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The ABC of Solute Carriers

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The SLC22 drug transporter family

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Abstract The SLC22 family comprises organic cation transporters (OCTs), zwitterion/cation transporters (OCTNs), and organic anion transporters (OATs). These transporters contain 12 predicted α-helical transmembrane domains (TMDs) and one large extracellular loop between TMDs 1 and 2. Transporters of the SLC22 family function in different ways: (1) as uniporters that mediate facilitated diffusion in either direction (OCTs), (2) as anion exchangers (OAT1, OAT3 and URAT1), and (3) as Na^+/L-carnitine cotransporter (OCTN2). They participate in the absorption and/or excretion of drugs, xenobiotics, and endogenous compounds in intestine, liver and/or kidney, and perform homeostatic functions in brain and heart. The endogenous substrates include monoamine neurotransmitters, choline, L-carnitine, α-ketoglutarate, cAMP, cGMP, prostaglandins, and urate. Defect mutations of transporters of the SLC22 family may cause specific diseases such as "primary systemic carnitine deficiency" or "idiopathic renal hypouricemia" or change drug absorption or excretion.

Keywords Carnitine transporter · Drug transporters · Excretion · Organic anions · Organic cations · Polyspecific transporters · Urate transporter

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Introduction

This review gives a short overview about the transporters of the SLC22 family, which belongs to the major facilitator superfamily [26]. This superfamily comprises uniporters, symporters, and antiporters from bacteria, lower eukaryotes, plants, and mammals in 18 families. In 1994, the first member of the SLC22 family, the rat organic cation transporter OCT1, was identified by expression cloning [17]. Rat OCT2 was identified in 1996 [38] and the human zwitterion/cation transporters OCTN1 in 1997 [56]. In the same year, the first organic anion transporter OAT1 was cloned from rat and flounder [45, 52, 60]. In 1998, OCT3 was identified from rat and human [18, 22], and the human Na^+-carnitine cotransporter OCTN2 was cloned [54, 63]. Other highlights were the identification of the OAT-subtypes 2–5 [7, 8, 29, 43], the human urate transporter URAT1 [10], and the human testicular carnitine transporter hCT2 [12].

Most transporters of the SLC22 are polyspecific, i.e., they transport multiple different substrates; in addition, numerous other ligands can act as inhibitors. Since many of these transporters are expressed in intestine, liver and kidney, the SLC22 family plays a pivotal role in drug absorption and excretion. The family can be divided into various subgroups according to substrates and transport mechanisms (Table 1, Fig. 1). One subgroup comprises the OCT subtypes 1–3 which translocate organic cations, including weak bases. Transport of organic cations by any of the three OCT subtypes is: (1) electrogenic, (2) independent from Na^+, and (3) reversible with respect to direction. The driving force is supplied solely by the electrochemical gradient of the transported organic cation. A second subgroup comprises the transporters OCTN1–3 and hCT2 (FLIPT2) [12, 13, 54, 55, 56, 63]. These transporters may function either as (1) an organic cation uniporter or H^+/organic cation antiporter (e.g., OCTN1), or as (2) uniporters for organic cations or Na^+/carnitine cotransporters (e.g., OCTN2). A third subgroup comprises the organic anion transporters OAT1–5 and the human urate transporter URAT1 [7, 8, 10, 19, 29, 39, 43,

Table 1 SLC22—the organic cation/anion/zwitterion transporter family. SLC review series. (*P* Pseudogene)

Human gene name	Protein name	Aliases	Predominant substrates	Transport type/ coupling ions[a]	Tissue distribution and cellular/subcellular expression	Link to disease[b]	Human gene locus[c]	Sequence accession ID	Splice variants and their specific features
SLC22A1	hOCT1		Organic cations, polyspecific	F	Liver, sinusoidal membrane of hepatocytes		6q26	X98332 U77086	Three splice variants from liver with no uptake in vitro [29]
SLC22A2	hOCT2		Organic cations, polyspecific	F	Kidney, basolateral membrane of proximal tubules; brain, neurons		6q26	X98333	hOCT2-A from kidney with uptake in vitro (AB075951)
SLC22A3	hOCT3	hEMT	Organic cations, polyspecific	F	Liver, skeletal muscle, placenta, kidney, heart, lung, brain		6q26-27	AJ001417	
SLC22A4	hOCTN1		Organic cations, polyspecific	F or E/H^+	Kidney, skeletal muscle, placenta, prostate, heart		5q23.3	AB007448	
SLC22A5	hOCTN2	CT1	L-Carnitine, organic cations, polyspecific	C/Na^+ and L-carnitine, F (for organic cations)	Skeletal muscle, kidney (luminal membrane of proximal tubules), prostate, lung, pancreas, heart, small intestine, adrenal gland, thyroid gland, liver, etc.	Primary systemic carnitine deficiency/G	5q23.3	AF057164	
SLC22A6	hOAT1		Organic anions, polyspecific	E/organic anions	Kidney, basolateral membrane of proximal tubules; placenta, brain		11q12.3	AF057039	hOAT1-1 from kidney with uptake in vitro (AB009697), two further variants with no uptake in vitro [4]
SLC22A7	hOAT2		Organic anions, polyspecific	F or E	Liver, sinusoidal membrane of hepatocytes; kidney, basolateral membrane of proximal tubules		6q21.1-2	AF210455, AF097518, AY050498	Kidney and liver specific splice variants with no uptake in vitro [4]
SLC22A8	hOAT3		Organic anions, polyspecific	E/organic anions	Kidney, basolateral membrane of proximal tubules; brain, luminal membrane of choroid plexus; skeletal muscle, developing bone	Osteosclerosis/ osteopetrosis in mice/G	11q12.3	AF097491	
SLC22A10	hOAT5		Not determined	O	Liver		11q12.3	AA705512	
SLC22A11	hOAT4		Organic anions, polyspecific	F or E	Kidney, luminal membrane of proximal tubules; placenta		11q13.1	AB026116	
SLC22A12	hURAT1		Urate	E/organic anions	Kidney	Idiopathic renal hypo-uricaemia/G			

