Chapter 1
Introduction to the Cellular Transport of Organic Cations

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Abstract Organic cations (OCs) are substances of endogenous and exogenous origin to which belong important neurotransmitters such as histamine and serotonin and also drugs such as metformin. Because OCs are positively charged they need membrane transporters to permeate the plasma membrane. Membrane transporters which translocate OCs according to their electrochemical gradient belong to the Solute Carrier (SLC) families 22 (organic cation transporters (OCT) 1–3, and organic cation transporters novel (OCTN) 1–2) and 47 (multidrug and toxin extrusion (MATE) 1–2). This chapter collects the information on expression and function of these transporters present in the literature, comparing the characteristics of human and rodent transporters. These data show that OCTs play an important physiological role for neurotransmitter balance in the body. Moreover, they are also important uptake routes for intracellular drug delivery and, considering their high expression in excretory organs, together with MATEs are responsible for drug excretion. For this reason, OCTs and MATEs can be important determinants of drug efficacies and also toxicities. OCTNs are transporters involved in the cellular uptake of substances, which are important in cell metabolism and in signal transmission, such as ergothioneine, carnitine and acetylcholine. Even though the expression and function of orthologs of transporters for OCs is generally similar, still there are important differences that have to be considered for a proper interpretation of translational studies. Paralogs of transporters for organic cations often display similar characteristics, however they show also important differences e.g. with regard to interaction with substrates and to regulation. Other important functional aspects of transporters for organic cations, such as the molecular correlates of polyspecificity, regulation, interaction with drugs, genetic variations, role in the central nervous system, and distribution in the plants are discussed in the other sections of this book.

Keywords Organic cations • Transporters • Neurotransmitters • Drugs • Plasma membrane

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G. Ciarimboli et al. (eds.), *Organic Cation Transporters*,
DOI 10.1007/978-3-319-23793-0_1

Introduction

The development of a plasma membrane was a fundamental step in the evolution of the cell, because it allowed the separation of an internal milieau from the external environment, which is of special importance to protect the genetic material. However, this important evolutionary progress created new challenges, because now the cell had to find solutions able to guarantee the entry of all essential nutrients into the cytoplasmatic compartment, the distribution of cellular products such as proteins, complex carbohydrates and lipids into and beyond the plasma membrane, and the handling of waste products and toxic substances, processes aimed at keeping the intracellular milieau constant [1]. The solution of these problems was the development of specialized transport systems of proteinic nature (transporters) embedded in the plasma membrane. Thus, it is evident that transporters are essential to sustain life and adaptation to changes in the environment. Their malfunction can result in diseases and, therefore, they are target of therapeutic intervention. Some transporters are also responsible for efficacy and also dangerous side-effects of chemotherapy [2, 3].

A total of 40,678 transport proteins classified into 134 families were predicted by whole-genome transporter analysis of 141 species, including 115 Eubacteria, 17 Archaea and 9 Eukaryota [4]. Eukaryotic cells, especially those of multicellular eukaryotic organisms, express the largest total number of transporters, which display a high number of paralogs generated by gene duplication or expansion within certain transporter families. The formation of paralogs is a sign of specialization, since closely related paralog transporters become expressed in specific tissues or at specific subcellular localisation and developmental time points [4].

Based on mode of transport and energy-coupling source, molecular phylogeny, and substrate specificity, there are five main recognised classes of transporters: pores and channels, electrochemical-potential-driven transporters, primary active transporters, group translocators, and transmembrane electron carriers ([1], http://www.tcdb.org). Each transporter category is further classified into individual families and subfamilies (Table 1.1).

This book focuses on transporters for organic cations, which are not directly ATP dependent and mediate the substrate movement through the plasma membrane according to the electrochemical gradient. According to the "*Transporter Classification Database*" (http://www.tcdb.org), these transporters belong to the family 2, subfamily 2.*A* (Table 1.1). Here a special attention will be payed at organic cation transporters (OCTs), novel organic cation transporters (OCTNs), and multidrug and toxin extrusion transporters (MATEs).

Basing on the amino acid sequences, the Human Genome Organisation (HUGO), classified human transporters in 54 **Sol**ute **C**arrier (SLC) families (a transporter has been assigned to a specific family if it has at least 20–25 % amino acid sequence identity to other members of that family [5]). These SLC families comprise 386 different SLC human transporters [6], additional new members being identified constantly [5].

Table 1.1 Transporter classification (classes and subclasses) according to the International Union of Biochemistry and Molecular Biology (http://www.tcdb.org)

1. Pores and channels	1.A α-Helical channels
	1.B β-Strand porins
	1.C Pore-forming toxins
	1.D Non-ribosomally synthesized channels
	1.E Holins
These proteins catalyze facilitated diffusion by passage through a transmembrane aqueous pore or channel. They do not exhibit stereospecificity but may be specific for a particular molecular species or class of molecules	
2. Electrochemical-potential-driven transporters	2.A Transporters or carriers (uniporters, symporters and antiporters)
	2.B Non-ribosomally synthesized transporters
These transporters utilize a carrier-mediated process not directly linked to a form of energy other than chemiosmotic energy to catalyze uniport (a single species is transported by facilitated diffusion), antiport (two or more species are transported in opposite directions) and/or symport (two or more species are transported together in the same direction)	
3. Primary active transporters	3.A P–P-bond-hydrolysis-driven transporters
	3.B Decarboxylation-driven transporters
	3.C Methyltransfer-driven transporters
	3.D Oxidoreduction-driven transporters
	3.E Light-driven transporters
These transporters use a primary source of energy (chemical, electrical and solar) to drive active transport of a solute against a concentration gradient	
4. Group translocators	4.A Phosphotransferases
Transport systems of the bacterial phosphoenolpyruvate: sugar phosphotransferase system. The product of the reaction, derived from extracellular sugar, is a cytoplasmic sugar-phosphate. The enzymatic constituents, catalyzing sugar phosphorylation, are superimposed on the transport process in a tightly coupled process	
5. Transmembrane electron carriers	5.A Two-Electron Carriers
	5.B One-Electron Carriers
Systems that catalyze electron flow across a biological membrane, from donors localized to one side of the membrane to acceptors localized on the other side. These systems contribute to or subtract from the membrane potential, depending on the direction of electron flow. They are therefore important to cellular energetics	

According to this classification, OCTs and OCTNs belong to the SLC22 and MATEs to the SLC47 family (Table 1.2). The HUGO nomenclature system is also informally used with lowercase letters for rodents and this notation has been also extended to the spelling of protein (e.g., *Slc22a1* and Oct1 denote the rodent orthologs of the human *SLC22A1* gene and hOCT1 protein, respectively).

