition	Transport	Inhibition
Sulindac		36.2–77.8		99.9		+
Tolmetin		5.08		15.4		
<i>Antihistaminic</i>						
Fexofenadine	–					
<i>Antiepileptic</i>						
Valproate		+		+		
<i>Uricosurics/antihyperuricemia drugs</i>						
Allopurinol		+				
Benzbromarone		4.6				
Probenecid		3.9–12.5		1.44–31		6.4

+, transport of inhibition was observed without determination of K_m , K_i , or IC_{50} ; –, no transport or no inhibition was observed; (+), weak transport or inhibition; blank, not determined; numbers, reported K_m , K_i , or IC_{50} values in micromoles/liter (μM); abbreviations: PMEDAP, 9-(2-phosphonyl-methoxyethyl)-diaminopurine; PMEG, 9-(2-phosphonyl-methoxyethyl)-guanidine. For references see text in Sect. 2.6.2

Diuretics. Table 4 shows *carbonic anhydrase blockers* (acetazolamide, ethoxzolamide, methazolamide), *loop diuretics* (bumetanide, ethacrynate, furosemide, torasemide), and *thiazide diuretics* (bendroflumethiazide, chlorothiazide, cyclothiazide, hydrochlorothiazide, trichloromethiazide). Loop and thiazide diuretics have to reach their downstream target salt transporters from the lumen and thus must be secreted in the proximal tubules. Human OAT1 may be involved in the secretion, because it interacted with many diuretics with high affinity (IC_{50} between 1 and 10 μM : bumetanide, chlorothiazide; Hasannejad et al. 2003) or intermediate affinity (IC_{50} between 10 and 100 μM : furosemide, torasemide, ethacrynate, trichloromethiazide, hydrochlorothiazide, cyclothiazide, acetazolamide; Hasannejad et al. 2003; Bahn et al. 2004; Hagos et al. 2007a). Few quantitative data are available for the interaction of rat and mouse Oat1 with diuretics (see Table 4; Sekine et al. 1997; Uwai et al. 2000b; Shikano et al. 2004; Vallon et al. 2008b). In comparison, OAT1 appears to have a higher affinity for most of the thiazide diuretics whereas loop diuretics exhibit higher affinities for OAT3 (see later). Translocation of diuretics was shown for acetazolamide by rat Oat1 (Uwai et al. 2000b), and for bumetanide and furosemide by human and rat OAT1/Oat1 (Hasannejad et al. 2003; Uwai et al. 2000b). It is likely that other diuretics are transported as well, but direct experimental evidence for transport is still lacking. In Oat1 knockout mice, renal furosemide excretion and, hence, its diuretic action was decreased (Eraly et al. 2006). Furosemide and bendroflumethiazide excretion was not only decreased in Oat1 knockouts, but also in Oat3 knockout mice, indicating that both Oat1 and Oat3 contribute to proximal tubular secretion of diuretics and their targeting to the salt transporters in the distal tubule (Vallon et al. 2008b).

Statins. Fluvastatin (IC_{50} 26.3 μM) and simvastatin (IC_{50} 73.6 μM), but not atorvastatin and rosuvastatin, inhibited human OAT1 (Takeda et al. 2004; Windass et al. 2007). For pravastatin, mixed results for the inhibition of human OAT1 were

obtained (inhibition: Enomoto et al. 2003; Khamdang et al. 2004; Sugawara et al. 2005; no inhibition: Windass et al. 2007). Monkey OAT1 (Tahara et al. 2005b) and rat Oat1 were inhibited by pravastatin (Hasegawa et al. 2002; Khamdang et al. 2004). Pravastatin and rosuvastatin were not transported by any OAT1 (Hasegawa et al. 2002; Takeda et al. 2004).

Antibiotics. The antibiotics tested with OAT1/Oat1 include *penicillines* (amoxicillin, ampicillin, benzylpenicillin, carbenicillin, cloxacillin, nafcillin, piperacillin, ticarcillin), *cephalosporines* (cefaclor, cefadroxil, cefamandol, cefazolin, cefdinir, cefoperazone, cefoselis, cefotaxime, cefotiam, cefsulodin, ceftazidime, ceftibuten, ceftiozime, ceftriaxone, cephalixin, cephaloridine, cephalotin, cephradine), *tetracyclines* (doxycyclin, minocyclin, oxytetracycline, tetracycline), *quinolones* (cinoxacin, ciprofloxacin, grepofloxacin, levofloxacin, nalidixate, norfloxacin, ofloxacin), *aminoglycoside antibiotics* (gentamycin, streptomycin), *macrolide antibiotics* (erythromycin, vancomycin) and others (chloramphenicol).

With exception of benzylpenicillin (Table 4, mixed results; Hosoyamada et al. 1999; Lu et al. 1999) no other penicillins were tested with human OAT1. With rat Oat1, most penicillins inhibited transport. When determined, the affinity of rat Oat1 to benzylpenicillin and carbenicillin and of mouse Oat1 to ticarcillin was low (IC_{50} values greater than 100 μ M; Jariyawat et al. 1999; Nagata et al. 2002; Alebouyeh et al. 2003; Hasegawa et al. 2002, 2003; Deguchi et al. 2004; Kaler et al. 2007a). As shown in Table 4, IC_{50} values are available for the interaction of most cephalosporines with human OAT1. With the exception of cefamandol, the tested compounds inhibited OAT1-mediated transport with low affinities, ranging from 100 μ M to 6.14 mM (Cihlar and Ho 2000; Takeda et al. 2002a; Ueo et al. 2005, 2007). Generally speaking, the affinities of OAT1/Oat1 to penicillins tended to be lower, and to cephalosporines higher than those of OAT3/oat3 to these antibiotics (IC_{50} values compared in Rizwan and Burckhardt 2007).

Tetracyclines inhibited human OAT1, and tetracycline was weakly transported (Babu et al. 2002a). IC_{50} values were not determined, leaving open whether OAT1 contributes to the renal secretion of tetracycline. The quinolones showed weak or no interaction with human, rat, and mouse OAT1/Oat1 (Sekine et al. 1997; Uwai et al. 1998; Jariyawat et al. 1999; Sugawara et al. 2005; VanWert et al. 2008). Erythromycin, gentamycin, streptomycin, and vancomycin did not interact with rat Oat1, and chloramphenicol showed only a weak inhibition of Oat1-mediated transport (Jariyawat et al. 1999).

Antivirals. Due to their nephrotoxicity, antivirals were amply tested on OAT1/Oat1-mediated transport. Antiviral drugs can be structurally classified into *acyclic nucleoside analogues* (acyclovir, ganciclovir), *nucleoside analogues* (didanosine, lamivudine, stavudine, trifluridine, vidarabine, zalcitabine, zidovudine), *nucleotide analogues* (adefovir, cidofovir, tenofovir), and others (amantadine, foscarnet). Although they do not bear a negative charge, the acyclic nucleoside analogues acyclovir (K_m 342 μ M) and ganciclovir (K_m 896 μ M) were transported by human OAT1 with low affinity (Takeda et al. 2002b). Rat Oat1 also transported acyclovir with low affinity (K_m 242 μ M; Wada et al. 2000; Hasegawa et al. 2003), and mouse Oat1 was inhibited by acyclovir with low affinity (IC_{50} 209 μ M; Truong et al.

2008). Among the nucleoside analogues, transport was demonstrated for didanosine, lamivudine, stavudine and trifluridine (rat Oat1; Wada et al. 2000), as well as for zalcitabine and zidovudine (human and rat OAT1; Wada et al. 2000; Takeda et al. 2002b; Hasegawa et al. 2003; Jin and Han 2006). For mouse Oat1, IC_{50} values were determined for didanosine, lamivudine, stavudine, zalcitabine and zidovudine (see Table 4; Truong et al. 2008). The lowest K_m values (highest affinities for transport) were observed with the negatively charged nucleotide analogues adefovir (K_m between 17.2 and 30 μM), cidofovir (K_m between 30 and 63.4 μM), and tenofovir (K_m 22.3 μM) at human OAT1 (Cihlar et al. 1999; Cihlar and Ho 2000; Ho et al. 2000; Bleasby et al. 2005; Aslamkhan et al. 2006; Perry et al. 2006; Chu et al. 2007). As compared to human OAT1, rat Oat1 transported adefovir and cidofovir with lower affinity (Table 4; Cihlar et al. 1999). Mouse Oat1 was inhibited with high affinity by adefovir, cidofovir, and tenofovir (Table 4; Truong et al. 2008). Amantadine and foscarnet showed low or no interaction with rat Oat1 (Lu et al. 1999; Wada et al. 2000). Taken together, OAT1/Oat1 is involved in uptake of most antivirals from the blood into proximal tubule cells. Within the cells, antivirals may be nephrotoxic, an effect that is mediated by OAT1 (Ho et al. 2000), and coadministration with probenecid or NSAIDs attenuated cytotoxicity (Mulato et al. 2000).

Antineoplastics. Methotrexate was transported by rat Oat1 with high affinity (Table 4; Nozaki et al. 2004; inhibition without evaluation of affinity: Sekine et al. 1997; Uwai et al. 1998). Transport of methotrexate was reported also for human OAT1 (K_m 724 μM ; Uwai et al. 2004; other reports: Ueo et al. 2005, 2007) and mouse Oat1 (Kaler et al. 2007a). No transport by human and monkey OAT1 (Lu et al. 1999; Tahara et al. 2005b), and no inhibition of human OAT1 by methotrexate (Lu et al. 1999; Srimaroeng et al. 2005a) were found in other investigations, leaving a somewhat mixed picture of the involvement of OAT1/Oat1 in renal methotrexate handling. 6-mercaptopurine was transported with intermediate affinity by rat Oat1 (Motohashi et al. 2004); azathioprine (Uwai et al. 2007b), cisplatin (Kuze et al. 1999) and imatinib (Hu et al. 2008) did not interact with OAT1/Oat1 (see Table 4).

Immune suppressants. Cyclosporin A and tacrolimus did not interact with human and rat OAT1/Oat1 (Sweet et al. 1997; Cihlar et al. 1999; Uwai et al. 2007b). For mycophenolate, no transport by human OAT1 was found; this compound and its glucuronide metabolites, however, potently inhibited this transporter (Uwai et al. 2007b; Wolff et al. 2007).

Antidiabetics. Glibenclamide (IC_{50} 1.6 μM) and nateglinide (IC_{50} 9.2 μM) inhibited rat Oat1 with high, and chlorpropamide (IC_{50} 39.5 μM) and tolbutamide (IC_{50} 55.5 μM) with intermediate affinities (Uwai et al. 2000a). No transport and no inhibition were observed for metformin and sitagliptin at human OAT1 (Kimura et al. 2005; Chu et al. 2007).

Histamine receptor 2 (HR2) blockers. Cimetidine and ranitidine, but not famotidine were found to be transported by human OAT1 (Burckhardt et al. 2003; Motohashi et al. 2004; Tahara et al. 2005a; Ueo et al. 2005, 2007), monkey OAT1 (Tahara et al. 2006a), rabbit (Zhang et al. 2004), and rat Oat1 (Nagata et al. 2002). No transport and no inhibition were found in another study on rat

Oat1 (Prueksaritanont et al. 2004). Taken together, most studies indicate the transport of cimetidine by OAT1 (and preferably by OAT3, see Sect. 4.6.2).

Nonsteroidal anti-inflammatory drugs (NSAIDs). Numerous NSAIDs were tested on OAT1 as shown in Table 4. Diclofenac (IC_{50} values in μM in brackets) (between 4 and 6.07), diflusalinal (0.85), flurbiprofen (1.5), ibuprofen (1.38; 8.0; 55.6), indomethacin (between 3.0 and 6.72), ketoprofen (between 0.89 and 4.43), mefenamate (0.14; 0.83), naproxen (between 1.18 and 5.8), and tolmetin (5.08) inhibited human OAT1 with IC_{50} values below 10 μM , that is, with high affinity (Cihlar and Ho 2000; Mulato et al. 2000; Khamdang et al. 2002; Kimura et al. 2007; Nozaki et al. 2007b). Inhibition of OAT1 with intermediate affinity (IC_{50} between 10 and 100 μM) was observed with etodolac, loxoprofen, phenylbutazon, piroxicam, and sulindac (see Table 4; Mulato et al. 2000; Jung et al. 2001; Khamdang et al. 2002; Uwai et al. 2004; Nozaki et al. 2007b), and with low affinity with acetaminophen, acetylsalicylate, phenacetin, and salicylate (see Table 4; Cihlar and Ho 2000; Mulato et al. 2000; Khamdang et al. 2002; Ichida et al. 2003; Nozaki et al. 2007b). Data on translocation by OAT1 are conflicting for ibuprofen and ketoprofen (Mulato et al. 2000; Khamdang et al. 2002); no transport was found for acetylsalicylate, but was demonstrated for salicylate (Khamdang et al. 2002). Interaction with rat Oat1 occurred with high affinity (IC_{50} below 10 μM) for diclofenac, ibuprofen, indomethacin, ketoprofen, and naproxen (Apiwattanakul et al. 1999; Uwai et al. 2000c; Nozaki et al. 2004, 2007b). Oxyphenbutazone, phenylbutazone, piroxicam, salicylurate, sulindac, and tometin inhibited rat Oat1 with intermediate affinity (IC_{50} between 10 and 100 μM), and acetylsalicylate, paracetamol, phenacetin, and salicylate with low affinity (see Table 4; Apiwattanakul et al. 1999; Uwai et al. 2000c; Hasegawa et al. 2003; Mori et al. 2004; Nozaki et al. 2004). For mouse Oat1, a few IC_{50} values are available, that is, for acetylsalicylate, ibuprofen, and salicylate (Kaler et al. 2007a). Transport was demonstrated only for salicylate by rat Oat1 (Apiwattanakul et al. 1999; Hasegawa et al. 2003).

Miscellaneous. The antihistaminic fexofenadine was not transported by OAT1 (Tahara et al. 2006a). The antiepileptic drug valproate (valproic acid) inhibited human and rat OAT1/Oat1, but it is not known whether this organic anion is translocated (Sekine et al. 1997; Mori et al. 2004; Sugawara et al. 2005). The uricosuric drug, benzbromarone, inhibited with high affinity human OAT1 (Ichida et al. 2003). For probenecid, see Sect. 2.7.

2.7 Inhibitors

The prototypical, though not OAT1-specific inhibitor is *probenecid* (*p*-(dipropylsulfamoyl) benzoate). This drug was initially developed to decrease the renal excretion of penicillin (Beyer et al. 1951). Following oral administration, absorption is complete involving an unknown uptake system in the intestine. The half-life of probenecid in man is 4–12 h. Probenecid and its metabolites are mainly renally excreted (reviewed in: Cunningham et al. 1981). Meanwhile it is known that

probenecid inhibits several renal organic anion transporters, explaining its action on the excretion of various anionic drugs. Using different expression systems and test anions, human OAT1 was inhibited by probenecid with IC_{50} or K_i values between 4.29 and 12.5 μM (Cihlar and Ho 2000; Ho et al. 2000; Mulato et al. 2000; Jung et al. 2001; Takeda et al. 2001; Ichida et al. 2003; Hashimoto et al. 2004; Khamdang et al. 2004; Chu et al. 2007). A single study reported a higher IC_{50} (45.7 μM ; Kimura et al. 2007). Most of the reported IC_{50} values are below the therapeutic free plasma concentration of probenecid (18.7 μM ; Nozaki et al. 2007b). Rat Oat1 was also inhibited by probenecid with IC_{50} values ranging between 1.44 and 31 μM (Uwai et al. 2000c; Sugiyama et al. 2001; Khamdang et al. 2004; Minematsu et al. 2008). For mouse Oat1, a K_i of 5.2 μM was reported (Kaler et al. 2007a). Monkey and rabbit OAT1/Oat1 were inhibited by probenecid (no IC_{50} or K_i available; Bahn et al. 2002; Tahara et al. 2005b). Probenecid was not transported by rat Oat1 (Uwai et al. 1998). Thus, probenecid binds to OAT1/Oat1 with high to intermediate affinity, but may not be translocated, thereby blocking transport of other organic anions.