Table 1 (continued)

Human gene name	Protein name	Aliases	Predominant substrates	Transport type/ coupling ions[a]	Tissue distribution and cellular/subcellular expression	Link to disease[b]	Human gene locus[c]	Sequence accession ID	Splice variants and their specific features
	11q13.1	AB071863							
–	hCT2	hFLIPT2 hOCT6	Carnitine	F	Testis, Sertoli cells and epididymal duct cells; bone marrow, leukocytes, kidney		6q21-22.1	AB055798, AF268892, AY145502	
–	FLIPT1		Not determined	O	Kidney, brain, liver, skeletal muscle, heart, placenta, lung, spleen		1p13.1	AY145501	
–	OCTL1	hORCTL3	Not determined	O	Kidney, colon, small intestine		3p22.2	AB010438	
–	OCTL2	hORCTL4	Not determined	O	Kidney, colon, small intestine		3p22.2	AB011082	
–	BOIT	BOCT	Not determined	O	Brain		14q11.2	AJ243122	Splice variant: NM_020372, NM_016609
SLC22A9	hUST3		Not determined	O	Liver		11q12.3	AB062418	

[a] (*C* Cotransporter, *E* exchanger, *F* facilitated transporter, *O* orphan transporter)
[b] (*A* Acquired defect, *G* genetic defect), [c] Gene loci were corrected according to [13]

Fig. 1 Phylogenetic tree of the human transporters of the SLC22 family, including two transporters from rodents that have not been detected in human. Distance along the branches is inversely related the degree of sequence identity. For example, sequence identities are 70% between hOCT1 and hOCT2, 32% between hOCT1 and hOCTN1, and 32% between hOCT1 and hOAT1. Polyspecific transporters for organic cations are indicated in *red*, transporters for organic cations and zwitterions in *yellow*, and transporters for organic anions in *blue*

45, 52]. These transporters are able to translocate anions in either direction; some of them (OAT1, OAT3 and URAT1) mediate exchange with divalent organic anions [45, 50, 52]. The transporters of the SLC22 family have a similar predicted membrane topology consisting of 12 α-helical transmembrane domains (TMDs), a large glycosylated extracellular loop between TMDs1 and 2, and a large intracellular loop between TMDs 6 and 7 with consensus sequences for phosphorylation (Fig. 2). For reviews on selected transporters of the SLC22 family see [4, 25, 26, 42].

SLC22A1 (OCT1)

OCT1 has been isolated from rat, mouse, rabbit, and humans, and splice variants have been detected in rat and human [15, 17, 26, 65]. In all species studied, OCT1 is mainly expressed in liver. In rodents, there is additional strong expression of OCT1 in kidney, small intestine, colon, skin, and spleen (for references see [26]). The OCT1 protein was localized to the sinusoidal membrane of hepatocytes in rat liver, to the basolateral membrane of proximal tubules in rat kidney, to the basolateral membrane of enterocytes, and to serotoninergic neurons in mouse small intestine [9, 21, 26]. There is a broad overlap of the substrate and inhibitor specificities of OCT1 as compared to OCT2 and OCT3 [26]. Most substrates of OCT1 are organic cations, but some weak bases, non-