Many of the SLC families present in *H. sapiens* (among these also the SLC22 family) are highly evolutionary conserved in Bilaterian species [7]; moreover, the high representation of the SLC22 family in the plant *Arabidopsis thaliana*, suggests that it has an ancient origin [7]. More information about transporters for organic cations in plants will be presented in the Chap. 10 by T. Eggen and C. Lillo in this book.

Table 1.2 The SLC22A and SLC47A families

Gene name	Gene locus	Protein name	Function
SLC22A1	**6q25.3**	**hOCT1**	Electrogenic cation transport
SLC22A2	**6q25.3**	**hOCT2**	
SLC22A3	**6q25.3**	**hOCT3**	
SLC22A4	**5q23.3**	**hOCTN1**	Carnitine and cation transport
SLC22A5	**5q23.3**	**hOCTN2/CT1**	
SLC22A16	**6q21**	**hCT2/hFLIPT2/hOCT6**	
SLC22A6	11q12.3	hOAT1	Anion transport
SLC22A7	6q21.1	hOAT2	
SLC22A8	11q12.3	hOAT3	
SLC22A9	11q12.3	hOAT7	
SLC22A11	11q13.1	hOAT4	
SLC22A12	11q13.1	hURAT1	
SLC22A13	3p22.2	hOAT10	
SLC22A20	11q13.1	hOAT6	
SLC22A10	11q12.3	hOAT5	Predominant substrates not yet determined
SLC22A14	3p22.2	OCTL2/hORCTL4	
SLC22A15	1p13.1	FLIPT1	
SLC22A17	14q11.2	BOIT/BOCT	
SLC22A18	11p15.5	TSSC5/hORCTL2	
SLC22A23	6p25.2		
SLC22A24	11q12.3		
SLC22A25	11q12.3	UST6	
SLC22A31	16q24.3		
SLC47A1	**17p11.2**	**hMATE1**	H^+-coupled electroneutral exchange of organic cations
SLC47A2	**17p11.2**	***hMATE2***	

The transporters presented in this book are in bold characters

Substrates of Transporters for Organic Cations

The substrates of the three types of transporters for organic cations discussed in this book (OCTs, OCTNs, MATEs) are mainly organic cations, even though also inorganic substances such as Cd^{2+} [8] and cisplatin [9, 10] have been demonstrated to be accepted as substrate by some of these transporters. Moreover, some of these proteins can transport also zwitterions such as L-carnitine [11, 12] (OCTNs) and cephalexin and cephradine [13] (human MATE1, hMATE1) and anionic substances such as estrone sulphate (hMATE1, [13]), acyclovir, and ganciclovir (hOCT1 and hMATE, [13, 14]).

Organic cations (OCs) can derive from endogenous and also exogenous sources. Endogenous OCs are important neurotransmitters such as histamine, serotonin and dopamine [15] and polyamines such as putrescine and spermidine [16], which have an important function in many cellular processes such as DNA stabilization,

regulation of ion channel activity, gene expression, and cell proliferation [17]. In general, neurotransmitters and polyamines seem to be low affinity substrates of transporters for OCs, underlying the importance of these transport systems in places, where the concentration of such substances is high. Exogenous OCs are drugs (up to 40 % of the prescribed drugs are OCs [18]), xenobiotics such as the herbicide paraquat and the DNA intercalating agent ethidium bromide [19, 20], and also several natural contents of fungi, fruits and vegetables. Of practical experimental interest are fluorescent OCs such as 4(4-dimethylaminostyryl)-*N*-methylpyridinium (ASP^+), and rhodamine 123, which are substrates for several transporters for OCs and are therefore useful for investigating transporter activity [21–24].

OCs are also classified as type I and type II OCs depending on their chemical structure. Type I OCs are small (below 500 Da), strongly hydrophilic cations, such as tetraethylammonium (TEA^+) and 1-methyl-4-phenylpyridinium (MPP^+), while Type II OCs are large, more hydrophobic and mostly polyvalent substances, such as D-tubocurarine and quinine [25].

Even though many substrates are common between OCTs, OCTNs, and MATEs, every single transporter has a specific interaction spectrum with the substrates and inhibitors. For example, TEA^+ is a substrate for OCT1 and OCT2 [26], but not for OCT3 [15]. Some substances are known to bind to, but not to be transported by these transporters, as for example shown for proton pump inhibitors [27].

From this brief description it is evident why these transporters are called polyspecific. The translational relevance of studies on OCs with laboratory animals should be cautionally inferred, since rodent and human transporter orthologs can differ in substrate specificity, tissue expression [28] and also regulation (see Chap. 5 by E. Schlatter of this book), even though the global substrate preference of the SLC22 family seems to be conserved over a long evolutionary time [7].

Integration of OC Transport

Since many transporters for OCs are expressed in liver and kidney, they play a pivotal role in drug and xenobiotic absorption and excretion [29]. In these organs, SLC22A and SLC47 transporters are expressed in hepatocytes and renal proximal tubules cells, which are highly polarized cells, and mediate the coordinated movement of OCs across the cell by a concerted activity, mainly resulting in excretion of OCs into bile or urine. The first step for hepatic and renal OC secretion is their absorption from the basolateral side into the cells. While in human kidney this process is mainly mediated by OCT2 (Fig. 1.1), in rodent kidney it is supported by Oct1 and Oct2. OCT3 shows only a tiny expression in the basolateral membrane of proximal tubule cells, and for this reason is probably less important than OCT2 under normal conditions. OCs are secreted in a second step from the tubular cell into the tubular lumen. In the kidney this process is mediated by different transporters: the Na^+-carnitine cotransporter OCTN2, and *P*-glycoprotein (also named MDR1), an ATP-dependent transporter that probably mediates the efflux of bulky