2.8 Drug/Drug Interactions

Since OAT1/Oat1 handles numerous drugs, interactions are very likely to occur whenever two or more anionic drugs are coadministered and inhibit each other during renal proximal tubular secretion (for reviews see Eraly et al. 2003a; Mizuno et al. 2003; Shitara et al. 2005; Sweet 2005; Li et al. 2006). Here, we mention few examples of drug/drug interaction that may relate to the action of OAT1.

Probenecid/ β -lactam antibiotics interaction. As mentioned previously, a classic example of (desired) drug/drug interaction is the decrease of renal penicillin excretion by probenecid in man (Beyer et al. 1951; Overbosch et al. 1988). Probenecid also inhibited the uptake of benzylpenicillin into rat kidney (Tsuji et al. 1990). Nowadays, it appears that the probenecid-*penicillin* interaction takes place mainly at OAT3, the main transporter for penicillin excretion (see Sect. 4.6.2). Probenecid also decreased the renal excretion of various cephalosporins (Brown 1993), a drug/drug interaction that may well take place at OAT1.

Probenecid/methotrexate interaction. The reported interaction between probenecid and *methotrexate* in man (Aherne et al. 1978) may not only relate to drug/drug interaction at OAT1 because OAT3 has a much higher affinity for methotrexate than does OAT1 (Takeda et al. 2002c). Nevertheless, probenecid inhibited competitively the uptake of methotrexate by rat Oat1 with a K_i of 15.8 μM (Uwai et al. 2000c), that is, in the range of the free plasma concentration of probenecid (18.7 μM ; Nozaki et al. 2007b).

Probenecid/furosemide interaction. The renal clearance of furosemide (frusemide) was decreased by coapplication of probenecid in man (Homeida et al. 1977; Honari et al. 1977; Vree et al. 1995; for further literature see Uwai et al. 2000b). The interaction may take place at OAT1 and OAT3, the latter having a slightly higher affinity for the diuretic (see Rizwan and Burckhardt 2007). It is highly likely

that probenecid also decreases renal excretion of other loop and thiazide diuretics and thus prolongs their action.

Probenecid/antiviral drug interaction. Oral probenecid decreased the renal excretion of cidofovir in man and attenuated the nephrotoxic effect of this antiviral drug (Cundy et al. 1995; Lalezari et al. 1995). Also in rabbits and cynomolgus monkeys, probenecid decreased cidofovir renal accumulation and toxicity (Cundy et al. 1996; Lacy et al. 1998). Thus, probenecid can be used in antiviral therapy to prevent kidney damage.

NSAID/antiviral drug interaction. Nonsteroidal anti-inflammatory drugs potently inhibited OAT1, the transporter involved in renal excretion of, and in nephrotoxicity caused by, antiviral drugs. Indeed, NSAIDs decreased the adefovir-mediated cytotoxicity in OAT1-expressing cells (Mulato et al. 2000). Thus, NSAIDs may be used clinically to overcome the nephrotoxic effects of antiviral drugs.

NSAID/methotrexate interaction. The coadministration of NSAIDs with methotrexate may cause a life-threatening suppression of hematopoiesis due to the accumulation of methotrexate (e.g., Thyss et al. 1986; Frenia and Long 1992). The affinity of OAT1 for methotrexate is low as compared to OAT3 (Takeda et al. 2002c). Hence, at lower dosages, NSAID/methotrexate interaction may preferably take place at OAT3; at higher dosages of methotrexate, however, OAT1 may become an additional site of drug interaction. As indicated previously and shown in Table 4, NSAIDs inhibited OAT1/Oat1 with affinities ranging between 0.14 and 2,110 μM . Importantly, both affinity and free plasma concentration determine the inhibition of OAT1/Oat1 and, hence, the degree of interaction of NSAIDs with methotrexate. For practically all NSAIDs the plasma concentrations are considerably lower than their IC_{50} values at rat Oat1, suggesting that NSAID/methotrexate interaction does not take place at Oat1 (Nozaki et al. 2004). With human OAT1, salicylate may well be involved in NSAID/methotrexate interaction because its free plasma concentration is 431 μM and its IC_{50} was 84.5 μM (Takeda et al. 2002c).

2.9 Pharmacogenomics

The amino acid diversity (nonsynonymous single nucleotide polymorphisms) in human OAT1 is less frequent than average diversity, suggesting a lower mutability or relatively high selection pressure against mutated OAT1 (Fujita et al. 2005; Urban et al. 2006). Within the promoter region, no polymorphism was found in 63 human nephrectomy specimens (Ogasawara et al. 2008). In another study (Bhatnagar et al. 2006), an A \rightarrow G exchange was found 3,655 bp upstream from the starting point in a subject of Icelandic descent. In noncoding or intronic regions, five SNPs in genomic DNA samples from 92 humans (Bleasby et al. 2005), and 19 SNPs in 276 DNA probes (Fujita et al. 2005) were reported. The functional consequence of these SNPs is not known. In coding regions (exons), nine SNPs were found, seven of which were synonymous and two nonsynonymous, leading to the amino acid substitutions R50H and K525I (Bleasby et al. 2005). Fujita et al.

(2005) detected 12 SNPs in coding regions, six of them being nonsynonymous, leading to the amino acid replacements R50H, P104L, I226T, A256W, R293W, and R454Q. Xu et al. (2005) found two nonsynonymous SNPs, causing the amino acid replacements L7P and R50H (for an overview see Srinaroeng et al. 2008). The mutant R50H found in probes from subjects of African descent (frequency: 0.032 in 160 probes) and in Mexican-Americans (frequency 0.01 in 100 probes), exhibited an unaltered affinity for *p*-aminohippurate, ochratoxin A, and methotrexate (Fujita et al. 2005). The affinities for adefovir, cidofovir, and tenofovir, however, were significantly higher for R50H than for the wild type, suggesting that subjects carrying this SNP may be more prone to toxic side effects of antiviral drugs on the kidneys (Bleasby et al. 2005). The R454Q replacement leads to a nonfunctional transporter (Fujita et al. 2005). Three members of an African family carrying this SNP did not show any change in adefovir clearance, an unexpected finding given the importance of OAT1 for the renal secretion of antivirals. Possibly, another step besides uptake by OAT1 is rate-limiting in the secretion of antivirals.

3 Organic Anion Transporter 2 (OAT2/Oat2, Gene Name SLC22A7/Slc22a7)

3.1 Cloning, Structure

OAT2/Oat2 was cloned from man (Sun et al. 2001), rat (“novel liver transporter NLT”: Simonson et al. 1994; recloned by: Sekine et al. 1998), and mouse (Kobayashi et al. 2002b). The gene coding for human OAT2 is located on chromosome 6p21.1, and is not paired with any other SLC22 gene (Eraly et al. 2003b). The next relative to OAT2 is OAT3 with 37% amino acid identity (Jacobsson et al. 2007). OAT2/oat2 proteins consist of 535–548 amino acids, arranged in 12 putative transmembrane helices with intracellularly located *N*- and *C*-termini (topology not yet experimentally proven). For rat Oat2, two *N*-glycosylation sites, and each two putative phosphorylation sites for protein kinase A and C were described (Simonson et al. 1994). Mouse Oat2 contains three potential *N*-glycosylation and six putative protein kinase C phosphorylation sites (Kobayashi et al. 2002b). The functional importance of these sites is unknown.

3.2 Tissue Distribution of mRNA

Northern blot analysis indicated that hOAT2 and rOat2 mRNA are expressed predominantly in the liver, with lower levels in the kidney and other tissues including choroid plexus (Simonson et al. 1994; Sekine et al. 1998; Sun et al. 2001; Buist et al. 2002; Kobayashi et al. 2002b; Kojima et al. 2002; Sweet et al. 2002; Augustine et al. 2005; Nishimura and Naito 2005; Hilgendorf et al. 2007).

On a quantitative basis, OAT2/Oat2 mRNA was higher in liver, but considerably lower than mRNAs for OAT1 and OAT3 in kidneys (Buist et al. 2002; Hilgendorf et al. 2007).

3.3 Immunolocalization of OAT2/Oat2 Protein

Whereas human OAT2 was documented in the basolateral membrane of proximal tubules (Enomoto et al. 2002b; Kojima et al. 2002), the mouse and rat orthologs were localized to the luminal membrane in the late S3 segment or even the connecting duct (Kojima et al. 2002; Ljubojevic et al. 2007; Zlender et al. 2009). Though it is assumed that OAT2/Oat2 is located in the sinusoidal membrane of hepatocytes, an immunolocalization of Oat2 has not yet been performed to substantiate this hypothesis.

3.4 Species Differences, Age and Gender Dependence of Expression

As indicated previously, the subcellular localization of OAT2/Oat2 in kidneys differs between species. A basolateral localization in the proximal tubules of human kidneys suggests a role of OAT2 in uptake of organic anions from the blood as the first step in secretion. The apical localization in rodent kidneys indicates a different, as yet undefined role of Oat2, for example, the release of organic anions into the urine or the uptake of organic anions from the filtrate.

In rats, there are clear cut gender differences in Oat2 expression. Male rats showed greater mRNA abundance in liver than in kidneys, whereas in adult female rats, Oat2 mRNA in kidneys was higher than in the liver (Buist et al. 2002, 2003; Kato et al. 2002; Kobayashi et al. 2002a; Ljubojevic et al. 2007). In male rats, mRNA expression in rat kidneys remained low, whereas in female rats, mRNA rose sharply after postnatal day 30 (Buist et al. 2002). Gonadectomy decreased renal Oat2 expression, and growth hormone increased it in female rats (Buist et al. 2003). The gender differences were visible also at the level of the protein: female rats showed more immunoreactive protein in the brush-border membrane of S3 cells than male animals; testosterone decreased expression and estrogens and progesterone slightly elevated it (Ljubojevic et al. 2007). In mice, renal Oat2 mRNA expression was also low until day 25 and rose thereafter, however, with no obvious gender differences (Buist and Klaassen 2004; Cheng et al. 2008). However, immunohistological data suggested the presence of gender differences in mice similar to those in the rat (Ljubojevic et al. 2007). An increasing Oat2 expression with no gender differences was observed for rabbit kidneys (Groves et al. 2006). For man, no information is available on gender

differences. Taken together, Oat2 expression in the kidneys is highly age-dependent and, at least in rats, gender-dependent.

3.5 *Factors Influencing Activity and Abundance of OAT2/Oat2*

Oat2 was much less expressed in kidneys and liver of HNF-1 α knockout mice, suggesting an important positive influence of this transcription factor on both renal and hepatic expression (Maher et al. 2006). HNF-4 α stimulated the expression of a human OAT2/reporter gene construct (Popowski et al. 2005). Interestingly, HNF-4 α is downregulated by endogenous and exogenous compounds interacting with the hepatocyte farnesoid receptor (FXR); chenodeoxycholate, for instance, attenuated both HNF-4 α and OAT2 expression (Popowski et al. 2005).

A nitric oxide (NO) donor decreased Oat2 mRNA expression in rat liver slices (Aoki et al. 2008), and an inhibitor of iNOS prevented the decrease of expression following intraperitoneal injection of lipopolysaccharide (LPS) in rats (Cha et al. 2002), suggesting that NO leads to a downregulation of Oat2 expression in hepatocytes. In another study, LPS had no effect on Oat2 expression in rats (Cherrington et al. 2004). Phenobarbital strongly, and rifampicin slightly suppressed hepatic Oat2 expression, indicating that interaction of drugs with nuclear receptors (CAR, CXR, and others) has an impact on Oat2 (Jigorel et al. 2006). In the kidneys, Oat mRNA fell in diabetic rats (Manautou et al. 2008) as well as in cisplatin-treated mice (Aleksunes et al. 2008). Methotrexate treatment, which reduced Oat1 and Oat3, did not change Oat2 expression in rats (Shibayama et al. 2006). The influence of renal disorders on Oat2 has, to our knowledge, not been studied.

3.6 *Substrates*

The mode of operation of OAT2/Oat2 is, to our opinion, not clear. Conflicting results have been published with respect to the interaction with dicarboxylates of 4 and 5 carbons lengths. α -Ketoglutarate (5 carbons), for instance, was transported by human OAT2, but did not inhibit OAT2-mediated transport (Sun et al. 2001) nor did it *trans*-stimulate uptake of estrone-3-sulfate (Kobayashi et al. 2005). Rat Oat2 was reported to either transport α -ketoglutarate (Sekine et al. 1998) or not (Morita et al. 2001). Glutarate (C5) was transported by human OAT2, but did not exert a *trans*-stimulation (Kobayashi et al. 2005). On the other hand, fumarate and succinate (both 4 carbons) *trans*-stimulated OAT2-mediated estrone-3-sulfate uptake (Kobayashi et al. 2005), suggesting that OAT2 may be an organic anion/dicarboxylate exchanger with preference for C4 dicarboxylates.

In most studies OAT2/Oat2 was probed with radiolabeled salicylate, *p*-aminohippurate, and prostaglandin F_{2 α} . Especially PGF_{2 α} appears to be well suited because of a high affinity for OAT2/Oat2 and low background uptake in nonexpressing control cells (Enomoto et al. 2002b).

3.6.1 Endogenous Substrates

Citric acid cycle intermediates. As mentioned previously, α -ketoglutarate may or may not be a substrate of OAT2. Fumarate and succinate *trans*-stimulated OAT2-mediated transport of estrone sulfate and therefore acted as counter anions for exchange (Kobayashi et al. 2005). A systematic survey on citric acid cycle intermediates is, however, missing.

Nucleobases, nucleosides, nucleotides. Adenine, adenosine, cytidine, guanidine, guanosine, GMP, GDP, GTP, and inosine, but not cytosine, thymine, and thymidine were found to be transported by human OAT2 (Cropp et al. 2008).

Cyclic nucleotides. cAMP and cGMP were translocated by OAT2, the latter with a K_m of 88 μM (Sun et al. 2001; Cropp et al. 2008).

Bile acids. Chololate and taurochololate were not transported themselves by rat Oat2 (Sekine et al. 1998), but taurochololate inhibited Oat2 (Morita et al. 2001).

Local hormones. Prostaglandin E_2 (PGE_2) was transported by human OAT2 with an exquisite affinity (K_m 0.71 μM ; Kimura et al. 2002). Rat Oat2 also transported PGE_2 , but with lower affinity (K_m 38.5 μM ; Morita et al. 2001). The K_m values for prostaglandin $\text{F}_{2\alpha}$ ($\text{PGF}_{2\alpha}$) for human and rat OAT2/Oat2 were even lower (0.425 and 0.414 μM , respectively; Kimura et al. 2002; Khamdang et al. 2003).

Sulfated steroid hormones. Estrone-3-sulfate was taken up by human OAT2 (Kobayashi et al. 2005), but not by rat Oat2 (Sekine et al. 1998). Dehydroepiandrosterone sulfate was transported by human OAT2 in one study (Kobayashi et al. 2005), but not in another (Sun et al. 2001).

3.6.2 Drugs

ACE inhibitors. Enalaprilat did not interact with rat Oat2 (Sekine et al. 1998).

Diuretics. As shown in Table 5, loop and thiazide diuretics have been tested with human OAT2, all showing inhibition of OAT2-mediated transport with IC_{50} values ranging from 39.2 μM (cyclothiazide) to 2.2 mM (chlorothiazide) (Hasannejad et al. 2003; Kobayashi et al. 2005). Bumetanide was transported with high affinity in one study (Kobayashi et al. 2005), but not in another (Hasannejad et al. 2003). The carboanhydrase inhibitors acetazolamide and methazolamide did not inhibit transport by OAT2 (Hasannejad et al. 2003). Rat Oat2 was inhibited by bumetanide (Sekine et al. 1998), and mouse Oat2 transported labeled bumetanide with high affinity (Kobayashi et al. 2005). As compared to OAT1/Oat1, the affinities for most diuretics for OAT2/Oat2 are smaller (higher IC_{50} values).