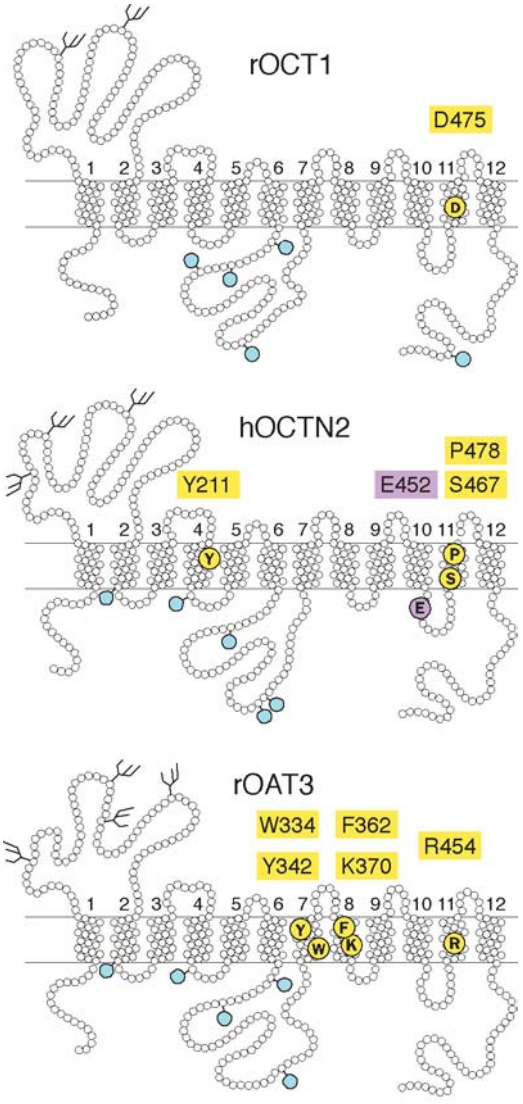

Fig. 2 Predicted topology of SLC22 transporters with functional relevant point mutations. Predicted glycosylation sites on the large extracellular loops of rOCT1, hOCTN2 and rOAT3 (ψ) and predicted phosphorylation on the large intracellular loops (*blue*) are indicated. Amino acids where point mutations resulted in changes of the substrate selectivity are indicated in *yellow*. Glutamate 452 in hOCTN2 (*pink*) is thought to be involved in Na^+ binding to hOCTN2 (for discussion see [26])

charged compounds and anions are also transported. Substrates of human OCT1 include model cations such as tetraethylammonium (TEA), *N*-methylquinine, the xenobiotic 1-methyl-4-phenylpyridinium (MPP), drugs such as desipramine, aciclovir, ganciclovir, metformin, and endogenous compounds such as serotonin, prostaglandin E_2 and prostaglandin $F_{2\alpha}$ (for references see [26]). Expression and selectivity of OCT1 is regulated. For example, after expression in human embryonic kidney cells (HEK–293), transport by rOCT1 was stimulated by PKC, PKA and tyrosine kinase and inhibited by cGMP [31, 40], and stimulation by PKC was associated with altered substrate selectivity. Site-directed mutagenesis experiments identified aspartate 475 in TMD11 of rOCT1 as part of the cation binding pocket [16] (Fig. 2).

Physiological roles

In the human, OCT1 mediates the first step in hepatic excretion of many cationic drugs and xenobiotics, i.e., the uptake across the sinusoidal membrane into the hepatocyte. Excretion across the sinuosoidal membrane into the bile is mediated by an as yet unidentified polyspecific H^+/organic cation antiporter and/or by P-glycoprotein MDR1 [25, 26].

Pathological implications

In human OCT1, eight single nucleotide polymorphisms (SNPs) have been detected. Three of these mutations affect transport [23]. After targeted disruption of OCT1 in mice, the biliary excretion of some but not all substrates of OCT1 was largely reduced [20]. This indicates that defect mutations in OCT1 may reduce the biliary excretion of specific drugs and affect their efficacy and/or toxicity.

Therapeutic aspects

The hepatotoxicity of drugs that are transported by OCT1 may be reduced by co-medication of other substrates or inhibitors of OCT1. Detailed knowledge on the regulation of OCT1 may provide therapeutic tools to up-regulate OCT1 in order to improve the hepatic excretion of drugs.

SLC22A2 (OCT2)

OCT2 has been cloned from rat [38], human [15], mouse, rabbit, and pig (for references see [26]). It is mainly expressed in the kidney, but has also been found in human placenta, rat thymus, rat choroid plexus, and neurons of the human CNS [5, 15, 26, 38, 48]. In rat and human kidney, OCT2 protein was localized to the basolateral membrane of renal proximal tubules [21, 32]. Most substrates of human OCT1 are also transported by human OCT2 (hOCT2), albeit with different affinities in some cases [26]. Well-characterized substrates of hOCT2 are TEA, MPP, choline, dopamine, histamine, norepinephrine, serotonin, amantadine, cimetidine, and memantine [5, 26]. Inward and outward currents mediated by rat OCT2 (rOCT2) at different membrane potentials were investigated in giant excised patches of *Xenopus laevis* oocytes injected with rOCT2 cRNA [3]. Choline-induced currents were potential dependent and symmetrical with respect to substrate application from outside vs. inside. The data were consistent with a transport model of a simple uniporter. At 0 mV, similar K_m values were obtained for organic cation influx compared to efflux;