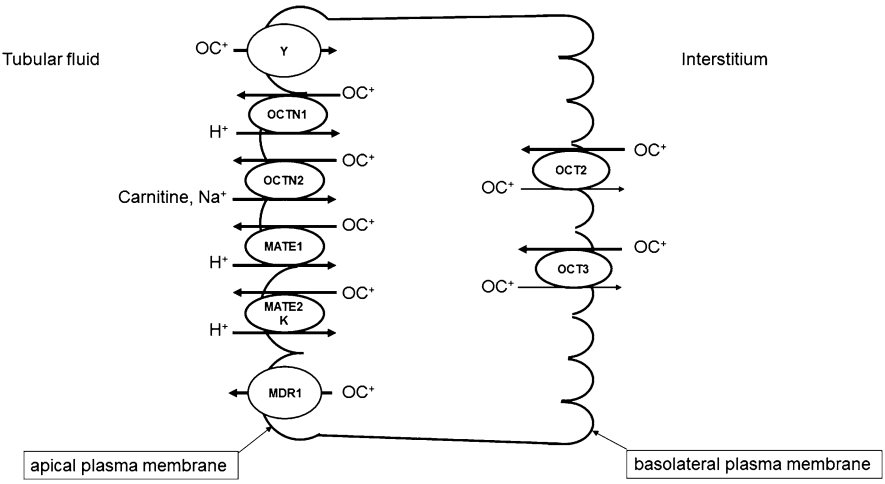

Fig. 1.1 Transport systems for organic cations in human renal proximal tubules. The basolateral uptake of organic cations (OCs) from interstitium is mainly mediated by hOCT2, where there is also a much lower expression of hOCT3. Secretion of OCs into the tubular fluid is mediated by MATE1, MATE2K, and OCTN1 in exchange with H^+. The necessary H^+ gradient is substained by the activity of NH3, an apically expressed Na^+/H^+ exchanger (not shown). Bulky OCs are secreted into the urine under energy consumption by the Multidrug Resistance protein 1 (MDR1). OCs can be also reabsorbed from the tubular fluid by an not yet identified transport system (Y), and then transported into the interstitium by OCT. Modified from Koepsell et al. [30] and Ciarimboli and Schlatter [31]

hydrophobic OCs, and other H^+/organic cation antiporters (OCTN1, MATE1, and MATE2K in Fig. 1.1). According to their electrochemical gradient, in the kidney OCs can be also reabsorbed from the lumen into the interstitium. For this process, a polyspecific cation transport system mediating their uptake across the luminal membrane of proximal tubular cells has been proposed, but not yet molecularly identified (system Y in Fig. 1.1). The efflux across the basolateral membrane into the interstitium may be mediated by OCTs. The hepatic transport pathways of OCs in humans are illustrated in Fig. 1.2. The uptake of OCs into human hepatocytes is mediated by OCT1 present on the sinusoidal membrane. The extrusion of OCs in the canalicular space is mediated by *P*-glycoprotein (MDR1 in Fig. 1.2) and MATE1.

Genetic Organisation of Transporters for Organic Cations

Some of the *SLC22A* genes (e.g. the genes for OCT1 and 2, OCTN1 and 2, and also OAT1 and 3) are organized in the mouse and in humans as tightly linked pairs [32]. The gene coding for OCT3 is also in close proximity of the *SLC22A1-2* pair, and also *SLC47A1* and *SLC47A2* are adjacent. The gene pairing probably originates

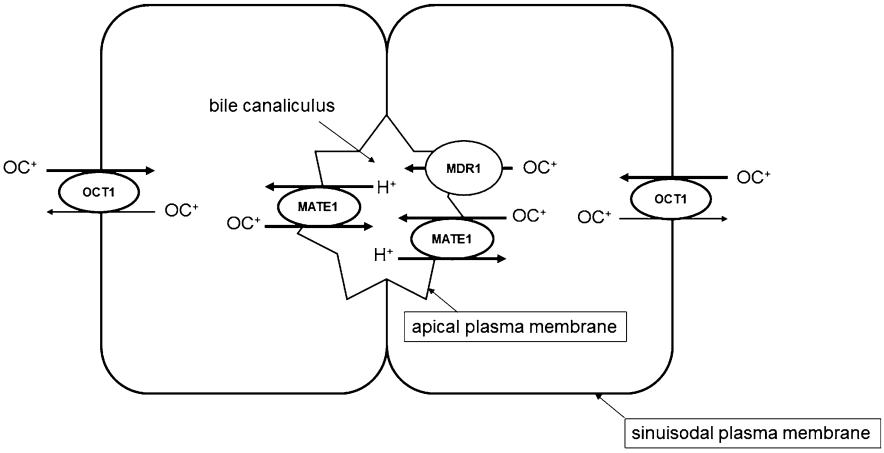

Fig. 1.2 Transport systems for organic cations in human hepatocytes. OCs are transported through the sinusoidal membrane (corresponding to the basolateral side) of hepatocytes by hOCT1. Secretion of OCs into the bile canaliculus is mediated by MATE1 expressed in the apical membrane in exchange with H^+. Bulky OCs are secreted into the bile under energy consumption by MDR1. Modified from Koepsell et al. [30] and Ciarimboli and Schlatter [31]

from an evolutionary duplication event, aimed at conferring the advantages of redundancy or broader substrate specificity [33].

The genes encoding for Oct1-3 are clustered within a 300-kb genomic region between the insulin-like growth factor receptor 2 (*Igf2r*) and the *Plg* (plasminogen) genes on mouse chromosome 17 and on rat chromosome 1. Also in humans, the genes encoding for OCT1-3 are clustered in a region between the *IGF2R* and the *APO*(*a*)*-like* genes on chromosome 6 [34].

Interestingly, expression of *Slc22a2* and *Slc22a3* in mouse placenta is predominantly maternally imprinted, at least till embryonic day 15.5 for *Slc22a3* [35]. Imprinting is an epigenetic modification, which leads to preferential expression of a determined parental allele in somatic cells of the progeny. After evolutionary divergence, imprinting of only 29 transcripts has been conserved in mice and humans [36]. Imprinted genes often have key roles in embryonic development, but also in postnatal functions including energy homeostasis and behaviour [37]. In humans, imprinting of the *SLC22A2* and *SLC22A3* genes in the placenta is not a general phenomenon, but is present only in few subjects with a temporal expression pattern resembling that of the murine genes [38].