Statins. Pravastatin inhibited OAT2 and rat Oat2 with low affinity (IC_{50} greater than 100 μM ; Khamdang et al. 2004)

Antibiotics. Table 5 shows the antibiotics tested with human OAT2. For most of the cephalosporins the IC_{50} values were in the millimolar range, indicating a low affinity of OAT2 toward these antibiotics (Khamdang et al. 2003). In general, OAT1 had a higher affinity for the same cephalosporins (cf. Table 4). Erythromycin was transported with good affinity by human OAT2 (K_m 18.5 μM ; Kobayashi et al.

Table 5 Drugs interacting with OAT2/Oat2

	Human		Rat		Mouse	
	Transport	Inhibition	Transport	Inhibition	Transport	Inhibition
<i>ACE inhibitor</i>						
Enalaprilat				–		
<i>Diuretics</i>						
Bumetanide	7.52 or –	77.5		+		9.12
Chlorothiazide		2,205				
Cyclothiazide		39.2				
Ethacrynate		121				
Furosemide	–	603				
Hydrochlorothiazide		1,023				
Methazolamide		–				
Trichlormethiazide		1,220				
<i>Statin</i>						
Pravastatin		352		449		
<i>Antibiotics</i>						
Benzympenicillin				+		
Cefadroxil		6,410				
Cefamandol		430				
Cefazolin		5,090				
Cefoperazone		1,140				
Cefotaxime		5,210				
Ceftriaxone		6,760				
Cephaloridine		2,090				
Cephalothin		1,040				
Chloramphenicol		+				
Doxycyclin		(+)				
Erythromycin	18.5	+		–		
Minocyclin		(+)				
Oxytetracycline		(+)				
Rifampicin				+		
Tetracycline	440	+				
<i>Antivirals</i>						
Acyclovir	–	–				
2',3'-Dideoxycytidine			3,080			
Ganciclovir	–	(+)				
Valacyclovir	–					
Zidovudine	26.8	81	26			
<i>Antineoplastics</i>						
6-Fluorouracil	0.054					
Imatinib	–					
6-Mercaptopurine	–					
Methotrexate	+	8.9	+ or –	(+)		
Taxol	0.142					
<i>Histamine receptor 2 blockers</i>						
Cimetidine	+	–		+ or –		
Famotidine	–					
Ranitidine	+					

(continued)

Table 5 (continued)

	Human		Rat		Mouse	
	Transport	Inhibition	Transport	Inhibition	Transport	Inhibition
<i>NSAIDs</i>						
Acetaminophen		+ or –				
Acetylsalicylate	–	–	(+)			
Diclofenac		14.3–18.7		49.3		
Ibuprofen		692		155		
Indomethacin	–	49.5–64.1	0.37			
Ketoprofen	–	272.8–400		1.84		
Mefenamate		20.6–21.7				
Naproxen		486				
Phenacetin		1,878				
Piroxicam		70.3				
Salicylate	+ or –	–	81.2–122			
Sulindac		440				
Tolmetin						

+, transport of inhibition was observed without determination of K_m , K_i , or IC_{50} ; –, no transport or no inhibition was observed; (+), weak transport or inhibition; blank, not determined; numbers, reported K_m , K_i , or IC_{50} values in micromoles/liter (μ M). For references see text in Sect. 3.6.2

2005), and tetracycline with low affinity (K_m 439.9 μ M; Babu et al. 2002a). Other tetracyclines showed weak inhibition. Chloramphenicol inhibited OAT2 (Kobayashi et al. 2005). Benzylpenicillin was only tested with rat Oat2 and inhibited transport (Morita et al. 2001) as did rifampicin (Sekine et al. 1998; Morita et al. 2001), but not erythromycin (Sekine et al. 1998).

Antivirals. With exception of zidovudine no other antiviral drugs were transported by OAT2 (Takeda et al. 2002b). Rat Oat1 transported 2',3'-dideoxycytidine and zidovudine (Morita et al. 2001).

Antineoplastic drugs. Human OAT2 was found to have a very high affinity for 5-fluorouracil and for taxol with half-maximal transport rates at 0.054 μ M and 0.142 μ M, respectively (Kobayashi et al. 2005). Methotrexate was transported by OAT2 and inhibited transport with an IC_{50} of 8.9 μ M (Sun et al. 2001; Kimura et al. 2007). Imatinib and 6-mercaptopurine were not translocated by OAT2 (Mori et al. 2004; Hu et al. 2008). Rat Oat1 did or did not transport methotrexate (Sekine et al. 1998; Morita et al. 2001).

Histamine receptor 2 blockers. Cimetidine and ranitidine, but not famotidine were translocated by human OAT2 (Tahara et al. 2005a). At odds, cimetidine did not inhibit OAT2-mediated $PGF_{2\alpha}$ transport (Khamdang et al. 2004). Weak or no inhibition at all by cimetidine were reported for rat Oat2 (Morita et al. 2001; Khamdang et al. 2004; Minematsu et al. 2008)

NSAIDs. As shown in Table 5, a number of NSAIDs inhibited human OAT2 with IC_{50} values ranging from 14.3 μ M to 1.8 mM. Diclofenac, indomethacin, mefenamate, and piroxicam showed an intermediate affinity (IC_{50} between 10 and 100 μ M); ibuprofen, ketoprofen, naproxen, and sulindac had a low affinity, and phenacetin a very low affinity for OAT2 (Khamdang et al. 2002; Kimura et al. 2007). Acetylsalicylate, indomethacin, and ketoprofen were not transported by

OAT2; and for salicylate, mixed results have been reported (Sun et al. 2001; Khamdang et al. 2002; Kobayashi et al. 2005). Rat Oat2 did transport indomethacin and salicylate and, to some extent, acetylsalicylate (Sekine et al. 1998; Morita et al. 2001; Minematsu et al. 2008), and was inhibited by diclofenac, ibuprofen, and ketoprofen (Morita et al. 2001). In general, the affinity of OAT2/Oat2 toward NSAIDs is considerably lower than that of OAT1/Oat1.

3.7 Inhibitors

No specific inhibitor is present for OAT2/Oat2. The general inhibitor, probenecid, has only a low affinity for OAT2/Oat2 with IC₅₀ values ranging between 410 and 977 μM (Enomoto et al. 2002b; Khamdang et al. 2004; Kimura et al. 2007).

3.8 Drug/Drug Interactions

To our knowledge, no drug/drug interactions have been reported for OAT2.

3.9 Pharmacogenomics

In 63 probes from human kidneys, no single nucleotide polymorphisms were detected in the promoter region (Ogasawara et al. 2008). In the coding region, one synonymous SNP and three nonsynonymous SNPs leading to the amino acid changes T110I, V192I, and G507D were reported (Xu et al. 2005). The functional consequences of these changes have not been tested.

4 Organic Anion Transporter 3 (OAT3/Oat3, Gene Name SLC22A8/Slc22a8)

4.1 Cloning, Structure

The organic anion transporter has been cloned from man (Race et al. 1999; Cha et al. 2001), monkey (Tahara et al. 2005b), pig (Hagos et al. 2005), rabbit (Zhang et al. 2004), rat (Kusuhara et al. 1999), and mouse (alias: roct for reduced in osteosclerosis; Brady et al. 1999). As shown in Table 1, the gene SLC22A8 is located on chromosome 11q12.3, and is paired with SLC22A6, the gene for OAT1 (Eraly et al. 2003b). The close pairing suggests a common ancestor and concerted

regulation of expression of OAT1 and OAT3. Functionally, the flounder organic anion transporter shares substrates with OAT1 and OAT3 and may be related to this presumed common ancestor that is possibly found also in killifish and zebrafish (Aslamkhan et al. 2006). A concerted regulation of expression, however, may not take place, because OAT3 is found also at places where no OAT1 is expressed, for example, the distal tubule or in the liver (see the following). Mammalian OAT3/Oat3 proteins are composed of 536–542 amino acids; secondary structure predictions suggested 12 transmembrane helices with intracellularly located *N*- and *C*-termini. The large extracellular loop between helices 1 and 2 carries potential *N*-glycosylation sites, the large intracellular loop between helices 6 and 7 potential phosphorylation sites for regulation by protein kinases (Cha et al. 2001; reviewed in: Burckhardt and Wolff 2000). In rat Oat3, amino acid residues in transmembrane helix 7, 8, and 11 have been identified by directed mutagenesis to be involved in substrate binding (Feng et al. 2001, 2002).

4.2 Tissue Distribution of mRNA

Northern blot analyses have detected OAT3/Oat3 mRNA in the kidneys of humans (Cha et al. 2001; Sun et al. 2001; Nishimura and Naito 2005; Bleasby et al. 2006), monkeys (Tahara et al. 2005b; Bleasby et al. 2006), dogs (Bleasby et al. 2006), pigs (Hagos et al. 2005), rats (Kusuhara et al. 1999) and mice (Kobayashi et al. 2004). OAT3/Oat3 mRNA was also found in brain (Kusuhara et al. 1999; Cha et al. 2001; Buist et al. 2002; Choudhuri et al. 2003), brain capillaries (Ohtsuki et al. 2002; Kikuchi et al. 2003), liver (Kusuhara et al. 1999; Buist et al. 2002, 2003), skeletal muscle (Cha et al. 2001), and adrenal gland (Asif et al. 2005; Table 2). In all species, OAT3 mRNA expression was highest in the kidneys (Nishimura and Naito 2005; Bleasby et al. 2006). In human kidneys, the mRNA for OAT3 was expressed to a considerably higher extent than that for OAT1 (Motohashi et al. 2002)

4.3 Immunolocalization of OAT3/Oat3 Protein

In the kidneys, OAT3/Oat3 is localized in the basolateral membrane of proximal tubular cells (Cha et al. 2001; Hasegawa et al. 2002; Motohashi et al. 2002). Whereas, in rat kidneys, OAT1 was highest in the S2 segment, OAT3 was present in all proximal tubule segments (S1–S3; Kojima et al. 2002; Ljubojevic et al. 2004). The basolateral localization fits with the assumption that OAT3/Oat3 is involved in the uptake of organic anions from the blood into proximal tubule cells. Later on, Oat3 immunoreactivity was found at the basolateral cell side also in distal tubule segments (thick ascending limb, connecting tubule, collecting duct; Kojima et al. 2002; Ljubojevic et al. 2004; Di Giusto et al. 2008). The function of OAT3/Oat3 in these nephron segments is unclear. At the blood–brain barrier, Oat3 was detected in

the basal membrane of endothelial cells (Kikuchi et al. 2003; Mori et al. 2003; Ohtsuki et al. 2004). Furthermore, Oat3 was immunolocalized to the choroid plexus (Alebouyeh et al. 2003). It is assumed that Oat3 is involved in the efflux of, for example, penicillin from cerebrospinal fluid and brain tissue into the blood.

4.4 Species Differences, Age and Gender Dependence of Expression

During rat embryogenesis, Oat3 alias Roct appeared in liver and brain, and vanished toward birth (Pavlova et al. 2000). After birth, renal Oat3 mRNA expression in rats rose steadily to reach a plateau around day 30 with no gender difference (Buist et al. 2002). Also in rabbits, Oat3 message increased with age and did not exhibit gender differences (Groves et al. 2006). In immunohistological studies on rat renal Oat3, a higher protein expression was found for proximal tubules, whereas for the distal tubule and collecting duct, no gender differences were seen (Ljubojevic et al. 2004). In contrast, clear gender differences were seen in the liver: male rats had much more Oat3 mRNA than female animals (Buist et al. 2003). In mice, however, the male dominant expression was much less accentuated than in rats (Buist and Klaassen 2004).

4.5 Factors Influencing Activity and Abundance of OAT3/Oat3

Transfection of hepatocyte nuclear factor (HNF)-1 α and HNF-1 β induced the expression of OAT3 that is otherwise not existent in human embryonic kidney (HEK) 293 cells (Kikuchi et al. 2006). HNF-1 α knockouts had a diminished renal expression of Oat3, but a largely increased expression in the duodenum (Maher et al. 2006). Inhibition of promoter methylation increased Oat3 expression, suggesting that an epigenetic regulation takes place (Kikuchi et al. 2006).

OAT3 is subject to regulation by various factors. Activation of the conventional protein kinase C by phorbol esters downregulated the activity of rat Oat3 expressed in mouse proximal tubules (Takeda et al. 2000b) and of Oat3-mediated estrone-3-sulfate uptake into isolated rabbit renal proximal tubules (Soodvilai et al. 2004). Thus, ligands working through PKC inhibit tubular secretion of organic anions (Terlouw et al. 2003). On the other hand, insulin and epidermal growth factor (EGF) increased Oat3 activity in rat kidney, involving the atypical isoform PKC ζ (Barros et al. 2009). EGF also stimulated Oat3-mediated transport in rabbit kidney proximal tubules (Soodvilai et al. 2004). A complex signal cascade (Sauvant et al. 2002, 2003, 2004) involving MAP kinases, phospholipase A₂, cyclooxygenase (COX) 1, prostaglandin E₂ release and PGE₂ receptor-mediated intracellular cAMP elevation finally leads to Oat3 activation; indeed, dbcAMP directly stimulated Oat3 in rabbit tubules (Soodvilai et al. 2004, 2005). In addition, cAMP increased the promoter activity of human OAT3 (Ogasawara et al. 2006).

Although PGE₂ acutely stimulated Oat3 activity, long-term exposure to PGE₂ resulted rather in a decrease in Oat3 abundance (Sauvant et al. 2006). A COX2-inhibitor, parecoxib, prevented the LPS-induced decrease of Oat3 in rat kidneys, suggesting that prostaglandins were involved (Höcherl et al. 2009).

The following maneuvers led to a reduction in OAT3 (and OAT1) protein abundance in homogenates, in basolateral plasma membranes, and/or in reduced uptake of the prototypical substrates: ischemia and reperfusion of the kidneys (Matsuzaki et al. 2007; Schneider et al. 2007; Di Giusto et al. 2008; Schneider et al. 2009), bilateral ureteral obstruction (Villar et al. 2005, 2008), several kidney diseases (Sakurai et al. 2004), and inflammation and fever (Sauvant et al. 2006). In contrast, experimental simulation of hepatic failure by biliary obstruction increased Oat3 abundance, both in the cytoplasm and, after three days, also in the basolateral membrane (Brandoni et al. 2006a, b; Torres 2008). In a rat model of hyperuricemia, the decrease in Oat3 was only transient and Oat3 function was completely restored within 14 days upon stopping the diet, which induced hyperuricemia (Habu et al. 2005). In rats devoid of the multidrug resistance-associated protein 2, Eisai hyperbilirubinemic rats, protein expression of Oat3 was significantly increased as compared to unaffected wild-type animals (Chen et al. 2008), and no change in Oat1 protein abundance was observed. 5/6-nephrectomized rats showed a higher Oat3 protein expression and an increased uptake of indoxyl sulfate (Enomoto et al. 2002c), whereas Oat1 was only slightly affected.

Methotrexate treatment of rats decreased renal Oat3 abundance (Shibayama et al. 2006). A decrease was also observed after treatment of rats with cisplatin and with tripterygium glycosides from Chinese herbs (Huang et al. 2001; Dan et al. 2008).

An Oat3 knockout mouse has been developed (Sweet et al. 2002). These mice are normal, but show a decreased renal excretion of diuretics (Vallon et al. 2008b), benzylpenicillin (Van Wert et al. 2007), quinolones (VanWert et al. 2008), and methotrexate (VanWert and Sweet 2007). In the brain, the choroid plexus showed a reduced accumulation of the organic anion fluorescein (Sweet et al. 2002).