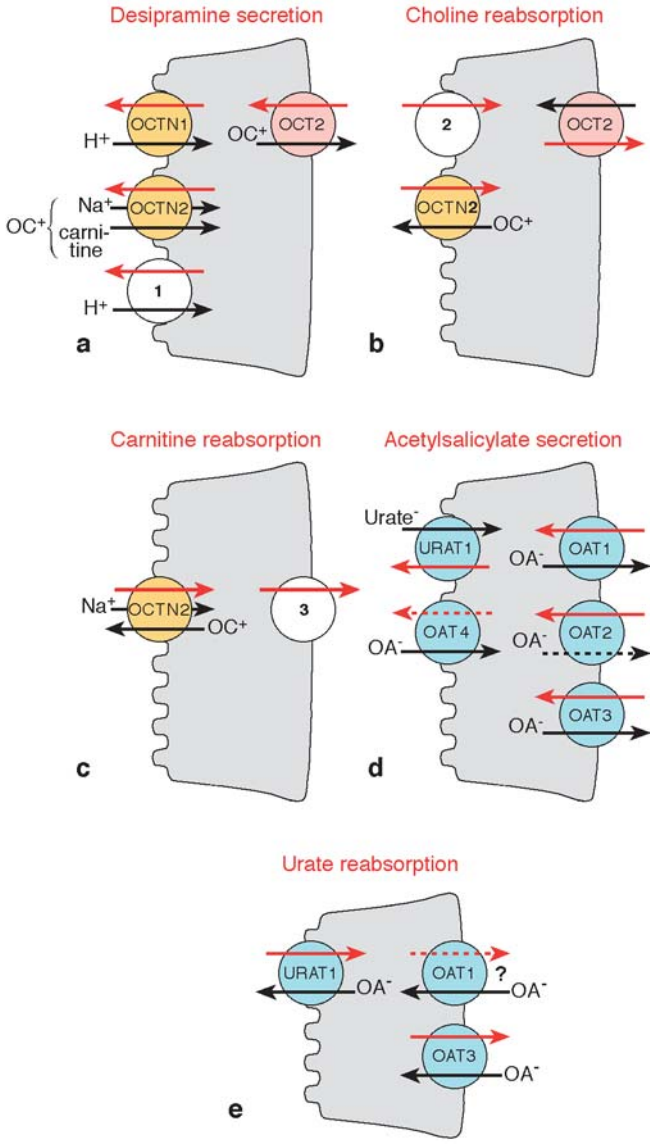

Fig. 3a–e Functional subcellular arrangement of SLC22 transporters in human renal proximal tubules. Examples for solute secretion or reabsorption by cooperative function of SLC22 transporters in the basolateral (*right*) and luminal membrane (*left*) of renal proximal epithelial cells. The transporters are color coded as in Fig. 1. *Broken arrows* indicate assumed substrate movements that have not been demonstrated experimentally. Functionally characterized transporters that have not been identified at the molecular level are indicated by numbers (*1* Cation/proton antiporter, *2* polyspecific electrogenic cation transporter at the luminal membrane, *3* basolateral carnitine transporter.) A role of OAT1 in urate reabsorption is discussed

however, the membrane potential exhibited opposite effects on these K_m values. The expression of OCT2 is dependent on the gender and undergoes short-term regulation. Renal expression of rOCT2 was higher in male rats than in females, and administration of testosterone to females increased OCT2 expression (for references see [26]). hOCT2 is constitutively activated by the Ca^{2+}/calmodulin complex and inhibited by the muscarinic receptor agonist carbachol [6].

Physiological roles

hOCT2 mediates the first step in renal excretion of many organic cations drugs such as the antidepressant desipramine (Fig. 3a). This transporter also mediates the second step in the reabsorption of choline (Fig. 3b). In CNS, hOCT2 participates in the regulation of interstitial and intracellular concentrations of monoamine neurotransmitters and cationic drugs (for references see [26]).

Pathological implications

In hOCT2, SNPs were identified that caused single amino acid substitutions at seven positions [30]. In one of these, the apparent K_m value for expressed uptake was decreased compared to wildtype. Mutations in hOCT2 with impaired function may lead to decreased renal excretion of cationic drugs and/or to increased interstitial concentrations of monoamine neurotransmitters in brain.

Therapeutic aspects

The efficacy of cationic drugs that are mainly excreted by the kidney can be improved by co-medication of substrates and/or inhibitors of hOCT2. Pharmaceuticals that up-regulate hOCT2 in the kidney can increase the renal excretion of cationic drugs.