Topology of Transporters for Organic Cations

The transporters of the SLC22 family have a similar predicted membrane topology consisting of 12 alpha-helical transmembrane domains (TMDs), a large glycosylated extracellular loop between the first and the second TMD, and a large intracellular

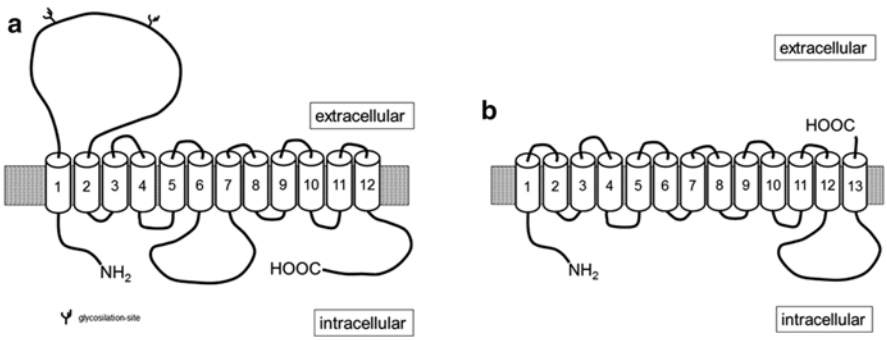

Fig. 1.3 Panel (**a**) shows the proposed secondary structure of OCTs and OCTNs. These transporters have 12 TMD, a big extracellular and a big intracellular loop with type and subtype specific glycosylation and phosphorylation sites, respectively. Amino- and carboxy-termini are intracellular. Panel (**b**) shows the proposed secondary structure of MATEs. These transporters have 13 TMD, an intracellular and an extracellular terminus. Modified from Ciarimboli and Schlatter [31]

loop between TMDs 6 and 7 with consensus sequences for phosphorylation (Fig. 1.3a). Both the amino- and carboxy-termini are intracellularly localized.

The topology of SLC47 transporters seems to be somewhat different, as these transporters possess 13 TMDs, an intracellular amino- and an extracellular carboxy-terminus, no glycosylation sites and few intracellularly located putative phosphorylation sites (Fig. 1.3b) [39, 40]. However, there are data demonstrating that the functional core of MATE1 consists of 12 TMDs [41].

In the following the basic information on OCT, OCTN, and MATE present in the literature will be summarized, focussing on human and rodent transporters, which will be separately described, because of the known differences between species.

Organic Cation Transporters (OCTs)

Transport of organic cations by the three OCT subtypes (OCT1, OCT2, and OCT3) is electrogenic, Na^+- and H^+-independent and bidirectional [29]. The driving force is supplied exclusively by the electrochemical gradient of the substrate. The first member of the SLC22 transporter family was isolated and identified by expression cloning from rat kidney and was named rat organic cation transporter 1 (rOct1) [42]. In this initial study, it was shown that rOct1 has functional characteristics resembling those of the organic cation transport processes previously described in the basolateral membrane of renal proximal tubule cells and of hepatocytes. Mammalian orthologs of *OCT1* have been cloned also from human [43, 44], rabbit [45], and mouse [46].

Mouse Organic Cation Transporter 1 (mOct1)

The gene *Slc22a1* encodes for a 556 amino acids (aa) protein, which is mainly expressed in the liver and the kidneys [46, 47]. Upstream sequences for *mOct1* contain putative binding motifs for hepatocyte (HNF5 and H-APF-1), and mammary (WAP and MGF) specific expression, and potential binding sites for metallothioneine-regulated gene expression (MBF-1, GR-MT-IIA, and AP-2) [48]. *Slc22a1* transcripts have been shown to turn up in the mouse kidney at midgestation, at the time when the proximal tubules begin to differentiate, and to increase gradually in the course of nephron maturation. *Slc22a1* transcripts are also transiently expressed in other tissues than the kidneys such as the ascending aorta and the atrium [49]. In the liver, ontogenic expression data showed that *Oct1-3* approach adult expression levels at an age of about 3 weeks [50]. The highest hepatic Oct1 mRNA labelling intensity was detected in the hepatocytes which are localized in the proximity of the vena centralis, while in the kidney Oct1 mRNA appeared to be unevenly distributed throughout the renal cortex but not in glomeruli [51]. The mOct1 has been found to be higher expressed than mOct2 and mOct3 in the S1, S2, and S3 segments of the proximal tubules (relative mRNA expression of Oct1/Oct2/Oct3: 1/0.3/0.01) [52]. Expression and function of mOct1 has been detected also in other organs: in the luminal blood-retina barrier [53] Oct1 and Oct2 have been found to be expressed in an age-dependent manner (with decreased expression in aged mice [54]) in endothelial cells of mouse brain microvessels (BMVs). Elevated Oct1 mRNA levels were measured in mammary glands of lactating mice, suggesting that this transporter may be involved in the transfer of drugs into milk [55].

Generally, when expressed in polarized cells, such as hepatocytes and proximal tubule cells, mOct1 localizes to the basolateral plasma membrane [56]. However, in enterocytes this transporter has been shown to be expressed on the apical plasma membrane [57].

The transport mediated by mOct1 has been demonstrated to be pH- and Na^+-independent and potential dependent [58]. In mice, Oct1 and Oct2 have been identified also in the respiratory epithelium, where they seem to be involved in the acetylcholine (ACh) release [59]. Interestingly, Oct1 and Oct3 have been also found to be expressed in mouse urothelium, where they may mediate ACh secretion [60]. Transport studies showed that the mOct1 mediates the uptake of choline with a K_m of 42 μM [61] and the low-affinity transport of serotonin [51]. Moreover, mOct1 accepts also exogenous OCs such as [^{14}C]-TEA^+ and MPP^+ as substrates (K_m = 38 μM [47] and 10 μM [62], respectively).