4.6 Substrates

OAT3/Oat3 most likely operates as an organic anion/ α -ketoglutarate exchanger (Bakhiya et al. 2003; Sweet et al. 2003). Thereby, uptake of organic anions from the blood into the cell is coupled to and energized by the release of α -ketoglutarate into the blood. Thus, cellular localization and mode of operation of OAT1 and OAT3 are the same. The substrate specificities of OAT1 and OAT3 overlap but are not identical. In general, OAT3 handles bulkier and more lipophilic organic anions than does OAT1.

The usual test substrate for OAT3/Oat3 is estrone-3-sulfate (ES), because the uptake is easily detectable (low background in nonexpressing cells) and the affinity of OAT3/Oat3 to ES is high. Expressed in various cells, the K_m of human OAT3 for

ES varied between 2.2 and 21.2 μM in 12 publications with a mean of $8.8 \pm 5.3 \mu\text{M}$ (Takeda et al. 2000a, 2001; Cha et al. 2001; Feng et al. 2002; Sakurai et al. 2004; Erdman et al. 2005; Srimaroeng et al. 2005a; Tahara et al. 2005b; Ueo et al. 2005, 2007; Uwai et al. 2007b; Windass et al. 2007). ES was transported also by monkey (K_m 10.6 μM ; Tahara et al. 2005b), rabbit (4.5 μM ; Zhang et al. 2004), rat (2.34–7.13 μM ; Kusuhara et al. 1999; Takeda et al. 2000b; Feng et al. 2001; Hasegawa et al. 2003; Minematsu et al. 2008) and mouse Oat3 (5.5–12.4 μM ; Ohtsuki et al. 2004; VanWert et al. 2008).

4.6.1 Endogenous Substrates

Second messengers. Human OAT3 transported cAMP (Cha et al. 2001) and cGMP (Cropp et al. 2008).

Citric acid cycle intermediates. Citrate did not inhibit human OAT3 and slightly decreased the transport by rabbit Oat3 (Bakhiya et al. 2003; Zhang et al. 2004). α -Ketoglutarate transport was, surprisingly, not proven experimentally, but inhibition of OAT3 activity was demonstrated for human (Bakhiya et al. 2003; Hagos et al. 2008), monkey (Tahara et al. 2005b), and rabbit (Zhang et al. 2004); for the latter species, an IC_{50} of 50.3 μM was determined. Fumarate and succinate, but not oxaloacetate, slightly inhibited OAT3 (Bakhiya et al. 2003). Succinate was not transported by human OAT3 (Cha et al. 2001) and did not inhibit rabbit and rat Oat3 (Zhang et al. 2004; Anzai et al. 2005); malate and oxaloacetate did not inhibit rabbit Oat3 (Zhang et al. 2004). It appears that OAT3/Oat3 interacts with 5-carbon, but not with 4-carbon dicarboxylates. Accordingly, the nonphysiologic C5 dicarboxylate, glutarate, was transported by human, rat, and mouse OAT3/Oat3 (Bakhiya et al. 2003; Ohtsuki et al. 2004; Bahn et al. 2005; Nilwarangkoon et al. 2007).

Vitamins. Folate inhibited mouse Oat3 (VanWert and Sweet 2007). Nicotinate did not inhibit rabbit Oat3 (Zhang et al. 2004).

Bile salts. Several bile salts interacted with OAT3. The bile salts, cholate and taurocholate, were taken up into cells expressing the human and rat OAT3/Oat3 (Cha et al. 2001; Chen et al. 2008), and they inhibited transport mediated by these transporters with IC_{50} values between 230 and 554 μM for cholate and between 790 and 2,360 μM for taurocholate (Sugiyama et al. 2001; Chen et al. 2008). Among the other bile salts, transport was demonstrated only for glycocholate by rat Oat3, but not by human OAT3 (Chen et al. 2008). K_i values for inhibition of human and rat OAT3/Oat3 have been published for chenodeoxycholate, deoxycholate, glycochenodeoxycholate, glycocholate, and taurochenodeoxycholate (Chen et al. 2008). In kidney cortex slices obtained from Oat3 knockout mice, the accumulation of taurocholate was defective, proving bile salt transport by Oat3 (Sweet et al. 2002). In the same study, liver slices did not show abnormalities, suggesting that Oat3 does not play a role in the uptake of bile salts into hepatocytes.

Hormones and sulfated hormones. Human OAT3 transported radiolabeled cortisol with a K_m of 2.4 μM (Asif et al. 2005) and was inhibited by unlabeled corticosterone (Cha et al. 2001). Oat3 knockout mice, however, responded normally to ACTH

infusion, suggesting that Oat3 does not play a role in cortisol release from adrenal cells (Vallon et al. 2008a). Furthermore, OAT3 transported dehydroepiandrosterone sulfate (Cha et al. 2001; Ueo et al. 2005; Nozaki et al. 2007a) as well as the prototypical substrate, estrone-3-sulfate (for K_m values and literature on human, monkey, rabbit, rat, and mouse OAT3/Oat3 see previous). Mouse Oat3 was inhibited by aldosterone (IC_{50} 12 μ M), corticosterone (10 μ M), desoxycorticosterone (9 μ M), and progesterone (29 μ M) as well as by androsterone sulfate, estradiol disulfate, estradiol-17 β -glucuronide, 17 β -estradiol-3-sulfate, estrone-3- β D-glucuronide, and estrone-3-sulfate (Vallon et al. 2008a). Taken together, OAT3/Oat3 interacts with numerous steroid hormones and their sulfated or glucuronidated derivatives.

Local hormones. Prostaglandin E₂ was transported by human (K_m 0.35 μ M; Kimura et al. 2002), rat (K_m 1.4 μ M; Nilwarangkoon et al. 2007), and mouse OAT3/Oat3 (Kobayashi et al. 2004), and prostaglandin F_{2 α} by human (K_m 1.1 μ M; Kimura et al. 2002) and mouse OAT3/Oat3 (Kobayashi et al. 2004). Thus, this transporter has a very high affinity for these prostaglandins.

Nucleobases, purine metabolites, urate. Among the tested bases, only adenine slightly inhibited rat Oat3 (Mori et al. 2004). The nucleoside thymidine was transported by mouse Oat3 and inhibited its function with an IC_{50} of 384 μ M (Vallon et al. 2008a). Thymidine was found to decrease blood pressure in mice. For this reason, Oat3 knockout mice or mice treated with inhibitors of Oat3 such as eosin Y or probenecid showed a lower blood pressure due to impaired thymidine excretion (Vallon et al. 2008a).

The purine metabolite, urate, was transported by human and rabbit OAT3 (Cha et al. 2001; Zhang et al. 2004) and inhibited human, rabbit, and mouse Oat3 (Bakhiya et al. 2003; Zhang et al. 2004; Ohtsuki et al. 2004; VanWert and Sweet 2007). The K_m for urate uptake by human OAT3 was 380 μ M (Sato et al. 2008); IC_{50} values for inhibiting human and rabbit OAT3 were 255 μ M and 733 μ M, respectively (Bakhiya et al. 2003; Zhang et al. 2004). Thereby, the affinity of OAT3 toward urate is higher than that of OAT1.

Neurotransmitters and their metabolites. Dopamine, glutamate, histamine, and serotonin did not interact with rat Oat3 (Mori et al. 2003). Melatonin inhibited human and rat OAT3 (Kusuhara et al. 1999; Alebouyeh et al. 2003). A large number of acidic neurotransmitter metabolites were tested with human (h), rat (r), and mouse (m) transporters: 3,4-dihydroxymandelate (h: no inhibition, r: inhibition), 3,4-dihydroxyphenylacetate (h: IC_{50} 990 μ M; r: inhibition), homovanillate (h: no transport but inhibition with IC_{50} 760 μ M; r: transport with K_m 274 μ M; m: transport and inhibition), 5-hydroxyindole-3-acetate (h: IC_{50} 910 μ M; r and m: inhibition), 4-hydroxy-3-methoxymandelate, 4-hydroxy-3-methoxyphenylacetate, 4-hydroxy-3-methoxyphenylglycol, imidazol-4-acetate (r: inhibition), 5-methoxyindole-3-acetate (h: IC_{50} 70 μ M; r: inhibition), 5-methoxytryptamine (h: IC_{50} 610 μ M), 5-methoxytryptophol (h: IC_{50} 490 μ M; r: inhibition), 1-methyl-4-imidazolate (r: inhibition; Alebouyeh et al. 2003; Bahn et al. 2005; Kusuhara et al. 1999; Mori et al. 2003; Ohtsuki et al. 2004; VanWert and Sweet 2007). Neuroactive metabolites of the tryptophan metabolism inhibited mouse Oat3: 3-hydroxykynurenate,

kynurenate (IC_{50} 8 μ M), picolinate, and xanthurenate (IC_{50} 11.5 μ M; Bahn et al. 2005). In summary, OAT3/Oat3 located at the blood–brain barrier and the choroid plexus is probably involved in the efflux of acidic metabolites from brain tissue.

4.6.2 Drugs

ACE inhibitors. Quinapril was transported by human (K_m 13.4 μ M) and rat OAT3/Oat3 (Yuan et al. 2009); inhibition of OAT3 by quinapril occurred with an IC_{50} of 6.2 μ M (Chu et al. 2007). Captopril was transported by human OAT3 (Ueo et al. 2005), and enalapril inhibited human and mouse OAT3/Oat3 (Chu et al. 2007; Kobayashi et al. 2004). Temocaprilat was taken up into rat Oat3-expressing cells with high affinity (K_m 1.4 μ M; Hasegawa et al. 2003).

Angiotensin II receptor 1 blockers. Candesartan, losartan, olmesartan, prazosin, telmisartan and valsartan inhibited human OAT3 with very high affinities (Table 6; IC_{50} values between 0.027 and 1.6 μ M; Sato et al. 2008). For olmesartan, transport by OAT3 was demonstrated (Yamada et al. 2007). Inhibition of rat Oat3 with high affinity was found for prazosin and telmisartan (Li et al. 2008).

Diuretics. As shown in Table 6, for human OAT3 a near-complete set of IC_{50} values is available for carbonic anhydrase inhibitors (acetazolamide, methazolamide), loop diuretics (bumetanide, ethacrynate, furosemide, torasemide), and thiazide diuretics (chlorothiazide, cyclothiazide, hydrochlorothiazide, trichlormethiazide). The highest affinities were observed for bumetanide, ethacrynate and furosemide (IC_{50} values between 0.58 and 7.31 μ M; Hasannejad et al. 2003; Chu et al. 2007), intermediate ones for torasemide and most thiazides (IC_{50} values ranging between 27.9 and 97.5 μ M; Hasannejad et al. 2003; Hagos et al. 2007a), and low affinities for acetazolamide and hydrochlorothiazide (Hasannejad et al. 2003). Transport by human OAT3 was demonstrated for bumetanide and furosemide (Hasannejad et al. 2003). Bumetanide was also transported by mouse Oat3 with very high affinity (K_m 1.1 μ M; Kobayashi et al. 2005). Inhibition of monkey OAT3 by bumetanide and furosemide (Tahara et al. 2005b), rat Oat3 by bumetanide and furosemide (Kusuhara et al. 1999; Erdman et al. 2005), and of mouse Oat3 by bendroflumethiazide and furosemide (Kusuhara et al. 1999; Feng et al. 2001; Vallon et al. 2008b) were also reported. From these data it is likely that OAT3/Oat3 is, together with OAT1/Oat1, involved in proximal tubular secretion of diuretics. Indeed, renal excretion of furosemide and bendroflumethiazide was decreased in both Oat1 and Oat3 knockout mice (Vallon et al. 2008b).

Statins. Pravastatin and rosuvastatin were translocated by human and rat OAT3/Oat3 with high to moderate affinities (Table 6: K_m values between 4.7 and 13.4 μ M; Hasegawa et al. 2002; Takeda et al. 2004; Windass et al. 2007). Atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin inhibited human OAT3 with IC_{50} values between 5.79 and 96.5 μ M, that is, with high to moderate affinities (Khamdang et al. 2004; Takeda et al. 2004; Windass et al. 2007). Inhibitions of

Table 6 Drugs interacting with OAT3/Oat3

	Human		Rat		Mouse	
	Transport	Inhibition	Transport	Inhibition	Transport	Inhibition
<i>ACE inhibitors</i>						
Captoprilat	+					
Enalaprilat		+ or -				+
Quinaprilat	13.4	6.2	+			
<i>Angiotensin II receptor blockers</i>						
Candesartan		0.3				
Losartan		1.6				
Olmesartan	0.12	0.027				
Prasartan		0.095		1.285		
Telmisartan		1.6		0.723		
Valsartan		0.2				
<i>Diuretics</i>						
Acetazolamide		816				
Bendroflumethiazide						21.3
Bumetanide	1.59	0.75		+	1.01	
Chlorothiazide		65.3				
Cyclothiazide		27.9				
Ethacrynate		0.58				
Furosemide	+	1.7-7.31		+		2.8
Hydrochlorothiazide		942				
Methazolamide		97.5				
Toraseamide		89.9				
Trichlormethiazide		71.2				
<i>Statins</i>						
Atorvastatin		13.1				
Fluvastatin		5.79				
Pravastatin	+	13.7-96.5	13.4	15.6		+
Rosuvastatin	7.4	25.7	4.7			
Simvastatin		32.3-48.1				
<i>Antibiotics</i>						
Benzylpenicillin	52.1	+	82.6-85.1	52.8-132	40	+
Cefaclor	+	120.2				
Cefadroxil		8,620		1,780		
Cefamandol		46		90		
Cefazolin	+	116.6-550		780		
Cefdinir	+	271.5				
Cefoperazone		1,890		670		
Cefoselis	+	2,925				
Cefotaxime		290		800		
Cefotiam	+	212.6	+			
Ceftibuten	+	247.3				
Ceftizoxime	+	956.7				
Ceftriaxone		4,390		-		
Cephalexin				630		
Cephaloridine	+	626.4	+	1,140		
Cephalothin		40		48		
Ciprofloxacin		+			69.8	198
Doxycyclin		-				

(continued)

Table 6 (continued)

	Human		Rat		Mouse	
	Transport	Inhibition	Transport	Inhibition	Transport	Inhibition
Gatifloxacin		+				941
Minocyclin		–				
Norfloracin		–				558
Ofloxacin		–				745
Oxytetracycline		–				
Tetracycline	566.2	–				
<i>Antivirals</i>						
Acyclovir	–	+	(+)	1,460		729
Adefovir	(+) or –		–			
Amantadine						–
Cidofovir	(+)					+ or –
Didanosine						136.9
Lamivudine						140
Stavudine						2,113
Tenofovir	(+)					384
Valacyclovir	+					
Zalcitabine					125.9	203
Zidovudine	145.1	(+) or –	(+)	143		38.5
<i>Antineoplastics</i>						
5-Fluorouracil					0.054	
6-Mercaptopurine			50.5	+	4.01	
Methotrexate	10.9	+	+	28	60.6	+
6-Thioguanine				172		
Topotecan	56.5		21.9			
<i>Immune suppressants</i>						
Azathioprine		–		15.7		
Cyclosporin A		–				
Mycophenolate	–	0.52–1.5				
Tacrolimus		–				
<i>Histamine receptor 2 blockers</i>						
Cimetidine	40.0–174	42.9–92.4	40.0–90.7	8.74–166	105	85.0
Famotidine	124	179	345			+
Ranitidine	234		155			
<i>NSAIDs</i>						
Acetaminophen		–				
Acetylsalicylate		717				
Anthranilate						+
Diclofenac		6.57–7.78		3.17		–
Etodolac		12.0		9.98		
Flufenamate		+				
Ibuprofen	+ or –	3.7–6.0		3.57		+
Indomethacin	(+)	0.61–0.979		1.29	+	+
Ketoprofen	+	5.04–5.98		4.31		
Loxoprofen		8.7				
Mefenamate		0.78				
Naproxen		4.67–7.15		19.1		
Phenacetin		19.4				
Phenylbutazone		6.82		8.48		

(continued)

Table 6 (continued)

	Human		Rat		Mouse	
	Transport	Inhibition	Transport	Inhibition	Transport	Inhibition
Piroxicam		4.83–4.88		4.19		
Salicylate	+	50.0–111	–	511–519	+	+
Sulfapyrazone				+		
Sulindac		3.62–6.89		7.72		
Tolmetin						

+, transport of inhibition was observed without determination of K_m , K_i , or IC_{50} ; –, no transport or no inhibition was observed; (+), weak transport or inhibition; blank, not determined; numbers, reported K_m , K_i , or IC_{50} values in micromoles/liter (μM). For references see text in Sect. 4.6.2

monkey (Tahara et al. 2005b), rat (Khamdang et al. 2004), and mouse Oat3 (Ohtsuki et al. 2004) by pravastatin have also been reported.