SLC22A3 (OCT3)

OCT3 has been isolated from rat, mouse and human [18, 22, 26]. In the human, OCT3 is mainly expressed in skeletal muscle, liver, placenta, kidney and heart, and to a lesser extent in brain. In situ hybridization showed the presence of OCT3 mRNA in hippocampal and cerebellar neurons of rat and mice [41]; similarly, neuronal localization of OCT3 was also observed by single cell RT-PCR on neurons of the superior cervical ganglion of the rat [28]. Human OCT3 (hOCT3) has substrate and inhibitor specificities that broadly overlap with those of hOCT1 and hOCT2 [26]. For example, hOCT3 translocates TEA, MPP, guanidine, dopamine, norepinephrine, and histamine [18, 22, 62]. Organic cation uptake by rat and human OCT3 showed sensitivities to some inhibitors of norepinephrine uptake into cardiac myocytes and human Caki-1 cells that are similar to the sensitivities of the previously described extra-neuronal norepinephrine "uptake$_2$ system" (for references see [26]). Since OCT3 is localized in neurons, and OCT1 and OCT2 also translocate norepinephrine, OCT3 cannot be equated with the functional defined "uptake$_2$ system" (for further discussion see [26]).

Physiological roles

hOCT3 is thought to be involved in the biliary excretion of cationic drugs. In CNS, ganglia and heart, hOCT3 regulates the interstitial concentrations of monoamine neurotransmitters and cationic drugs. In placenta, hOCT3 is responsible for the release of acetylcholine during non-neuronal cholinergic regulation [58].

Pathological implications

Pharmacokinetic studies in OCT3 knock out-mice showed that this transporter is required for the uptake of MPP into heart and placenta [66]. Mutations that impair the expression or function of hOCT3 should reduce the hepatic excretion and materno–fetal passage of cationic drugs. They may have complex effects on neurotransmission.

Therapeutic aspects

Inhibitors of hOCT3 may be employed to suppress the cardiotoxicity of cationic drugs and to prevent fetal intoxication when pregnant women are treated with cationic drugs.

SLC22A4 (OCTN1)

OCTN1 has been cloned from human, rat, and mouse; the human transporter (hOCTN1) is expressed in kidney, skeletal muscle, placenta, prostate, and heart [26, 56]. hOCTN1 is polyspecific and transports the monovalent organic cations TEA, quinidine, pyrilamine, verapamil, and the zwitterion carnitine, whereas it is inhibited by other organic cations, zwitterions and anions [56, 64]. hOCTN1 mediates TEA transport in either direction. TEA uptake by hOCTN1 is independent from an inwardly directed sodium gradient and membrane potential. Since an inwardly directed H^+ gradient stimulates TEA efflux [64], hOCTN1 may work as an electroneutral H^+/organic cation antiporter that mediates the cellular efflux of organic cations. OCTN1 is probably localized in the luminal membrane of renal proximal tubules (Fig. 3a) where electroneutral H^+/organic cation exchange activity has been described (for further discussion, see [26]). Large species differences exist with regard to the localization and transport mechanism of OCTN1. For example, OCTN1 could not be detected in liver from adult humans whereas it is strongly expressed in liver from rats [61]. Also, carnitine uptake by OCTN1 was Na^+ dependent for mouse OCTN1, but not for rat OCTN1 [55, 64].

Physiological roles

In renal proximal tubules hOCTN1 participates in the secretion of organic cations (Fig. 3a). Since it transports in both directions it may also participate in the reabsorption of organic cations.

Pathological implications and therapeutic aspects

Defect mutations in hOCTN1 increase the nephrotoxic potential of cationic drugs that enter proximal tubules via hOCT2 (Fig. 3a). Pharmaceutical up-regulation of hOCTN1 should improve the renal secretion of cationic drugs or xenobiotics without increasing their intracellular concentrations.

SLC22A5 (OCTN2)

OCTN2 has been cloned from human, mouse, and rat [33, 44, 54, 63]. In humans, it is expressed in skeletal muscle, kidney, heart, brain, and several other tissues (for references see [26]). In mouse and rat kidney, OCTN2 protein has been localized to the brush-border membrane of renal proximal tubules [53]. OCTN2 is a Na^+/carnitine cotransporter with a high affinity for carnitine, but can function alternatively as a polyspecific and Na^+-independent organic cation uniporter (Fig. 3a, b). Human OCTN2 (hOCTN2) exhibits an apparent K_m for L-carnitine of ~5 μM [54, 57]. In the presence of Na^+, hOCTN2 transports short-chain acyl esters of carnitine, the zwitterionic β-lactam antibiotic cephaloridine, L-lysine and L-methionine (for references see [26, 57]). Independently from Na^+, hOCTN2 translocates the cations TEA, pyrilamine, verapamil and choline, and the weak base quinidine [36, 57]. The zwitterions and organic cations probably interact with the same, single substrate binding pocket of hOCT2 because carnitine uptake by hOCTN2 was competitively inhibited by TEA, and TEA uptake by hOCTN2 was competitively inhibited by carnitine [34, 46]. Mutations in TMDs 4 and 11 lead to inhibition of carnitine uptake by hOCTN2, but do not affect organic cation uptake (Fig. 2). Mouse OCTN2 can translocate organic cations in either direction. Furthermore, carnitine uptake is *trans*-stimulated by TEA, and TEA efflux is *trans*-stimulated by carnitine [35]. In mice with a defect mutation of OCTN2 (*jvs*-mice), the renal excretion of intravenously injected [^{14}C]TEA was reduced by 50% [35].