To better understand the physiological role of Oct1, Oct1 knockout (*Slc22a1*$^{-/-}$) mice were generated [63]. These mice were viable, healthy, and fertile and did not appear to have obvious phenotypic abnormalities; they only showed a decreased hepatic accumulation and intestinal excretion of exogenously administered TEA^+ [63]. Further studies with *Slc22a1*$^{-/-}$ mice showed that Oct1 is important for the hepatic and intestinal uptake of metformin, a hypoglycemic agent used for the oral treatment of type 2 diabetes mellitus, whereas its renal distribution and excretion are

mainly governed by other transport mechanisms [64, 65]. Since a high-fat diet for 19 weeks up-regulated the Oct1 expression in the mouse liver and this increased transporter expression was associated with a higher hepatic metformin uptake, it has been suggested that obesity might have an effect on the absorption or distribution pharmacokinetics of metformin through an up-regulation of hepatic Oct1 expression [66]. Also mice fed with a lithogenic diet, which increases the biliary cholesterol and phospholipid secretion and the probability of gallstone formation, showed an up-regulation of hepatic Oct1 mRNA levels during lithogenic bile formation, probably resulting in an increased uptake of choline, necessary to substain phospholipid synthesis under conditions of biliary phospholipid hypersecretion [67]. The hepatic expression of mOct1 is transcriptionally increased by peroxisome proliferator agonist receptor (PPAR)-α and -γ agonists, which are commonly used agents able to regulate several hepatocellular transport functions [68]. Oct1 is not expressed in the mouse brain [51].

Rat Organic Cation Transporter 1 (rOct1)

The rOct1 is a 556 aa membrane protein [42] mapped to chromosome 1q11-12 [69], which has been identified by Northern blot analysis in rat kidney, small intestine, colon and liver [42]. In the kidney, rOct1 protein expression has been localized at the basolateral membrane of S1 and S2 segments of proximal tubule cells [70, 71]. rOct1 mRNA was detected primarily in the superficial and juxtamedullary proximal convoluted tubules [72]. Renal rOct1 mRNA levels are gradually up-regulated from day 0 through day 45 [73]. In the liver, rOct1 has been localized in the sinusoidal membranes of hepatocytes. Translational regulation is suggested since even though the mRNA of rOct1 is distributed throughout the liver lobules, the rOct1 protein is expressed only in hepatocytes surrounding the central veins [74]. rOct1 has been also identified in the airway epithelia in the luminal membrane of ciliated epithelial cells [75].

The transport mediated by rOct1 has been characterized as electrogenic, Na^+- and pH-independent and bidirectional [76]. rOct1 can translocate organic cations like TEA^+ (K_m = 38 μM) [77] and choline [78], catecolamines and other biogenic amines [79], nucleosides like 2′-deoxytubercidin [80], while cations like tetrapentylammonium (TPA^+) and cyanine 863 are nontransported inhibitors of the transporter [78, 81]. Superfusion of rOct1-expressing *Xenopus* oocytes with dopamine, serotonin, noradrenaline, histamine and acetylcholine induced saturable inwardly directed currents with K_m values ranging from 20 to 100 μM [82]. Transport of dopamine was also demonstrated by uptake measurements in oocytes and in renal mammalian cells (**h**uman **e**mbryonic **k**idney cells, HEK293 cells) transfected with rOct1. The high uptake rates measured in rOct1-expressing oocytes and in transfected HEK293 cells suggested that rOct1 is a high capacity transporter, which in vivo mediates the first step in the excretion of monoamine neurotransmitters [82].

The cysteins of the large extracellular loop of rOct1 have been suggested to be involved in the formation of oligomers, which influence the insertion of the transporter in the plasma membrane, but not its affinity for the substrates [83].

An alternatively spliced variant of rOct1 (rOct1A), which lacks the first two TMDs has been cloned from rat kidney. This variant is also present in the intestine and liver [84] and encodes a 430 aa protein that is 92 % identical to rOct1. rOct1A exhibited similar functional characteristics to those of rOct1, implying that the first two transmembrane domains and the three potential glycosylation sites normally present in this protein domain are not essential for transport function, even though other characteristics such as synthesis, targeting, and sorting of the transporter have been supposed to be different between the two isoforms [84].

Rabbit Organic Cation Transporter 1 (rbOct1)

A cDNA encoding a 554 aa protein highly homologous to other mammalian OCTs has been isolated from rabbit kidney (rbOct1) [45]. rbOct1 mediated a [^{3}H]MPP$^+$ transport, which was saturable, sensitive to membrane potential, and inhibited by various OCs. rbOct1 mRNA transcripts were found to be expressed in the kidney, liver, and intestine.

Human Organic Cation Transporter 1 (hOCT1)

The *hOCT1* encodes a 553 aa protein with 80 % identity to rOct1. Northern blot analysis showed that *hOCT1* is mainly transcribed in the liver [43], differently to what was observed for *rOct1*, that is mainly transcribed in kidney, liver and small intestine [42]. *hOCT1* has been localized on chromosome 6q26 [85].

Functionally, hOCT1 together with hOCT3 have been also identified in the placenta [86], where they possibly mediate the release of non-neuronal ACh.

The presence of hOCT1 has been also demonstrated in bronchial tissue by immunofluorescence, where a luminal and also an intracellular staining of ciliated epithelial cells was observed [75].

hOCT1 expressed in oocytes of *Xenopus laevis* could translocate ACh in either direction. An almost complete inhibition of hOCT1-mediated TEA$^+$ uptake was produced by the inhalational glucocorticoids beclomethasone and budesonide, suggesting that hOCT1 mediates a budesonide-inhibitable luminal ACh release in the respiratory epithelium [75].

Since hOCT1 is expressed in both subcutaneous and visceral adipose tissue, and its expression is significantly increased in obese subjects [87], it has been speculated that this is the reason for the increased metformin action in obese subjects [87].

The binding site of hOCT1 has been demonstrated to interact preferentially with elongated cationic molecules, which are able to interact with a “supraplanar

stabilizing structure" within a hydrophobic pocket of the transporter [88]. A balance between hydrophobic and hydrophilic properties was supposed to be necessary for binding and subsequent translocation by hOCT1 [89]. A comparative analysis of substrates of hOCT1 and hOCT2 showed that molecular volume was inversely correlated to transport by hOCT1, whereas H-bonding parameters like polar surface area dominated for hOCT2 mediated transport [90].

When expressed in polarized cells, hOCT1 was generally localized on the basolateral plasma membrane, except in airways and in the kidneys, where it seemed to be expressed on the apical cell membrane [75, 91]. These findings imply that the information for the insertion of the transporter in the suitable plasma membrane domain is not directly contained in the transporter aa sequence.