Antibiotics. Benzylpenicillin was transported by human, monkey, rat, and mouse OAT3/Oat3 with K_m values between 40 and 85.1 μM (Hasegawa et al. 2002; Nagata et al. 2002; Ohtsuki et al. 2004; Tahara et al. 2005b). Other studies have shown that benzylpenicillin inhibits human, rat, and mouse OAT3/Oat3 (Kusuhara et al. 1999; Cha et al. 2001; Hasegawa et al. 2002; Mori et al. 2003; Deguchi et al. 2004; Minematsu et al. 2008; VanWert and Sweet 2007; VanWert et al. 2008). Because OAT3 has a higher affinity for benzylpenicillin than OAT1, it is believed that OAT3 is mainly involved in renal penicillin secretion. Indeed, Oat3 knockout mice showed a decreased renal excretion of penicillin, but not of PAH, a substrate of Oat1 (VanWert et al. 2007).

A number of *cephalosporins* were tested on human OAT3 (see Table 6). Transport was demonstrated for cefaclor, cefazolin, cefdinir, cefoselis, cefotiam, ceftibuten, ceftizoxime, and cephaloridine (Ueo et al. 2005). The IC_{50} values for inhibition of OAT3-mediated transport ranged between 40 μM and 8.6 mM indicating a wide range from intermediate (cefamandol, cephalothin) to very low affinities (cefadroxil, ceftriaxone, cefoselis, cefoperazone; Jung et al. 2002; Takeda et al. 2002a; Ueo et al. 2005). Rat Oat3 transported cefotiam and cephaloridine, and was inhibited by several cephalosporins shown in Table 6 (Jung et al. 2002; Chen et al. 2008). Also for rat Oat3, IC_{50} values have been determined (data shown in Table 6 are taken from Jung et al. 2002).

The *quinolones* ciprofloxacin, gatifloxacin, norfloxacin, and ofloxacin inhibited mouse Oat3 with low affinity (IC_{50} values between 198 and 941 μM), and ciprofloxacin was transported with a K_m of 69.8 μM (VanWert et al. 2008). In the same study, ciprofloxacin and gatifloxacin, but not norfloxacin and ofloxacin, inhibited human OAT3. In Oat3 knockout mice, the AUC of quinolones was increased, proving an important role of Oat3 in the renal excretion of these compounds (VanWert et al. 2008). *Tetracyclines* did not inhibit human OAT3, although uptake of tetracycline with a K_m of 566 μM was reported (Babu et al. 2002a).

Antivirals. A weak transport by human OAT3 was shown for cidofovir, tenofovir, and valacyclovir; for zidovudine uptake a K_m of 145.1 μM was determined (Takeda et al. 2002b; Uwai et al. 2007a). Acyclovir was not transported, but inhibited OAT3 (Cha et al. 2001; Takeda et al. 2002b). For adefovir (weak

transport: Uwai et al. 2007a; no transport: Aslamkhan et al. 2006) and zidovudine (weak inhibition: Takeda et al. 2002b; no inhibition: Cha et al. 2001), conflicting data are found in the literature. Rat Oat3 transported weakly acyclovir and zidovudine, and was inhibited by these antivirals (Kusuhara et al. 1999; Hasegawa et al. 2003); adefovir was not transported (Aslamkhan et al. 2003). A more complete data set is available for the inhibition of mouse Oat3 by antivirals (see Table 6). The IC_{50} values range between 38.5 μ M (zidovudine) and 2.1 mM (stavudine; Truong et al. 2008). No inhibition was found for amantadine (Kobayashi et al. 2004) and either inhibition (Vallon et al. 2008a) or no inhibition (Truong et al. 2008) was reported for cidofovir. It appears that antivirals are primarily transported rather by OAT1/Oat1 than by OAT3/Oat3.

Antineoplastics. Methotrexate transport occurred with a K_m of 10.9 μ M by human OAT3 (Cha et al. 2001), monkey OAT3 (Tahara et al. 2005b), rat (Nozaki et al. 2004), and mouse Oat3 (K_m 60.6 μ M; VanWert and Sweet 2007). Unlabeled methotrexate inhibited human (Srimaroeng et al. 2005a, b), rat (IC_{50} 28 μ M; Mori et al. 2004), and mouse Oat3 (Ohtsuki et al. 2004; Vallon et al. 2008a). Thus, it is obvious that OAT3/Oat3 transports the antifolate methotrexate. In support of this conclusion, Oat3 knockout mice had a lower renal methotrexate excretion (VanWert and Sweet 2007). Mouse Oat3 transported 5-fluorouracil (K_m 0.054 μ M) and 6-mercaptopurine (K_m 4.01 μ M) with very high affinities (Kobayashi et al. 2004); rat Oat3 showed a higher K_m for 6-mercaptopurine (50.5 μ M; Mori et al. 2004). 6-thioguanine inhibited rat Oat3 (IC_{50} 172 μ M; Mori et al. 2004). Topotecan was transported by human (K_m 56.5 μ M) and rat (K_m 21.9 μ M) OAT3/Oat3 (Matsumoto et al. 2007).

Immune suppressants. Mycophenolate competitively inhibited human OAT3 with high affinity (IC_{50} 0.52–1.5 μ M), but was not transported (Uwai et al. 2007b; Wolff et al. 2007). A competitive inhibition was also found for the glucuronide and the acyl-glucuronide of mycophenolate (Wolff et al. 2007). Azathioprine, cyclosporin A, and tacrolimus did not interact with OAT3 (Uwai et al. 2007b). Azathioprine, however, inhibited rat Oat3 with an IC_{50} of 15.7 μ M (Mori et al. 2004).

Antidiabetics. Metformin was not transported by OAT3 (Kimura et al. 2005).

Histamine receptor 2 blockers. Cimetidine was transported by human (K_m values between 40 and 174 μ M; Feng et al. 2001; Erdman et al. 2005; Tahara et al. 2005a, b; Chu et al. 2007) and monkey OAT3 (K_m 68.5 or 70.9 μ M; Tahara et al. 2005a, 2006b), as well as by rabbit (K_m 89 μ M; Zhang et al. 2004), rat (K_m between 40 and 90.7 μ M; Feng et al. 2001; Tahara et al. 2005a), and mouse Oat3 (K_m 105 μ M, Ahn et al. 2009). The IC_{50} values reported for human (Hashimoto et al. 2004; Khamdang et al. 2004; Motohashi et al. 2004; Chu et al. 2007), rabbit (Zhang et al. 2004), rat (Nagata et al. 2002; Khamdang et al. 2004; Minematsu et al. 2008) and mouse (Ahn et al. 2009) were in the same range as the K_m values for uptake (see also Table 6). Another H2 blocker, famotidine, was transported by human (K_m 124 μ M; Tahara et al. 2005a), monkey (K_m 154 μ M; Tahara et al. 2006a), and rat OAT3 (K_m 345 μ M Tahara et al. 2005a), ranitidine by human (K_m 234 μ M), monkey (K_m 125 μ M), and rat Oat3 (K_m 155 μ M; references as for famotidine). Taken together it is clear that OAT3/Oat3 translocates H2 blockers, although they are not organic anions but rather organic cations at physiological pH.

Nonsteroidal anti-inflammatory drugs (NSAIDs). Transport by human OAT3 was shown for indomethacin, ketoprofen, salicylate, and, with mixed results, for ibuprofen (Cha et al. 2001; Khamdang et al. 2002). For most NSAIDs inhibitory constants are available for their interaction with human OAT3 (see Table 6). Interaction with very high and high affinities (IC_{50} values below 10 μM) occurred with diclofenac, ibuprofen, indomethacin, ketoprofen, loxoprofen, mefenamate, naproxen, phenylbutazone, piroxicam, and sulindac, with intermediate affinity (IC_{50} below 100 μM) with etodolac, phenacetin, salicylate, and with low affinity ($IC_{50} > 100 \mu M$) with acetylsalicylate (Jung et al. 2001; Khamdang et al. 2002; Srimaroeng et al. 2005b; Chu et al. 2007; Nozaki et al. 2007b; Uwai et al. 2004). Flufenamate inhibited human OAT3, but no IC_{50} was determined (Uwai et al. 2004), and acetaminophen did not inhibit OAT3-mediated transport (Khamdang et al. 2002). A series of IC_{50} values is available also for the inhibition by NSAIDs by rat Oat3 (see Table 6). Most NSAIDs showed IC_{50} values below 10 μM ; the only exceptions being naproxen and salicylate (Hasegawa et al. 2003; Nozaki et al. 2004). For sulfinpyrazone, inhibition of rat Oat3 has been shown (Mori et al. 2004). Mouse Oat3 transported indomethacin and salicylate, and was inhibited by anthranilate, ibuprofen, indomethacin, and salicylate (Kobayashi et al. 2004; Ohtsuki et al. 2004; Bahn et al. 2005; VanWert and Sweet 2007).

4.7 Inhibitors

Probenecid is a competitive inhibitor of human OAT3 (Hashimoto et al. 2004). The reported K_i or IC_{50} values range between 1.3 and 9 μM with a mean of 4.13 μM (Jung et al. 2001; Takeda et al. 2001; Hashimoto et al. 2004; Tahara et al. 2005a, 2006b; Chu et al. 2007). These values are below the therapeutical plasma concentration (18.7 μM ; Nozaki et al. 2007b). The IC_{50} values for monkey (2.97–5.67 μM ; Tahara et al. 2006a) and rat (1.13–9.0 μM ; Jung et al. 2001; Takeda et al. 2001; Khamdang et al. 2004; Tahara et al. 2005a; Minematsu et al. 2008) Oat3 are within the same range. Hence, OAT1 and OAT3 are similarly sensitive to probenecid.

4.8 Drug/Drug Interactions

OAT3/Oat3 interacts with numerous drugs. It is highly likely that drug–drug interaction takes place during drug uptake from the blood into renal proximal tubule cells by competition for OAT3/Oat3. The interactions mentioned in Sect. 2.8 for OAT1/Oat1 may well hold also for OAT3/Oat3 because of the overlapping substrate specificities.

Probenecid/benzylpenicillin interaction (for literature see Sect. 2.8) is likely to primarily occur at OAT3 rather than at OAT1, because (1) OAT3/Oat3 has a higher affinity to this β -lactam antibiotic (IC_{50} for rat Oat1: 418–2,763 μM ; Jariyawat et al. 1999; Hasegawa et al. 2002, 2003; Nagata et al. 2002; Deguchi et al. 2004; IC_{50} for

rat Oat3: 52.8–132 μM , Hasegawa et al. 2002; Deguchi et al. 2004), (2) OAT3/Oat3 clearly transported benzylpenicillin (K_m 40–85.1 μM ; Hasegawa et al. 2002; Nagata et al. 2002; Ohtsuki et al. 2004; Tahara et al. 2005b), and (3) OAT3/Oat3 is inhibited by probenecid at therapeutic plasma concentrations (see previous). The affinities of OAT1 and OAT3 for many cephalosporins (cefadroxil, cefamandol, cefazolin, cefdinir, cefoselis, ceftibuten, cephaloridine) are comparable, that is, IC_{50} values differ by a factor of less than three, indicating that *probenecid/cephalosporin* interaction (Brown 1993) may take place at both transporters to the same extent.

Probenecid/methotrexate interaction (Aherne et al. 1978) most probably occurs at OAT3, because this transporter has a much higher affinity (K_m 10.9 μM ; Cha et al. 2001) than OAT1 (K_m 724 μM ; Uwai et al. 2004) for this antineoplastic drug.

The *probenecid/furosemide* interaction (for literature see Sect. 2.8) may take place on both OAT1 (IC_{50} 14–20 μM ; Hasannejad et al. 2003; Bahn et al. 2004) and OAT3 (IC_{50} 1.7–7.31 μM ; Hasannejad et al. 2003; Chu et al. 2007) due to comparable affinities for this diuretic.

Because OAT1 readily transported several antiviral drugs, it is believed that *probenecid/antiviral drug* interaction takes place at OAT1 rather than at OAT3. Unfortunately, IC_{50} determinations for human OAT3 are scarce precluding a comparison of affinities. For mouse Oat1 and Oat3, comparable IC_{50} values have been found for a number of antivirals, however, data on transport are lacking. Hence, a final conclusion as to whether OAT1, OAT3 or both are involved in *probenecid/antiviral* interaction remains open. The same holds true for *NSAID/antiviral drug* interaction.

The *probenecid/fexofenadine* interaction is likely to take place at OAT3. The antihistaminic fexofenadine was taken up by OAT3-, but not by OAT1-expressing cells and probenecid inhibited uptake with a K_i of 1.3 μM (Tahara et al. 2005a).

As mentioned earlier, *NSAID/methotrexate* interaction can lead to life-threatening side effects. OAT3 has a higher affinity for methotrexate (K_m 10.9 μM ; Cha et al. 2001) than OAT1 (K_m 724 μM ; Uwai et al. 2004) and must thus be regarded as the main transporter for renal methotrexate excretion. The affinity of OAT3 for most NSAIDs is similar to that of OAT1. Exceptions are phenacetin, phenylbutazone, piroxicam, salicylate, and sulindac, for which OAT3 has a considerably higher affinity than OAT1. More important is to consider the IC_{50} values for NSAIDs in relation to their free plasma concentrations (Takeda et al. 2002c; Nozaki et al. 2004, 2007b). Only salicylate (IC_{50} at OAT3 50–111 μM ; Khamdang et al. 2002; Nozaki et al. 2007b; free plasma concentration: 55–440 μM), phenylbutazone (IC_{50} 6.82 μM ; free plasma concentration 6.3–19 μM ; Nozaki et al. 2007b), indomethacin (IC_{50} 0.61–0.98 μM ; Khamdang et al. 2002; Nozaki et al. 2007b; free plasma concentration 0.084–8.4 μM), and loxoprofen (IC_{50} 12.2 μM ; free plasma concentration 20 μM ; Uwai et al. 2004) can inhibit OAT3 in vivo in order to decrease renal methotrexate excretion (Takeda et al. 2002c). Why other NSAIDs are also causing side effects is not clear. Possibly this interaction takes place at other transporters, for example, MRP4 (Nozaki et al. 2007b).

Gemfibrozil/pravastatin interaction: the administration of the lipid lowering drug gemfibrozil decreased the renal clearance of pravastatin. Because OAT3, but not OAT1, transported labeled pravastatin and pravastatin was inhibited

by gemfibrozil, it is likely that OAT3 is involved in this drug–drug interaction (Nakagomi-Hagihara et al. 2007)

Gemcabene/quinaprilat interaction: the lipid lowering drug gemcabene increases the antihypertensive action of quinaprilat. Human and rat OAT3/Oat3 transport quinaprilat much more rapidly than OAT1/Oat1; gemcabene and its glucuronide inhibited quinaprilat transport, suggesting that drug interaction takes place at OAT3 (Yuan et al. 2009).