Physiological roles

hOCTN2 mediates the active step in reabsorption of L-carnitine in the proximal tubule (Fig. 3c) and transports L-carnitine into adipocytes and heart muscle cells. L-Carnitine is required for the transport of fatty acids into mitochondria by an L-carnitine-acyl cotransporter. In the

mitochondria fatty acids are degraded by β-oxidation. In addition to carnitine uptake, OCTN2 contributes to the secretion and reabsorption of organ cations in renal proximal tubules (see Fig. 3a, b).

Pathological implications

Homozygous nonsense or missense mutations in hOCTN2 cause a recessively inherited disorder called "primary systemic carnitine deficiency" [33]. The defect of carnitine reabsorption in kidney and carnitine uptake in cardiac muscle leads to the inhibition of β-oxidation of fatty acids. This results in hypoketotic hypoglycemia, hyperammonemia, cardiomyopathy, and progressive muscle weakness. Defect mutations in hOCTN2 may also lead to an impaired reabsorption and secretion of organic cations.

Therapeutic aspects

Patients with primary systemic carnitine deficiency are treated by oral supplementation of carnitine. In patients with partial defects of OCTN2, medication with cationic drugs interacting with OCTN2 should be avoided or supplemented with carnitine.

mOCTN3

This transporter was found only in mice [55] where it is expressed in testis and kidney. It translocates L-carnitine with an apparent K_m of 3 μM which is seven times lower than in mouse OCTN2. In contrast to OCTN subtype 2 from mouse and other species, mOCTN3 transports carnitine independently from Na^+. Given that carnitine uptake by OCTN3 was not inhibited by 0.5 mM choline, and inhibited only by 54% by 0.5 mM TEA, OCTN3 appears less relevant quantitatively for organic cation transport than OCTN1 and OCTN2.

hCT2

hCT2 is another high-affinity carnitine transporter that has been identified in humans [12]. Apart from several N-terminal amino acids, hCT2 is identical to a gene product named OCT6 found in hematopoietic cells [14]. hCT2 is mainly expressed in testes where it is localized to Sertoli cells and epithelial cells of the epididymal ducts [12]. hCT2 has a greater substrate selectivity than hOCT1–3 and hOCTN1–2 insofar as it interacts with carnitine and betaine, but not with TEA and several other organic anions. It translocates L-carnitine in either direction across the plasma membrane.

Physiological roles

hCT2 is essential for the secretion of L-carnitine into the lumen of epididymal duct which is required for the viability of spermatozoa.

Pathological implications and therapeutic aspects

Defect mutations in hCT2 may lead to male infertility that may be treated by supplementation with carnitine. Specific inhibitors of hCT2 might be able to be used as male contraceptives.

SLC22A6 (OAT1)

The first organic anion transporters of the SLC22 family, OAT1 from the kidneys of rat [45, 52] and flounder [60], were identified by expression cloning. Subsequent cloning efforts have identified the human ortholog hOAT1 [19, 39] with two splice variants, and orthologs from rabbit, pig, and mouse (for references see [4]). Northern blot analysis revealed that hOAT1 is strongly expressed in kidney, with the additional expression of differently sized transcripts in skeletal muscle, placenta, and brain (for references see [4]). By immunohistochemistry, OAT1 was localized to the basolateral membrane of the renal proximal tubule in rat and humans [19, 27]. OAT1 from different species displayed a remarkably wide substrate selectivity, covering endogenoussubstrates such as cyclic nucleotides, prostaglandins and uric acid as well as a variety of structurally different drugs such as antibiotics, nonsteroidal anti-inflammatory drugs, diuretics, antineoplastic drugs, and uricosuric drugs. The basic characterization of OAT1 transporters was performed with *p*-aminohippurate (PAH). PAH uptake was sodium-independent. The K_m of PAH uptake by hOAT1 measured in different laboratories varied largely; the mean value from eight investigations was 12 μM [4]. PAH uptake by rOAT1 and hOAT1 was increased by an outwardly directed concentration gradient of α-ketoglutarate or glutarate (for references see [4]). This is consistent with the idea that OAT1 is an organic anion/dicarboxylate exchanger and that the inside>outside concentration difference of α-ketoglutarate provides the driving force for the uptake of organic anions against the opposing force exerted by the inside-negative membrane potential [4]. Mutagenesis experiments suggested that arginine 478 in TMD11 of flounder OAT1 (equivalent to aspartate 475 in rOCT1, see Fig. 2) is part of the substrate binding site [59].