Both hOCT1 and mOct1 have been proposed to be high-capacity thiamine transporters, and for this reason, they are probably associated with its hepatic dietary uptake [92]. hOCT1 accepts TEA^+ as a substrate: other OCs, including clonidine, quinine, quinidine and verapamil, but also the neutral compounds corticosterone and midazolam significantly inhibited [^{14}C]-TEA^+ uptake by hOCT1 [93]. The K_i values of several compounds for interaction with hOCT1 are different from the K_i values determined in previous studies for rOct1 and hOCT2 [93]. hOCT1 has been shown to mediate a specific and membrane potential sensitive uptake of MPP^+, which showed remarkable differences in the interaction with some organic cations when compared to rOct1 [42, 43].

In the human glioma cell line SK-MG-1, four *hOCT1* isoforms were identified [94]. Two of these isoforms were also found in human liver cDNA. Several reports are dedicated to the study of drug interactions and how transporter mutations influence hOCT-drug interactions. These topics will be examined in the Chap. 4 by M. Tzvetkov, N. Dalila and F. Faltraco of this book. Here, it should be underlined that many drugs can interact with hOCT without being substrate of the transporters, as for example demonstrated for proton pump inhibitors, which potently inhibit hOCT but are not translocated into the cell [27]. Both the interaction as substrate and as inhibitor are of great pharmacological importance, in the first case determining drug tissue distribution and excretion and in the second case causing important drug–drug interaction effects.

The expression of hOCT1 in the sinusoidal membrane of hepatocytes is linked to drug hepatotoxicity, as shown for example for the quaternary alkaloid nitidine chloride [95] and the pyrrolizidine alkaloid retrorsine [96].

Mouse Organic Cation Transporter 2 (mOct2)

The mOct2 exhibits about 93 and 84 % amino acid identity with rat Oct2 and hOCT2, respectively, and only about 70 % amino acid identity with the mouse and rat Oct1 [48].

The promoter region of *mOct2* contains a TATA and a CCAAT box, and several binding sites for transcription factors (three E-box motifs, putative responsive

elements for interleukin 6 (IL-6), and tumour necrosis factor (TNF), and a putative histone H1 specific element HI-S) [48]. mOct2 is mainly expressed in the kidney, in the brain, ureter and in the developing embryo. In the central nervous system, mOct2 is expressed in the limbic system, where it plays a role in the control of the concentration of noradrenalin (NA) and serotonin (5-HT) [97]. For this reason, mOct2 may be implicated in anxiety and depression-related mouse behaviors. Indeed, genetic deletion of *mOct2* in mice produced a significant reduction in brain concentrations of NA and 5-HT [97]. Expression of mOct2 has been demonstrated in the cochlea in hair cells of the Corti organ and also in cells of the stria vascularis, where it is involved in the development of acute ototoxicity induced by cisplatin [98]. In the peripheral nervous system, mOct2 is expressed in dorsal root ganglia, where it plays a prominent role for the development of oxaliplatin-induced peripheral neurotoxicity [99]. Together with mOct1, mOct2 is expressed in respiratory epithelium, where they mediate ACh release [59]. mOct2 is highly expressed in alveolar cells, where it seems to catalyze the transport of choline [100]. Interestingly, since adenoviruses increased both choline release from biomembranes and steady-state mOct2 mRNA and protein expression, it has been speculated that adenoviruses might transcriptionally activate the *mOct2* promoter or directly interact with regulatory domains in the primary structure of the transporter [100].

The transport properties of mOct2 are in general similar to those of mOct1, even though several organic cations had weaker inhibitory effects on MPP^+ uptake by mOct2 than by mOct1 [62].

mOct2 mediates the renal secretion of creatinine [101] and is involved in the renal uptake, secretion and toxicity of metals and metal containing compound such as Cd^{2+} [102] and cisplatin [98].

Rat Organic Cation Transporter 2 (rOct2)

rOct2 encodes a 593 aa protein with a calculated molecular mass of 66 kDa [103]. The rat *Oct2* cDNA (2205 bp) shows 67 % identity with the rat *Oct1*. Renal expression of rOct2 is evident in the basolateral cell membrane of S2 and S3 segments of the proximal tubule [71, 104, 105]. rOct2 mRNA has been found to be expressed in rat choroid plexus [106] and, together with rOct1 and rOct3, it was also identified in the luminal membrane of ciliated epithelial cells of respiratory tract, where, together with rOct1, it serves as an ACh transporter [75]. OCT-type transporters are probably responsible for non-neuronal ACh release [86]. A recent work demonstrates that rOct2 is expressed in cholinergic neurons, anterior horn motoneurons of the spinal cord, and in the neuromuscular junctions and plays a role in ACh recycling in presynaptic terminals, possibly acting as a low-affinity and high-capacity choline transporter at presynaptic terminals in cholinergic neurons [107].

rOct2 has been demonstrated to function also as a histamine transporter and thus to participate in histamine metabolism [108]. rOct2 transports dopamine, NA, adrenaline, 5-HT [104] and choline [106]. The IC_{50} values of many inhibitors were

similar for both rOct1 and rOct2, whereas those of others (mepiperphenidol, *O*-methylisoprenaline, and corticosterone) were significantly different [81]. The substrate binding site of rOct2 is like a pocket containing overlapping binding domains for ligands, which may undergo separate structural changes, and which can change its affinity depending on membrane potential [109]. Also rOct2 has been demonstrated to mediate the cellular uptake and hence the nephrotoxicity of cisplatin [110].

Rabbit Organic Cation Transporter 2 (rbOct2)

The rabbit ortholog of OCT2 (rbOct2) cloned from rabbit kidney is 71 % identical to its paralog rbOct1 [111]. The structure of rbOct2 postulated by computer analysis revealed 2 large hydrophilic loops and 12 transmembrane-spanning α-helices similar to what was described for rbOct1 and all other members of the OCT family [112]. Moreover, five potential N-linked glycosylation sites and three potential PKC phosphorylation sites in the two large hydrophilic loops were also identified [111]. Asparagines 71, 96, and 112 in rbOct2 are glycosylated to target the transporter to the cell membrane [113]. Even though the functional characteristics of rbOct1 and rbOct2 are similar, they interact with different potency with specific substrates, such as cimetidine and 2-(4-nitro-2,1,3-benzoxadiazol-7-yl)aminoethyl trimethylammonium (NBD-TMA), rbOct2 showing a greater apparent affinity than rbOct1 [111]. The Glu447 residue in rbOct2 exerted a marked influence on substrate selectivity, being probably located in a putative docking region within a hydrophilic cleft of the protein [111]. In the rabbit kidneys, rbOct1 was found to be expressed mainly in the S1 segment of proximal tubules, while rbOct2 is the main Oct in S2- and S3-segments [114, 115]. Both rbOct1 and rbOct2 have been demonstrated to be involved in the development of Cd^{2+}-induced nephrotoxicity [116].