4.9 Pharmacogenomics

The overall mutation rate for OAT3 was with 0.74×10^{-4} lower than the average rate for the whole genome (2×10^{-4} ; Urban et al. 2006). Within the 5'-untranslated region Bhatnagar et al. (2006) described seven polymorphisms found in probes of 96 persons. Of these, two were quite frequent ($G \rightarrow C$ at -1.882 ; $f = 0.47$; $G \rightarrow A$ at -1.851 ; $f = 0.2$) whereas the reminder showed frequencies of 0.0005 (Urban et al. 2006). Ogasawara et al. (2008) described five single nucleotide polymorphisms in the 5' untranslated region. None of them had an influence on the expression as tested with luciferase constructs. In 120 healthy Japanese, Nishizato et al. (2003) found five SNPs, one being nonsynonymous leading to the amino acid exchange A389V (frequency 0.017). None of the SNPs had an influence on the kinetics of pravastatin transport. Additional nonsynonymous SNPs were reported by Erdman et al. (2005) and Urban et al. (2006). These correspond to the following amino acid replacements: F129L, R149S, N239X, I260R, R277W, V281A, I305F, A399S, and V488I. Q239X and I260R occurred only in Asian-Americans ($f = 0.002$), and R277W in African-Americans ($f = 0.0002$); R149S was found in Europeans and Asian-Americans ($f = 0.004$), I305F in Asian-Americans ($f = 0.035$) and Mexican-Americans ($f = 0.011$). Following expression, the mutants F149S, Q239X, and I260R did not function at all, and the mutants R277W and I305F showed a slower transport of estrone-3-sulfate with a slight preference for cimetidine as compared to the wild type (Nishizato et al. 2003; Urban et al. 2006). Thus, three loss-of-function mutations (R149S, Q239X, I260R) occur in Asian-Americans with possible impact on their drug excretion.

5 Organic Anion Transporter 4 (OAT4, Gene Name SLC22A11)

5.1 Cloning, Structure

The organic anion transporter 4 (OAT4) is human-specific, that is, there is no known ortholog in rodents or other species. The OAT4 protein consists of 550 amino acids arranged in twelve putative transmembrane helices, and five potential

N-glycosylation sites and nine putative protein kinase C phosphorylation sites were reported (Cha et al. 2000). The glycosylation was required for targeting of OAT4 to the membrane and had an influence on the affinity toward estrone-3-sulfate (Zhou et al. 2005). The C-terminal three amino acids, threonine, serine, leucine (TSL), constitute a PDZ binding motif. Indeed, OAT4 was found to interact with the scaffolding proteins PDZK1 and NHERF1 (Kato et al. 2004; Miyazaki et al. 2005). In LLC-PK1 cells, coexpression of PDZK1 or NHERF1 increased the surface expression of OAT4, and truncation of the last three amino acids abolished the effect (Zhou et al. 2007b). Likewise, coexpression in HEK293 cells of PDZK1 or NHERF1 with OAT4 increased maximal transport rate without affecting the affinity (Miyazaki et al. 2005), indicating that the interaction of the PDZ domain of OAT4 is important for proper targeting to, and maintenance of the transporter in the apical cell membrane of renal cells. Mutational analysis on OAT4 revealed the importance for the glycine residues G241 and G400 as well as of several histidine residues for targeting and substrate affinity (Zhou et al. 2004a, b).

The gene for OAT4, SLC22A11, is located on chromosome 11q13.1 and is paired with the gene SLC22A12 coding for URAT1 (Eraly et al. 2003b). It should be noted that another transporter, cloned by Sun et al. (2001) and also named OAT4 (renamed OAT7; gene SLC22A9), is not identical to the OAT4 described here (see Sect. 10.1).

5.2 Tissue Distribution of mRNA

OAT4 mRNA transcripts were only found in kidney, placenta (Cha et al. 2000; Nishimura and Naito 2005; Bleasby et al. 2006), and adrenal gland (Asif et al. 2005). Adipose tissue, bladder, different regions of the brain, cervix, colon, duodenum, epididymis, heart, ileum, jejunum, liver, lung, lymph node, mammary gland, olfactory mucosa, ovary, pancreas, peripheral leukocytes, pituitary, prostate, retina, salivary gland, skeletal muscle, skin, spinal cord, stomach, testis, thymus, thyroid gland, trachea, and uterus were all negative (see Table 2; Nishimura and Naito 2005; Bleasby et al. 2006).

5.3 Immunolocalization of OAT4 Protein

Immunohistochemical staining of hOAT4 was found in the luminal membrane of proximal tubule cells (Babu et al. 2002b; Ekaratanawong et al. 2004). Thereby, OAT4 and the interacting scaffolding proteins PDZK1 and NHERF1 are colocalized at the apical cell pole (Miyazaki et al. 2005). It is clear from these findings that OAT4 is involved in the release of organic anions into the urine and/or in the uptake of organic anions from the primary filtrate into the proximal tubule cells. In the placenta, hOAT4 appears at the basal (fetal) side of the syncytiotrophoblast where it

takes up sulfated C19-steroid precursors for placental estrogen synthesis (Ugele et al. 2003, 2008).

5.4 Species Differences, Age and Gender Dependence of Expression

OAT4 is expressed only in humans. Presently, it is unclear which transporter in other species takes over the task of human OAT4. Data on age- and gender-dependent expression of OAT4 are not available.

5.5 Factors Influencing Activity and Abundance of OAT4

Because OAT4 is only expressed in humans, animal disease models cannot be used to study the influence of pathophysiological states on OAT4 expression.

5.6 Substrates

Similar to other OATs is OAT4 able to operate as an organic anion/dicarboxylate exchanger (Ekaratanawong et al. 2004). Later on, it became clear that OAT4 has several modes of operation. In the influx (absorption) mode it couples the uptake of estrone-3-sulfate or urate to the release of dicarboxylates (α -ketoglutarate); in the efflux (secretion) mode, organic anions such as *p*-aminohippurate and drugs can be exchanged against extracellular chloride (Hagos et al. 2007b). In addition, OAT4 is able to perform organic anion/hydroxyl ion exchange and can thus be functionally coupled to the Na^+/H^+ exchanger NHE3 in the brush-border membrane (Hagos et al. 2007b). Hence, OAT4 accepts inorganic (hydroxyl, chloride) and organic anions.

The prototypical organic anion to study OAT4 is estrone-3-sulfate (ES); the reported K_m values for ES uptake range between 1.01 and 21.7 μM (mean 9.89 μM in six determinations; Cha et al. 2000; Yamashita et al. 2006; Zhou et al. 2005, 2006, 2007a; Ugele et al. 2008). As a nonradioactive substrate, 6-carboxyfluorescein uptake into OAT4-expressing cells can be measured fluorimetrically (K_m for uptake: 108 μM ; Hagos et al. 2007b).

5.6.1 Endogeneous Substrates

Second messengers. *cGMP* was not transported (Cropp et al. 2008); *cAMP* was not tested.

Citric acid cycle intermediates, other dicarboxylates. Citrate, succinate, fumarate, and oxaloacetate, but not malate inhibited OAT4 (Hagos et al. 2007b). For α -ketoglutarate and its nonphysiologic derivative glutarate, contradictory results were obtained (inhibition: Ekaratanawong et al. 2004; Anzai et al. 2005; Yamashita et al. 2006; Hagos et al. 2007b; no inhibition: Cha et al. 2000; Hagos et al. 2008). Also for glutarate uptake by OAT4, mixed results were reported (uptake, Ekaratanawong et al. 2004; no uptake, Hagos et al. 2007b). However, *trans*-stimulation of OAT-mediated transport by intracellular glutarate was observed in both studies. The differing results probably reflect the asymmetry of transport: (α -keto-)glutarate is better accepted from the cytosolic side for *trans*-stimulation, and less so from the extracellular side, explaining mixed effects in *cis*-inhibition experiments.

Monocarboxylates. Lactate and pyruvate did not inhibit OAT4 (Hagos et al. 2007b). The short chain fatty acid octanoate, however, inhibited the transporter (Babu et al. 2002b).

Bile salts. Cholate and taurocholate inhibited OAT4 (Cha et al. 2000; Yamashita et al. 2006). Taurochenodesoxycholate did not interact with OAT4 (Yamashita et al. 2006).

Hormones and hormone derivatives. Transport was shown for estrone-3-sulfate (Cha et al. 2000; Zhou et al. 2004a, b, 2005; Miyazaki et al. 2005; Yamashita et al. 2006; Zhou et al. 2006, 2007a; Ugele et al. 2008). Based on the K_m values for uptake, OAT4 has a high affinity for ES (mean K_m at 9.89 μ M; see previous). Transport was also demonstrated for dehydroepiandrosterone sulfate (DHEAS; K_m between 0.63 and 29.2 μ M; Cha et al. 2000; Ugele et al. 2008). Corticosterone inhibited OAT4, but was not transported (Cha et al. 2000; Asif et al. 2005). Inhibitions were demonstrated for estrone, 17 β -estradiol-3-sulfate, β -estradiol-3-sulfate, β -estradiol-3,7-disulfate, but not for β -estradiol, β -estradiol-3 β D-glucuronide, and progesterone (Cha et al. 2000; Yamashita et al. 2006; Zhou et al. 2005, 2006)

Local hormones. Prostaglandin E_2 (K_m 0.154 μ M) and prostaglandin $F_{2\alpha}$ (K_m 0.692 μ M) were transported by OAT4 with very high affinities (Kimura et al. 2002).

Purine metabolite. Urate was transported by OAT4 and inhibited its function, indicating that urate is a substrate (Iwanaga et al. 2005; Hagos et al. 2007b; Sato et al. 2008).

5.6.2 Drugs

ACE inhibitors. The only substance tested, captopril, inhibited OAT4 (Zhou et al. 2005).

Angiotensin II receptor I blockers. Table 7 shows the IC_{50} values for a series of *sartanes*. OAT4 exhibited a high affinity for olmesartan and telmisartan, an intermediate one for candesartan, losartan, prazosartan, and valsartan, and a low affinity for candesartan cilexetil (Yamashita et al. 2006; Sato et al. 2008).

Diuretics. OAT4 transported the loop diuretic bumetanide with high affinity (K_m 0.31 μ M) although it inhibited OAT4-mediated ES transport with an IC_{50} of

Table 7 Drugs interacting with OAT4

	Human	
	Transport	Inhibition
<i>ACE inhibitor</i>		
Captopril		+
<i>Angiotensin II receptor blockers</i>		
Candesartan		60–88.9
Candesartan cilexetil		135.2
Losartan		18.0–24.8
Olmesartan		4.4
Prasartan		31
Telmisartan		1.2
Valsartan		19.9–26.0
<i>Diuretics</i>		
Acetazolamide		415
Bumetanide	0.31	348
Chlorothiazide		2,632
Cyclothiazide		–
Ethacrynate		8.76
Furosemide	–	44.5
Hydrochlorothiazide	+*	+ or –
Methazolamide		–
Torsemide	+*	47.0
Trichlormethiazide		1,505
<i>Statin</i>		
Pravastatin		+
<i>Antibiotics</i>		
Benzylpenicillin		+
Cefadroxil		+
Cefamandol		1,140
Cefazolin		1,740
Cefoperazone		2,800
Cefotaxime		6,150
Ceftriaxone		2,380
Cephaloridine		3,630
Cephalothin		200
Clarithromycin		–
Doxycyclin		–
Enoxacin		–
Erythromycin		–
Levofloxacin		–
Minocyclin		–
Oxytetracycline		–
Tetracycline	122.7	+
<i>Antivirals</i>		
Acyclovir	–	–
Ganciclovir	–	–
Tenofovir		
Valacyclovir	–	
Zidovudine	151.8	+ or –

(continued)

Table 7 (continued)

	Human	
	Transport	Inhibition
<i>Antineoplastics</i>		
Methotrexate	17.8	
Mitoxantrone		–
<i>Immune suppressant</i>		
Cyclosporin A		–
<i>Histamine receptor 2 blocker</i>		
Cimetidine		–
<i>NSAIDs</i>		
Acetaminophen		–
Acetylsalicylate	–	–
Diclofenac		34.5
Diflusal		+
Ibuprofen	–	103
Indomethacin		10.1
Ketoprofen	(+)	70.3
Mefenamate		61.7
Naproxen		85.4
Phenacetin		–
Phenylbutazone		+
Piroxicam		84.9–107.8
Salicylate	(+)	+ or –
Sulfinpyrazone		+
Sulindac		617
<i>Uricosurics</i>		
Benzbromarone		+ or –
Probenecid		44.4–67.7

+, transport of inhibition was observed without determination of K_m , K_i , or IC_{50} ; +*, trans-stimulation of uptake of a test anion; –, no transport or no inhibition was observed; (+), weak transport or inhibition; blank, not determined; numbers, reported K_m , K_i , or IC_{50} values in micromoles/liter (μM). For references see text in Sect. 5.6.2

348 μM (Hasannejad et al. 2003). Torasemide and two of its metabolites, M1 and M3, *trans*-stimulated ES uptake, indicating that OAT4 translocates also this loop diuretic (Hagos et al. 2007a). No transport could be demonstrated for furosemide (Hasannejad et al. 2003). The IC_{50} values for ethacrynate, furosemide, and torasemide were below 50 μM , suggesting that OAT4 has a high to intermediate affinity for these loop diuretics (Hasannejad et al. 2003; Hagos et al. 2007a). The thiazide diuretics showed very low (chlorothiazide, trichlormethiazide) or no (cyclothiazide, hydrochlorothiazide) affinity (Hasannejad et al. 2003). In another study (Hagos et al. 2007b), hydrochlorothiazide *trans*-stimulated ES uptake, suggesting that this diuretic is better bound at the cytosolic side of OAT4 and effluxed than it interacts with the extracellular side to be taken up. Among the carboanhydrase blockers, acetazolamide showed a low affinity, and methazolamide no affinity for OAT4 (Hasannejad et al. 2003).

Statins. Pravastatin inhibited OAT4 (Enomoto et al. 2003). Data on other statins are not available.

Antibiotics. Benzylpenicillin inhibited OAT4, but an IC_{50} has not been reported (Cha et al. 2000; Babu et al. 2002b; Takeda et al. 2002c; Yamashita et al. 2006). With exception of cefadroxil, IC_{50} determinations have been performed for a number of cephalosporines, most of which have a very low affinity for OAT4 (see Table 7; Takeda et al. 2002a). Tetracycline was transported by OAT4 with a K_m of 122.7 μM ; all other tetracyclines (doxycycline, minocycline, oxytetracycline) did not show an interaction with OAT4 (Babu et al. 2002a). Other antibiotics (clarithromycin, enoxacin, erythromycin, levofloxacin) did also not inhibit OAT4 (Yamashita et al. 2006). Taken together, OAT4 has a very limited capacity to interact with antibiotics, at least from the extracellular side.

Antivirals. Acyclovir, ganciclovir, and valacyclovir were not transported by OAT4, and acyclovir, ganciclovir did not inhibit OAT4; only zidovudine was translocated (K_m 151.8 μM) and inhibited OAT4-mediated transport (Takeda et al. 2002b). These data suggest that OAT4 is not primarily involved in transport of antiviral drugs.

Antineoplastics. The folate antagonist methotrexate was transported by OAT4 with appreciable affinity (K_m 17.8 μM ; Takeda et al. 2002c); mitoxanthrone did not interact with OAT4 (Yamashita et al. 2006).

Immune suppressants. Cyclosporin A did not interact with OAT4 (Yamashita et al. 2006).