Physiological roles

hOAT1 mediates the first step in the renal excretion of many anionic drugs and endogenous anions operating in parallel with hOAT2 and hOAT3 that have largely

overlapping substrate specificities (Fig. 3d). Basolateral uptake of organic anions by hOAT1 may stimulate urate/anion antiport at the luminal membrane. Mediating the cellular release of organic anions over the basolateral membrane, hOAT1 also participates in the renal reabsorption of organic anions (Fig. 3d). In placenta hOAT1 is involved in the materno–fetal passage of anionic drugs.

Pathological implications

Defect mutations in hOAT1 should lead to reduced renal secretion of drugs that are transported by hOAT1 but not by OAT2 and/or OAT3.

Therapeutic aspects

The efficacy of anionic drugs can be improved and their materno–fetal passage reduced by co-medication of substrates and/or inhibitors of hOAT1, hOAT2 and/or hOAT3.

SLC22A7 (OAT2)

In 1994, a gene product (NLT) with sequence motifs of the major facilitator superfamily was cloned from rat liver but not characterized functionally [47]. In 1998 NLT was re-cloned, expressed in *Xenopus* oocytes, identified as a polyspecific organic anion transporter, and renamed rOAT2 [43]. The human ortholog hOAT2 [37] is expressed in liver and to a lesser extent in kidney [37]. In rat, OAT2 was localized to the apical surface of the medullary thick ascending limb of Henle's loop and the collecting duct [27], whereas human OAT2 was localized to the basolateral membrane of the proximal tubule [11]. When expressed in *Xenopus laevis* oocytes, rOAT2 mediated the uptake of PAH, dicarboxylates, PGE_2, salicylate, and acetylsalicylate [43].

Physiological roles

hOAT2 participates in the renal reabsorption of organic drugs. In liver it mediates the uptake of small anionic drugs into hepatocytes where they may be metabolized or excreted into the bile.

Pathological implications and therapeutic aspects

Defect mutations of hOAT2 may lead to reduced metabolism of anionic drugs in the liver. Hepatotoxicity of anionic drugs or xenobiotics may by be reduced by co-medication with substrates or inhibitors of hOAT2.

SLC22A8 (OAT3)

OAT3 has been cloned from rat, human, and mouse [2, 7, 29]. Northern blot analysis revealed strong expression of rOAT3 in the liver, weaker expression in brain and kidney, and some expression in the eye. At variance, human OAT3 (hOAT3) was strongly expressed in kidney as well as in brain and skeletal muscle, but not in liver. In mice, OAT3 was also detected in developing bone [2]. In kidney, rOAT3 and hOAT3 were located to the basolateral membrane of proximal tubules (Fig. 3d, e). In brain, rOAT3 was located to the luminal membrane of the choroid plexus (for references see [4]). Rat and human OATs exhibited similar functional characteristics. For example, both transporters mediated the uptake of PAH and estrone sulfate with similar affinity (K_m for PAH: 65 vs. 87 μM, K_m for estrone sulfate: 2.3 vs. 3.1 μM, respectively). They also transported the weak base cimetidine. Estrone sulfate uptake and efflux via rOAT3 and hOAT3 were not *trans*-stimulated by PAH or estrone sulfate [7, 29]. In contrast, uptake of PAH and estrone sulfate via rOAT3 could be *trans*-stimulated by glutarate [50]. Thus, basolateral anion uptake by OAT3 may be driven by outwardly directed gradients of dicarboxylates. Point mutations in rOAT3 showed that the 7th, 8th and 11th predicted TMDs are involved in substrate binding and/or translocation (Fig. 2).

Physiological roles

hOAT3 participates in renal excretion and reabsorption of anionic drugs (Fig. 3d). It may also be involved in the absorption of organic anions from the cerebrospinal fluid by the choriod plexus. Since failure to express OAT3 during development may cause osteosclerosis in mice, OAT3 may influence the calcification of bone by a mechanism that remains to be clarified [2].

Pathological implications

Uptake measurements with kidney slices and choroid plexus of OAT3 knockout-mice showed that the renal excretion of organic anions and their absorption in the choroid plexus are impaired when the expression or function of OAT3 is disturbed [51].

Therapeutic aspects

Renal excretion and nephrotoxicity of anionic drugs that are transported by hOAT3 may be decreased by co-medication of substrates and/or inhibitors of this transporter.