Human Organic Cation Transporter 2 (hOCT2)

The *hOCT2* encodes a 555 aa protein with 81 % identity to rOct2 and 68 % identity to rOct1. hOCT2 could be detected in kidneys, spleen, placenta, small intestine and brain [43], and human bronchi, mostly in the apical membrane of ciliated cells, where, together with hOCT1 mediates cellular release of ACh [75]. In the kidneys, hOCT2 is expressed in the basolateral membrane of proximal tubule cells [117]. A splice variant of *hOCT2*, *hOCT2-A*, mainly expressed in the kidneys and weakly in brain, liver, colon, skeletal muscle, bone marrow, spinal cord, testis, and placenta, has been also identified. *hOCT2-A* codes for a 483-amino acid protein, which is predicted to have nine transmembrane domains and, when expressed in HEK293 cells, was able to interact with organic cations, even though with different substrate affinities compared with hOCT2 [118].

The *hOCT2* promoter region contains a combination of TATA box and Inr element, probably important as transcription start point and many other possible regulatory sites for specific factors, such as E boxes, GATA, IK2, and HFH-8, a member of the forkhead/winged helix class of regulators involved in specific tissue expression of proteins [119].

hOCT2 is a low affinity transporter of the monoamine neurotransmitters dopamine, NA, 5-HT, and histamine [120]. Since hOCT2 has a broad expression in the human brain, it might co-operate with high affinity uptake mechanisms [120] to control the local concentration and action of aminergic neurotransmitters. Cerebral hOCT2 and also hOCT3 have been proposed as a complementary target of antidepressant action [15, 121, 122]. hOCT2 together with hMATE1 transports asymmetric dimethylarginine (ADMA) and also L-arginine (hOCT2 has a much lower affinity for L-arginine than for ADMA, see Table 1.3) and are consequently involved in the renal elimination of these substances [143]. ADMA is an endogenous substance, which interferes with the synthesis of nitric oxide from L-arginine and with endothelium-relaxation and for this reason is a cardiovascular risk factor [143]. In an attempt to identify endogenous substrates of hOCT2, metabolites differentially present in urine samples collected from individuals carriers of wild type and mutated *SLC22A2* (*SLC22A2* wild type, *808GT* heterozygous, and *808TT* homozygous) were analyzed by gas chromatography–mass spectrometry. Tryptophan was the most significantly decreased compound associated with the *808GT* and *808TT* variants, compared with the levels in the individuals bearing the wild type *SLC22A2* [147].

Interestingly, hOCT2 has been demonstrated to transport metals and metal compounds such as Cd^{2+} [8], cisplatin [9] and oxaliplatin [99]. These substances are well-known to be nephrotoxic and their hOCT2-mediated uptake seems to be critical for their toxic effects.

The binding of the substrates to hOCT2 was demonstrated to be dependent on their ionization degree [151] and also on their hydrophobicity, molecular size, shape, and flexibility, as determined using quantitative structure activity relationship (QSAR) computational models [192]. The hydrophilic cleft, where the transporter interacts with its substrates, is supposed to be formed by several transmembrane helices, which contain cysteines at aa position 437, 451, 470, and 474, with cysteine 474 exposed to the aqueous milieu of the cleft [193] and being part of an interaction domain [194]. As already demonstrated for rOct1 [195], also the binding region of hOCT2 is characterized by multiple, possibly overlapping interaction sites [196]. The molecular basis of polyspecificity will be discussed in the Chap. 2 by T. Keller and H. Koepsell of this book. The six cysteines of the hOCT2 extracellular loop have been demonstrated to be important for transporter oligomerization and its correct trafficking to the plasma membrane [197]. hOCT2 is not only able to interact with itself to form oligomers [197], but it has also other proteinic interaction partners such as the lysosomal-associated protein transmembrane 4 α (LAPTM4A), which regulates the function of hOCT2 by influencing its trafficking to/from the cell membrane and processing it via the intracellular sorting machinery [198].

Table 1.3 Summary of proteins size (in amino acids = aa), tissue distribution, and of the known endogenous and exogenous substrates with K_m, K_i, and IC_{50} values, when available from the literature, of human cloned OCTs, OCTNs, and MATEs