Histamine receptor 2 blockers. Cimetidine showed no inhibition of OAT4 (Babu et al. 2002b; Hashimoto et al. 2004; Khamdang et al. 2004; Yamashita et al. 2006).

Nonsteroidal anti-inflammatory drugs (NSAIDs). A weak uptake of ketoprofen and salicylate was shown whereas acetylsalicylate and ibuprofen were not transported by OAT4 (Khamdang et al. 2002). An inhibition of OAT4 was reported for diclofenac, diflusalin, ibuprofen, indomethacin, ketoprofen, mefenamate, naproxen, piroxicam, sulfipyrazone, and sulindac (for IC_{50} values see Table 7). No inhibition was found for acetaminophen, acetylsalicylate, phenacetin, and mixed results are available for salicylate and ibuprofen (Cha et al. 2000; Babu et al. 2002b; Khamdang et al. 2002; Takeda et al. 2002c; Yamashita et al. 2006; Zhou et al. 2005). Taken together, OAT4 does interact with most NSAIDs with intermediate affinity, that is, NSAIDs can inhibit OAT4 without being appreciably transported.

Uricosurics. For benzbromarone, either no inhibition (Iwanaga et al. 2005) or a strong inhibition of OAT4 (Hagos et al. 2007b) was found. Probenecid inhibited OAT4 in several studies (Cha et al. 2000; Babu et al. 2002b; Enomoto et al. 2002b, 2003; Takeda et al. 2002c; Hashimoto et al. 2004; Yamashita et al. 2006; Hagos et al. 2007b). The determined K_i values fall into the narrow range between 44.4 and 67.7 μM (mean: 56.2 μM ; Babu et al. 2002b; Enomoto et al. 2002b; Hashimoto et al. 2004).

Miscellaneous. The antiepileptic, valproate, was not transported, but inhibited OAT4; a tranquilizer, carbamazepine, and a cardiotonic, digoxin, did not inhibit OAT4 (Yamashita et al. 2006).

5.7 *Inhibitors*

As indicated previously (Sect. 5.6.2; uricosurics), probenecid is a competitive inhibitor of OAT4 with reasonable affinity (mean K_i 56.2 μ M out of three publications).

5.8 *Drug/Drug Interactions*

Methotrexate/NSAID interaction was tested with human OAT1-4, but only OAT3 showed a high enough affinity for NSAIDs to be appreciably inhibited at pharmacologically meaningful free plasma concentrations (Takeda et al. 2002c). Because OAT4 is involved in the uptake of urate from the primary filtrate, the efflux of torasemide and its metabolites, M1 and M3, and of hydrochlorothiazide causes an increased renal urate reabsorption and consequently an increase in plasma urate (Hagos et al. 2007a, b).

5.9 *Pharmacogenomics*

In the promoter region, an SNP was found that, however, did not cause a change in gene expression (Ogasawara et al. 2008). In the coding region, three synonymous and eight nonsynonymous SNPs were reported. The latter ones gave rise to the amino acid exchanges V13M, R48X, T62R, V155M, A244V, E278K, V339M, and T392I (Xu et al. 2005). The deleterious R48X mutation was found in one probe out of 18 specimens of Northern Europeans. Ashkenazi-Jewish people did not show any SNPs; the other described SNPs occurred in Chinese, Mexican-Americans, and Sahara-Africans. The functional consequences of the mutations are unknown. In comparison to OAT1 and OAT3, much more nucleotide variations were found for OAT4 (and URAT1; Xu et al. 2005).

6 **Urate Transporter 1 (URAT1; Urat1/Rst, Gene Name SLC22A12/Slc22a12)**

6.1 *Cloning, Structure*

Initially, this transporter was cloned as “renal specific transporter” (Rst) from mouse kidney (Mori et al. 1997). The protein consisted of 553 amino acids arranged in twelve transmembrane helices. *N*-glycosylation sites in the large extracellular

loop between helices 1 and 2 as well as several potential phosphorylation sites for protein kinases A and C were found, but function was not demonstrated. The first functional cloning of the human ortholog revealed its involvement in renal urate reabsorption, and the name URAT1 was proposed without reference to RST and to the OAT family (Enomoto et al. 2002a). The human URAT1 protein consisted of 555 amino acids and showed 42% identity with OAT4. A functional clone of mouse Rst/Urat1 was also obtained (Hosoyamada et al. 2004; Imaoka et al. 2004). The gene, SLC22A12, for human URAT1 is located on chromosome 11q13.1, being paired with the gene SLC22A11 for OAT4 (Eraly et al. 2003b). A promoter fragment of the human URAT1 was cloned containing 1,863 bp of the 5'-untranslated region (Li et al. 2004). The 5'-UTR regions from human, rat, and mouse were 80% identical containing the same transcription factor binding sites including HNF1-, CEBP-, AP1-, and GATA1 sites.

6.2 *Tissue Distribution of mRNA*

URAT1/Rst expression has been detected in human and mouse kidneys. In situ hybridization localized Rst mRNA to the proximal tubules (Mori et al. 1997). Human URAT1 mRNA and protein were also detected in human vascular smooth muscle cells by RT-PCR and Western blot analysis (Price et al. 2006). Except for some expression in testis, all other human tissue samples were negative for URAT1 (Nishimura and Naito 2005). Bleasby et al. (2006), however, found URAT1 mRNA also in samples from human adrenal gland, brain, colon, heart, ileum, jejunum, liver, lung, pancreas, placenta, peripheral leukocytes, pituitary, prostate, salivary gland, skeletal muscle, stomach, and testis. Mouse Urat1/Rst was mainly found in the kidneys and additionally at the blood-brain barrier and the choroid plexus (Imaoka et al. 2004).

6.3 *Immunolocalization of URAT1/Urat1/Rst Protein*

Human and mouse URAT1/Rst are localized at the apical (brush-border) membrane of proximal tubule cells (Anzai et al. 2004; Hosoyamada et al. 2004; Xu et al. 2006a). Thereby, URAT1 interacts through its C-terminal amino acids STQF with the PDZ domains 1, 3, and 4 of the scaffolding protein PDZK1. Coexpression of PDZK1 with URAT1 increased surface expression and maximal transport velocity (Anzai et al. 2004). In addition, mouse Urat1/Rst interacted with NHERF1; mice deficient in NHERF1 showed less Urat1/Rst protein in the apical membrane, more protein in the cytoplasm, and a higher renal urate excretion (Cunningham et al. 2007).

6.4 *Species Differences, Age and Gender Dependence of Expression*

Species differences and age dependence of URAT1/Rst expression are unknown. However, in mice there are clear gender differences in Rst expression: male mice showed 2.3-fold more Urat1/Rst protein than female mice (Hosoyamada et al. 2004), indicating a higher urate reabsorption capacity in males. It appears likely that a similar gender difference is present in humans, because men have higher urate levels than women (Hediger et al. 2005).

6.5 *Factors Influencing Activity and Abundance of URAT1/Urat1/Rst*

HNF-1 α and HNF-1 β increased the expression of reporter constructs with human or mouse URAT1/Urat1 and bound to the respective HNF sites at the promoters (Kikuchi et al. 2007). Likewise, Urat1/Rst expression was diminished in HNF-1 α knockout mice. The Urat1/Rst promoter was found to be relatively hypomethylated in mouse kidney, suggesting that a potentially tissue-specific epigenetic control over Urat1/rst expression takes place (Kikuchi et al. 2007).

URAT1 transport activity depends on its proper localization in the apical plasma membrane. As for another transporter in the apical membrane, OAT4, binding to the apically located scaffolding proteins (PDZK1 and NHERF1) ensures insertion into and maintenance within the brush-border membrane (see previous). Factors influencing this process or triggering endocytotic retrieval are not known.

6.6 *Substrates*

Similar to the other family members, URAT1 operates as an anion exchanger. The predominant mode is most probably urate uptake from the filtrate into the cell in exchange for intracellular lactate being released into the filtrate (Enomoto et al. 2002a; Hosoyamada et al. 2004). Lactate, in turn, is taken back up into the cell via a sodium-coupled lactate transporter, SMCT (SLC5A8; Gopal et al. 2004). Thus, urate absorption is tertiary active with the Na⁺, K⁺-ATPase in the basolateral membrane being the primary active system, the SMCT the secondary active system utilizing the Na⁺ gradient for intracellular lactate accumulation, and URAT1/Rst the tertiary system being driven by the lactate gradient. URAT1 also transports chloride (Enomoto et al. 2002a; Hosoyamada et al. 2004). Given the higher chloride concentration in the tubule lumen, chloride influx could drive the efflux of lactate or other organic anions. The physiological importance of this transport mode is not clear. Uptake of organic anions by mouse Urat1/Rst was accelerated by an inside

positive membrane potential (Hosoyamada et al. 2004). It is not clear whether potential-dependent uniport is another operation mode of the transporter otherwise working as an electroneutral anion exchanger.

The prototypic test anion for URAT1/Rst is urate, which is transported with low affinity (human: K_m between 198.7 and 371 μM ; Enomoto et al. 2002a; Anzai et al. 2004; Iwanaga et al. 2007; mouse: K_m 1,213 μM ; Hosoyamada et al. 2004).

6.6.1 Endogenous Substrates

Inorganic anions. Extracellular chloride *cis*-inhibited urate uptake and intracellular chloride *trans*-stimulated urate efflux. Similar effects were seen with bromide, iodide, nitrate, but not fluoride (Enomoto et al. 2002a; Hosoyamada et al. 2004). Thus URAT1/Rst can perform the exchange between an inorganic anion (physiologically chloride) and an organic anion, for example, urate.

Monocarboxylates. Extracellular lactate *cis*-inhibited and intracellular lactate *trans*-stimulated urate uptake (Enomoto et al. 2002a). Similar effects were seen with nicotinate, and a number of drugs discussed in the following. For extracellular acetoacetate and β -hydroxybutyrate (10 mM each), an inhibition of URAT1 was shown, suggesting that these organic anions may interact with URAT1, at least at high concentrations (Enomoto et al. 2002a).

Dicarboxylates. Inhibition was found for α -ketoglutarate and succinate, again at high concentrations (Enomoto et al. 2002a). Whether URAT1 can perform organic anion/dicarboxylate exchange is unknown.

Purine metabolism. As already discussed, urate is the prototypic anion transported by URAT1/Rst. Orotate inhibited URAT1, but xanthine did not inhibit human and mouse URAT1/Rst (Enomoto et al. 2002a; Hosoyamada et al. 2004).

Hormones, hormone derivatives. Estrone-3-sulfate did not interact with human and mouse URAT1/rst (Enomoto et al. 2002a; Hosoyamada et al. 2004). To our knowledge, only OAT1 and URAT1 do not transport ES. Dehydroepiandrosterone sulfate inhibited mouse Urat1/Rst; uptake of DHEAS was stimulated by an inside positive membrane potential (Hosoyamada et al. 2004).

Anionic neurotransmitter metabolites. 3,4-dihydroxymandelate, 3-methoxy-4-hydroxymandelate, 5-hydroxyindole acetate, 3-methoxy-4-hydroxyphenylacetate, and 5-methoxyindoleacetate inhibited mouse Urat1/Rst (Imaoka et al. 2004). The importance of URAT1 in removing these metabolites from the brain across the blood–brain barrier and in secreting them into the urine remains to be elucidated.

6.6.2 Drugs

Not tested were ACE inhibitors, statins, antiviral drugs, immune suppressants, antidiabetics, and histamine receptor blockers.

Angiotensin II receptor 1 blockers. Losartan, which is uricosuric, inhibited human URAT1 with extremely high affinity (K_i 0.0077 μM ; Iwanaga et al. 2007).

Pratosartan (K_i 0.0067 μM) and telmisartan (K_i 0.0182 μM) were equally effective inhibitors. At 0.01 μM , candesartan and olmesartan did not inhibit URAT1. But, following intracellular preloading, candesartan, losartan, olmesartan, and prazosartan, but not telmisartan, *trans*-stimulated urate uptake, indicating that angiotensin receptor blockers are accepted from the cytosolic side and serve as counter anions for urate uptake (Iwanaga et al. 2007). Thus, all these drugs should accelerate urate absorption with exception of losartan and prazosartan that both are filtered at concentrations sufficient to effectively compete with urate for URAT1.

Diuretics. Furosemide inhibited URAT1 (Enomoto et al. 2002a). Other diuretics were not tested with exception of torasemide that did not inhibit URAT1 (Hagos et al. 2007a).

Antibiotics. The only antibiotic tested was benzylpenicillin that inhibited mouse Urat1/Rst and showed an uptake stimulated by an inside positive potential (Hosoyamada et al. 2004).

Antineoplastics. Methotrexate did not inhibit URAT1 (Enomoto et al. 2002a).

Nonsteroidal anti-inflammatory drugs. Indomethacin, phenylbutazone, salicylate, and sulfipyrazone inhibited human URAT1 (Enomoto et al. 2002a).

Uricosurics. The increased renal excretion of urate could be due to the inhibition of the dominant reabsorptive transporter, URAT1, by uricosurics. Indeed, benzbromarone and probenecid inhibited human and mouse URAT1/Rst (Enomoto et al. 2002a; Hosoyamada et al. 2004; Imaoka et al. 2004; Iwanaga et al. 2005; Hagos et al. 2007a). IC_{50} values are, however, not available.

Antiuricosuric. Pyrazinoate is known for a long time to increase urate reabsorption. It has been shown for human and mouse URAT1/Rst that intracellular pyrazinoate exchanges readily with extracellular urate, thus driving urate absorption in proximal tubules (Enomoto et al. 2002a; Hosoyamada et al. 2004; Iwanaga et al. 2007). Pyrazinoate may be taken back up into proximal tubule cells by the Na^+ -driven lactate transporter (SMCT; SLC5A8; Gopal et al. 2004).

6.7 Inhibitors

Special inhibitors are not known. We could recommend losartan as an inhibitor with very high affinity (Iwanaga et al. 2007).

6.8 Drug/Drug Interactions

Drug–drug interactions are not known. Clinically relevant are the drug/urate interactions, which either lead to a higher (losartan) or lower (pyrazine as precursor of pyrazinoate) renal urate excretion.

6.9 Pharmacogenomics

URAT1 is the only transporter of the SLC22 family for which mutations have been clearly related to a disease. Loss-of-function mutations cause the familial idiopathic hypouricemia (lowered plasma levels of urate), a disease detected in the Japanese and Korean populations. The first mutation to be reported was a truncation mutation, W258X (Enomoto et al. 2002a). Most of the hypouricemic patients (74.1%) carry this mutation (Enomoto and Endou 2005). Further mutations detected in the patients were R90H, V138M, G164S, T217M, Q382L, G412A, M430T, R477H, G490A (Ichida et al. 2004; Komoda et al. 2004; Cheong et al. 2005). In healthy persons, six synonymous single nucleotide polymorphisms were found (Xu et al. 2005).

7 Organic Anion Transporter 10 (OAT10/ORCTL3, Gene Name SLC22A13)

7.1 Cloning, Structure

The organic cation transporter like 3 (ORCTL3) and ORCTL4 were cloned as a byproduct in the search for tumor-associated genes on chromosome 3 (Nishiwaki et al. 1998). From the structure of ORCTL3 and ORCTL4, the authors concluded that the gene products must be organic cation transporters. A functional investigation was not performed at that time. Bahn et al. (2008) expressed human ORCTL3 and found it to transport organic anions, but not organic cations. Therefore, they proposed to rename ORCTL3 as OAT10. The gene for OAT10 is located on chromosome 3p21.2, shows 10 exons, and is paired with that of ORCTL4 (Nishiwaki et al. 1998). The predicted OAT10 protein has 551 amino acids. Evolutionarily speaking, OAT10 constitutes its own branch. BLAST searches revealed rat and mouse orthologs that have not been functionally tested so far (Bahn et al. 2008).