SLC22A11 (OAT4)

In 2000, human OAT4 (*SCL22A11*) was isolated and characterized functionally [8]. One year later, a different human gene product was cloned that was also named OAT4 [49]. We suggest calling this second gene product of unknown function hUST3 until a function has been established since an identical cDNA named UST3 exists (see Table 1). Northern blot analysis revealed that OAT4 (i.e., *SLC22A11*) is abundantly expressed in kidney and placenta. In kidney, hOAT4 protein was located to the apical side of proximal tubule cells [1]. OAT4 mediates Na^+-independent, high-affinity transport of estrone sulfate (K_m=1.0 μM), dehydroepiandrosterone sulfate, ochratoxin A, and prostaglandins E_2 and $F_{2\alpha}$ [8, 24]. Estrone sulfate transport via OAT4 is inhibited by sulfate conjugates (e.g., *p*-nitrophenyl sulfate, α-naphthylsulfate and 4-methylumbelliferyl sulfate), but not by the respective β-D-glucuronate conjugates.

Physiological roles

hOAT4 is thought to mediate the first step in the reabsorption of ultrafiltrated prostaglandins, anionic drugs and xenobiotics in renal proximal tubules (Fig. 3d). Since hOAT4 transports in both directions it may also be involved in anion secretion [8]. In the placenta, OAT4 is thought to be important for the excretion of toxic anionic substances from fetal into maternal circulation.

Pathological implications and therapeutic aspects

Defect mutations of hOAT4 may lead to renal loss of prostaglandins and fetal intoxication. This may be overcome by up-regulation of prostaglandins and/or hOAT4 expression.

OAT5

Recently, an additional anion transporter was isolated from a rat kidney cDNA library that encodes a protein with 551 amino acids and is named OAT5 (Endou and coworkers, unpublished data). This rat OAT5 has 55% amino acid identity to a human gene product named hOAT5 which has not been functionally characterized yet [49]. It seems to be, therefore, unlikely that hOAT5 is a human homolog of rat OAT5. Northern blot analysis demonstrated that rat OAT5 mRNA is exclusively expressed in the kidney, whereas hOAT5 is exclusively expressed in liver. When expressed in *Xenopus* oocytes, rOAT5 mediates the Na^+-independent transport of sulfo-conjugated steroids such as estrone sulfate (K_m=23.6 μM) and of ochratoxin A (K_m=0.3 μM). rOAT5 also interacts with nonsteroidal anti-inflammatory drugs, diuretics, sulfobromophthalein, penicillin G, and other sulfate conjugates such as 4-methylumbelliferyl sulfate and β-estradiol sulfate. By immunohistochemistry, OAT5 protein was found in the apical membrane of renal proximal tubules mainly at the cortico-medullary junction.

SLC22A12 (URAT1)

Urate is a naturally occurring product of purine metabolism. Its concentration in human blood is particularly high (200–500 μM) as compared to other mammals because the human kidney efficiently reabsorbs urate from the filtrate. The long-hypothesized urate transporter in human kidney turned out to be a member of the SLC22 family. It was identified by *in-silico* cloning and named URAT1 [10]. URAT1 was expressed exclusively in the kidney where it was located in the luminal membrane of proximal tubules. After expression in *Xenopus* oocytes, URAT1 showed Na^+-independent uptake of urate with an apparent K_m of 370 μM. Urate uptake via URAT1 was *trans*-stimulated by inorganic anions such as Cl^- and nitrate, and to a larger extent by the organic anions L-lactate, pyrazinecarboxylic acid, and nicotinate. Efflux of $^{36}Cl^-$ or [^{3}H]-nicotinate in oocytes expressing URAT1 was *trans*-stimulated by urate. This suggests that URAT1 functions as a urate/anion antiporter.

Physiological roles

URAT1 is involved in renal reabsorption of urate and helps to maintain blood levels of uric acid. It translocates urate over the luminal plasma membrane of proximal tubular cells in exchange for anions. At the basolateral membrane urate is released via the organic anion transporter OAT3.

Pathological implications

The pivotal role of URAT1 in renal reabsorption of urate was indicated by the finding that patients with idiopathic renal hypouricemia that exhibit increased renal urate excretion and decreased blood urate levels have defect mutations in the URAT1 gene [10]. This disorder is characterized by exercise-induced renal failure that is triggered by increased production of uric acid and reactive oxygen species during exercise. Tubular cell death may be caused by formation of uric acid crystals in combination with oxygen stress. Certain drugs that are used to treat inflammation may have "uricosuric" or "antiuricosuric" effects by inhibiting or stimulating URAT1. Antiuricosuric drugs increase the risk for gout.

Therapeutic aspects

Drugs that stimulate expression of transport activity of URAT1 may be employed for treatment of gout.

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