7.2 Tissue Distribution of mRNA

ORCTL3 was found to be ubiquitously distributed (Nishiwaki et al. 1998). Full-length OAT10, however, was expressed predominantly in the kidneys with weaker signals in brain, heart, and colon. Splice variants without exon 3 or/and exon 4 were expressed in many organs (Bahn et al. 2008). The model cell line for the investigation of intestinal absorption, Caco-2, expressed the full-length OAT10 (Bahn et al. 2008). Within the kidneys, mRNA for OAT10 was mainly expressed in proximal tubules and – to a lesser extent – in cortical collecting ducts (Bahn et al. 2008).

7.3 Immunolocalization of OAT10 Protein, Gender Differences

Western blots showed a 55 kDa band in brush-border, but not in basolateral membranes, suggesting a localization in the apical membrane of tubule cells. The band was stronger in brush-border membranes from female rats than from male rats, indicating a female-dominant expression (Bahn et al. 2008).

7.4 Substrates

Similar to other members of the SLC22 family, OAT10 can operate as an anion exchanger. Similar to other OATs located in the apical membrane, the 5-carbon dicarboxylate glutarate is not suited as exchange partner, but rather the 4-carbon succinate. Moreover, lactate and nicotinate can exchange for *p*-aminohippurate or urate. The pH dependence of OAT10 further suggests that an exchange against hydroxyl ions may be a mode of transport. The physiologically most important substrate is nicotinate; OAT10 has a high affinity for this vitamin and is responsible for its uptake from the diet in the intestine and for reabsorption in proximal tubules to avoid its loss with the urine. Next important is the ability of OAT10 to transport urate. Besides URAT1, this transporter should be involved in renal urate reabsorption. The driving force for urate uptake, that is, exchange of urate in the tubule lumen for intracellular lactate, also resembles URAT1, and couples OAT10 functionally to the Na⁺-driven lactate transporter SMCT (Bahn et al. 2008).

As a model test anion we suggest nicotinate, the uptake of which by OAT10 is high above background (nonexpressing cells). The K_m is 22 μ M (Bahn et al. 2008).

7.4.1 Endogenous Substrates (Bahn et al. 2008)

Monocarboxylates. Extracellular lactate *cis*-inhibited OAT10-mediated urate uptake and intracellular lactate *trans*-stimulated it, indicating that OAT10 transports lactate and can perform urate/lactate exchange. The affinity of OAT10 for lactate has not been determined. *cis*-inhibition and *trans*-stimulation have also been observed for nicotinate, for which a K_m of 22 μ M was determined.

Dicarboxylates. Succinate *cis*-inhibited and *trans*-stimulated OAT10-mediated urate transport, whereas the nonphysiologic 5-carbon glutarate showed *cis*-inhibition, but no *trans*-stimulation, suggesting a preference for C4 dicarboxylates.

Glutathione trans-stimulated urate uptake, suggesting that this tripeptide is transported by OAT10, at least from the intra- to the extracellular compartment.

7.4.2 Drugs (Bahn et al. 2008)

Diuretics. Furosemide and hydrochlorothiazide inhibited OAT10. Further diuretics were not tested. Hydrochlorothiazide was not able to *trans*-stimulate urate uptake, leaving open whether this thiazide can be transported by OAT10.

Immune suppressants. Cyclosporin A *cis*-inhibited OAT10-mediated nicotinate uptake and *trans*-stimulated urate uptake, suggesting that this compound is indeed translocated by OAT10. It is open whether OAT10 is involved in cyclosporin A-induced damage of proximal tubule cells.

Nonsteroidal anti-inflammatory drugs. Only sulfinpyrazone was tested that inhibited OAT10-mediated nicotinate transport.

7.5 Inhibitors, Drug/Drug Interactions, Pharmacogenomics

Probenecid showed a weak inhibition. An IC_{50} value has not been determined. At present, a good and specific inhibitor is not at hand. There are no reports on drug/drug interactions and single nucleotide polymorphisms.

8 Organic Anion Transporter 5 (Oat5, Gene Name Slc22a19)

8.1 Cloning, Structure

Oat5 was cloned from rat (Anzai et al. 2005) and mouse (Youngblood and Sweet 2004). A human orthologue is not existent, the human OAT5 cloned by Sun et al. (2001) being not related to rat and mouse Oat5. Rat Oat5 has 551 amino acids, twelve putative transmembrane helices, four *N*-glycosylation, and five putative protein kinase C phosphorylation sites.

8.2 Tissue Distribution of mRNA, Immunolocalization, Gender Differences

Rat and mouse Oat5 are restricted to the kidney with no gender difference (Youngblood and Sweet 2004). With antibodies a localization at the apical (brush-border) membrane has been shown in the late segments (S2 < S3) of the proximal tubule (Anzai et al. 2005; Kwak et al. 2005a). More recently, a female-dominant Oat5 protein expression was found in rats (Sabolic and collaborators, unpublished results).

8.3 Substrates

Oat5 did not interact with glutarate, a 5-carbon dicarboxylate, but – in one study (Anzai et al. 2005) – readily with succinate, a 4-carbon dicarboxylate. Because intracellular succinate *trans*-stimulated, Oat5 may operate as an organic anion/dicarboxylate exchanger similar to OAT1-4. Unlike the other OATs, however, C5 dicarboxylates may not be the preferred counter anion. In another study (Youngblood and Sweet 2004), intracellular succinate was unable to *trans*-stimulate Oat5. Thus, more work is needed to finally clarify the mode of transport.

In most tests, estrone-3-sulfate has been used as a test anion. The K_m of rat Oat5 for ES was 18.9 μM (Anzai et al. 2005), whereas the K_m of mouse Oat5 was 2.2 μM (Kwak et al. 2005a). Other researchers used ochratoxin A (K_m 0.34 μM and 2.0 μM for rat and mouse Oat5, respectively) as test organic anion (Youngblood and Sweet 2004). *p*-aminohippurate, the prototypic test anion for OAT1/Oat1, was not transported (Youngblood and Sweet 2004; Anzai et al. 2005).

8.3.1 Endogenous Substrates

Dicarboxylates. As already mentioned, mixed results have been published for the interaction of Oat5 with succinate. Malate, malonate, and oxalate did not interact with Oat5, but the nonphysiological longer dicarboxylates suberate, pimelate, and azelate inhibited (Youngblood and Sweet 2004; Anzai et al. 2005).

Hormones, hormone derivatives. ES (see previous) and DHEAS (K_m 2.3 μM for rat, and 3.8 μM for mouse Oat5; Anzai et al. 2005; Kwak et al. 2005a) were transported with high affinity. β -Estradiol sulfate, but not β -estradiol-3 β -D-glucuronide, inhibited rat Oat5 (Anzai et al. 2005). Rat Oat5 did not transport prostaglandins E₂ and F_{2 α} (Anzai et al. 2005).

Urate was not transported (Anzai et al. 2005).

8.3.2 Drugs (Rat Oat5: Anzai et al. 2005; Mouse Oat5: Youngblood and Sweet 2004)

Diuretics. Furosemide inhibited rat Oat5.

Antibiotics. Benzylpenicillin inhibited rat Oat5.

Nonsteroidal anti-inflammatory drugs. Diclofenac and ibuprofen inhibited rat Oat5, and salicylate both rat and mouse Oat5.

8.4 Inhibitors, Drug/Drug Interactions, Pharmacogenomics

Probenecid inhibited rat and mouse Oat5, but there were no IC₅₀ reported in the literature (Youngblood and Sweet 2004; Anzai et al. 2005). Drug/drug interactions

are not known. Single nucleotide polymorphisms have, to our knowledge, not been reported.

9 Organic Anion Transporter 6 (Oat6, Gene Name Slc22a20)

9.1 Cloning, Structure, Tissue Distribution

Oat6 was cloned from mouse; similar to the other members of the SLC22 family, the gene was organized in 10 exons and 9 introns (Monte et al. 2004). Unlike the other members, Oat6 was expressed in the nasal epithelium, but not in kidneys and liver. In testis, a low expression of Oat6 mRNA was detected. The exact localization of Oat6 in the nasal epithelium is unknown. Nevertheless it has been postulated that Oat6 is involved in odorant detection, a task for which it must be expressed in olfactory sensory cells. Due to its specificity partially overlapping with that of Oat1 it was hypothesized that mice can smell with Oat6 what has been excreted by Oat1 with the urine (Kaler et al. 2007b).

9.2 Species Differences, Age and Gender Dependence of Expression; Abundance

The message for Oat6 is detectable on embryonic day e7, that is, before the mRNA for other Oats appears (Monte et al. 2004). Further data are not available.

9.3 Substrates

Uptake of estrone-3-sulfate was *trans*-stimulated by preloading Oat6-expressing oocytes or CHO cells with glutarate, suggesting that this transporter, similar to Oat1 and Oat3, can perform organic anion/ α -ketoglutarate exchange (Schnabolk et al. 2006). Whether a Na⁺-coupled dicarboxylate transporter that fuels Oat1 and Oat3 in proximal tubules is present also in the nasal epithelium is unknown.

Estrone-3-sulfate appears to be a good test anion for Oat6. K_m values of 45 and 110 μ M have been reported (Schnabolk et al. 2006).

9.3.1 Endogenous Substrates

Monocarboxylates. The short chain fatty acids, propionate, butyrate, hexanoate, and heptanoate inhibited Oat6. The respective IC₅₀ values (in μ M) were 279 for

propionate, 82 for butyrate, 9.0 for hexanoate, and 8.2 for heptanoate (Kaler et al. 2007a), indicating that affinity increased with increasing lipophilicity. The hydrophilic pyruvate inhibited with an IC_{50} of 271 μ M; hydroxylated or methylated derivatives of lactate and butyrate also inhibited Oat6 (Kaler et al. 2007a).

Dicarboxylates. Fumarate and maleate did not inhibit Oat6. The nonphysiologic dicarboxylate glutarate showed a low affinity (IC_{50} 5.51 mM) but *trans*-stimulated ES uptake (Kaler et al. 2007a).

Bile salts. Cholate and taurocholate did not inhibit Oat6 (Kaler et al. 2007a).

Hormones, hormone derivatives. Estrone-3-sulfate inhibited uptake with an IC_{50} of 58 μ M and was transported with K_m between 45 and 110 μ M (Schnabolk et al. 2006; Kaler et al. 2007a). Estradiol disulfate had a much smaller affinity than ES (IC_{50} of 7.2 mM; Kaler et al. 2007a). Prostaglandin E_2 , however, had a high affinity for Oat6 (IC_{50} 18 μ M; Kaler et al. 2007a).

9.3.2 Drugs

Antibiotics. Benzylpenicillin (IC_{50} 452 μ M or 1.45 mM), carbenicillin (IC_{50} 1.33 mM), and ticarcillin (IC_{50} 533 μ M) inhibited Oat6 (Schnabolk et al. 2006; Kaler et al. 2007a).

Antiviral drugs. Stavudine (IC_{50} 1.67 mM), zalcitabine (IC_{50} 729 μ M), and zidovudine (IC_{50} 218 μ M) inhibited Oat6 whereas acyclovir, adefovir, cidofovir, didanosine, lamivudine, tenofovir did not (Truong et al. 2008).

Antineoplastic drugs. Methotrexate inhibited with an IC_{50} of 597 μ M (Kaler et al. 2007a).

Histamine receptor blockers. Cimetidine and histamine itself did not interact with Oat6 (Ahn et al. 2009).

Nonsteroidal anti-inflammatory drugs. Acetylsalicylate (IC_{50} 101 μ M), ibuprofen (1.1 μ M), and salicylate (IC_{50} 44 or 49 μ M) inhibited Oat6 (Schnabolk et al. 2006; Kaler et al. 2007a).

Miscellaneous cationic drugs. Buspirone, clonidine, metoclopramide, nicotine, procainamide, quinidine, and verapamil did not inhibit Oat6 (Ahn et al. 2009).

9.4 Inhibitors

Probenecid had a quite high affinity for Oat6 (IC_{50} 8.3 or 8.4 μ M; Schnabolk et al. 2006; Kaler et al. 2007a), suggesting that this uricosuric can be used to block Oat6 efficiently.

9.5 Drug/Drug Interactions: Pharmacogenomics

No data available.

10 Organic Anion Transporter 7 (OAT7, Gene Name SLC22A9)

10.1 Cloning, Structure, Tissue Distribution, Localization

OAT7 was cloned from a human liver library (Shin et al. 2007) and was previously known as human UST3 or OAT4 (Sun et al. 2001). The gene is located on chromosome 11q12.3 (Table 1), and the protein has 554 amino acids. OAT7 is only expressed in the liver where the protein has been detected at the sinusoidal membrane. Developmental changes and gender differences are unknown.

10.2 Substrates (Shin et al. 2007)

OAT7 transported estrone-3-sulfate (K_m 8.7 μ M) and dehydroepiandrosterone sulfate (K_m 2.2 μ M) with high affinity. A series of other sulfated compounds including β -estradiol-sulfate, 4-methylumbelliferyl sulfate, α -naphthylsulfate, and minodixil sulfate inhibited OAT7. Unlike many other OATs OAT7 was not inhibited by *p*-aminohippurate and probenecid. Also unlike OAT1 and OAT3, no interaction with α -ketoglutarate and glutarate was found, but a series of monocarboxylates/short chain fatty acids (nicotinate, lactate, acetate, propionate, butyrate, valerate, caproate) inhibited OAT7, and propionate, butyrate, valerate, and caproate *trans*-stimulated estrone sulfate transport. The authors postulated that OAT7 releases estrone sulfate from hepatocytes in exchange for butyrate. OAT7 does not play a role in uptake of bile acids into hepatocytes, because cholate and taurocholate did not interact. Among drugs, salicylate was not transported, and indomethacin and benzylpenicillin did not inhibit.

11 Organic Anion Transporter 8 (Oat8, Gene Name Slc22a9)

11.1 Cloning, Structure, Tissue Distribution, Localization

This transporter was previously cloned from a rat kidney library as unknown solute transporter 1, Ust1 (Schömig et al. 1998). Meanwhile, functional expression revealed transport of organic anions, and Ust1 was renamed as rat Oat8 (Yokoyama et al. 2008), although the human homologue was named OAT7 by the same group (Shin et al. 2007). Message was found in proximal tubules and collecting ducts of rat kidney, and nowhere else. With antibodies, a colocalization with the V-type H^+ -ATPase in intercalated cells was shown. In type A cells, immunoreactivity was found at the apical pole (apical membrane and subapical vesicles), in type B

intercalated cells at the basal cell pole, and in nonA, nonB cells distributed throughout the cell. The physiological role of Oat8 remains to be determined.

11.2 Substrates (Yokoyama et al. 2008)

Oat8 transported estrone-3-sulfate (K_m 3.1 μM) and dehydroepiandrosterone sulfate (K_m 2.1 μM), but not *p*-aminohippurate, urate, prostaglandin E_2 and prostaglandin $F_{2\alpha}$. The dicarboxylates succinate, glutarate, suberate, and azelate, but not malonate, adipate, and pimelate inhibited Oat8, and glutarate *trans*-stimulated Oat8-mediated ES uptake, suggesting that Oat8 functions as an organic anion/dicarboxylate exchanger. Taurocholate inhibited transport, suggesting an interaction of bile salts with Oat8. The diuretic furosemide, but not bumetanide, the NSAID salicylate, but not ibuprofen, inhibited Oat8. No inhibition was seen with penicillin G. The cytostatic methotrexate inhibited Oat8.

12 Organic Anion Transporter 9 (Oat9, Gene Name Unknown)

12.1 Cloning, Tissue Distribution, Substrates

Oat9 was cloned from mouse and is expressed in kidneys and brain (Anzai et al. 2006). Transported endogenous substrates were nicotinate and prostaglandin E_2 . Among drugs, only salicylate was tested and found to be transported (Anzai et al. 2006).

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