Transporter	Protein size (aa)	Tissue distribution	Endogenous substrates	Exogenous substrates
hOCT1 (SLC22A1)	553 [43]	Liver [43, 44], jejunum [123] (lateral membrane of enterocytes), luminal membrane of bronchial tissue epithelial cells [75], adipose tissue [87], peripheral blood mononuclear cells and $CD4^+$ T-cells [124]	Acetylcholine (IC_{50} for MPP^+ 580 μM) [75]	Acyclovir (K_m 151 μM) [14]; amiloride [90]; agmatine (K_m 18.7 mM) [125]; ASP^+ [23]; amisulpride (K_m 31.3 μM) [126]; ethidium bromide (K_m 0.8 μM) [20]; DAPI (K_m 8.9 μM) [127]; fenoterol [90]; furamidine (K_m 6.1 μM) [128]; ganciclovir (K_m 516 μM) [14]; glycopyrrolate [90]; HPP^+ (K_m 0.99 μM) [129]; imatinib [130, 131]; ipratropium [90]; irinotecan (IC_{50} for MPP^+ uptake 1.7 μM) [132]; lamivudine (K_m 1.25 mM) [133];metformin (IC_{50} for cimetidine uptake 2010 μM) [134]; monocrotaline (K_m 25 μM) [135]; morphine (K_m 3.4 μM) [136]; MPP^+ (K_m 14.6 μM) [44]; nitidine [95]; oxybutynin (K_m 8 μM) [137]; oxyphenomium [90]; paclitaxel (IC_{50} for MPP^+ uptake 50 μM) [132]; pentamidine (K_m 36.4 μM) [128]; phenformin (IC_{50} for cimetidine uptake 10 μM) [134]; phTCU compounds [90]; procaterol [90]; quercetin [138]; ranitidine (K_m 70 μM) [139]; retrorsine (IC_{50} for MPP^+ uptake 2.3 μM [96]); $RHPP^+$ (K_m 5.2 μM) [129]; rilpivirine (IC_{50} for TEA^+ uptake 28.5 μM) [140]; rhodamine 123 (K_m 0.54 μM) [24]; spermidine ($K_m \approx 1$ mM) [16]; sulpride (K_m 260 μM) [126]; sumatripan [90]; TEA^+ (K_m 229 μM) [93]; thiamine (K_m 780 μM) [92]; tiotropium [90]; trospium (K_m 17 μM) [137]; xamoterol [90]; YM155 (K_m 22 μM) [141]; zebularine (efflux transporter) [142]
hOCT2 (SLC22A2)	555 [43]	Kidney [43] (basolateral membrane of proximal tubules cells) [117]; small intestine [43, 120]; brain [43, 120]; luminal membrane of bronchial tissue epithelial cells [75]	Acetylcholine (K_m 150 μM) [75]; ADMA (K_m 967 μM) [143]; creatinine (K_m 4 mM) [101, 144]; cyclo(his-pro) (K_m 74 μM) [145]; dopamine (K_m 0.4 mM) [120]; histamine (K_m 1.3 mM) [120]; L-arginine ($K_m > 10{,}000$ μM) [143]; *N*-methylnicotinamide (K_m 318 μM) [146]; norepinephrine (K_m 1.9 mM) [120]; salsolinol (K_m 130 μM) [145]; serotonin (K_m 80 μM) [120]; tryptophan [147]	Agmatine (K_m 1.4 [148] and 1.8 mM [125]); albuterol [90]; amantadine (K_m 27 μM) [120]; amiloride (K_m 95 μM) [22]; aminoguanidine (K_m 4.1 mM) [149]; amisulpride (K_m 168 μM) [126]; ASP^+ (K_m 24 μM) [22]; atenolol (IC_{50} for ASP^+ uptake 93 μM) [150]; cadmium (K_m 54 μM) [8]; cimetidine (K_i for TEA^+ uptake 13 μM) [151]; cisplatin (K_m 11 μM) [9] and [99]; ethidium bromide (K_m 1.7 μM) [20]; fenoterol [90]; glycopyrrolate [90]; guanfacine (K_m 96 μM) [152]; HPP^+ (K_m 2.79 μM) [129]; ifosfamide (IC_{50} for ASP^+ uptake 624 μM) [153]; lamivudine (K_m 1.90 mM) [133]; memantine (K_m 34 μM) [120]; metformin (IC_{50} for cimetidine uptake 1.7 mM,) [134]; MPP^+ (K_m 19 μM) [43]; nitidine [95]; ofloxacin (IC_{50} for ASP^+ uptake 686 μM) [150]; oxaliplatin (IC_{50} for cimetidine uptake 1 μM) [99, 154]; oxyphenomium [90]; paraquat [19]; phenformin (IC_{50} for cimetidine uptake 65 μM) [134]; pindolol (IC_{50} for ASP^+ uptake 145 μM) [150]; pramipexole (K_m 15.4 μM) [155]; putrescine (K_m 11.3 mM) [125]; rhodamine 123 (K_m 0.61 μM) [24]; spermidine ($K_m \approx 1$ mM) [16]; sulpride (K_m 187 μM) [126]; TEA^+ (K_m 76 μM) [43]; thiamine (K_m 750 μM [92], and 60 μM [156]; tiotropium [90]; trospium (K_m 8 μM) [137]; YM155 (K_m 2.7 μM) [141]; zebularine (efflux transporter) [142]

hOCT3 (SLC22A3)	556 [157]	Brain cortex [157]; placenta, aorta, prostate, salivary gland, adrenal gland, fetal lung and skeletal muscle [34]; heart and liver [157]; submandibular salivary gland [158]; Jejunium [123]; monocytes [124]	Histamine [159]; monoamine neurotransmitters [148, 157]; norepinephrine (K_m 510 μM) [157]	Agmatine (K_m 2.14 mM) [148]; amisulpride (K_m 192 μM) [126]; antiarrhytmic drugs [160]; ethidium bromide (K_m 2 μM) [20]; HPP^+ (K_m 2.23 μM) [129]; lamivudine (K_m 2.14 mM) [133]; metformin (K_m 2.5 mM) [161]; MPP^+ ([157] and [161] K_m 157 μM);nitidine [95]; pramipexole (K_m 138 μM) [155]; $RHPP^+$ (K_m 8.21 μM) [129]; spermidine ($K_m \approx 1$ mM) [16]
hOCTN1 (SLC22A4)	551 [162]	Kidney, bone marrow and trachea and fetal liver [162]; skeletal muscle and placenta [163]; heart [164]; ocular epithelium [165]; lactating mammary epithelial cells [166]; monocytes [124]; mitochondria [167]	Acetylcholine [168]; L-carnitine (K_m 1.3 mM) [167]	Amisulpride (K_m 180 μM) [126]; ergothieneine (ingredient of human food, K_m 21 μM) [169]; gabapentin [170]; imatinib (IC_{50} for inhibition of ASP^+ uptake 31 μM) [21]; ipratropium (K_m 444 μM) [171]; pyrilamine, quinidine [11]; TEA^+ (K_m 436 μM) [162]; verapamil [11]

(continued)

Table 1.3 (continued)

Transporter	Protein size (aa)	Tissue distribution	Endogenous substrates	Exogenous substrates
hOCTN2 (SLC22A5)	557 [172]	Placenta, kidney, liver and brain [172]; heart and skeletal muscles [12]; brain capillary endothelial cells [173]; ocular epithelium [165]; peripheral blood mononuclear cells and $CD4^+$ T-cells [124]; bronchial epithelial cells [171]; nasal epithelium [174]; colon [175]; sperm [176]; lactating mammary epithelial cells [166]	Acetyl-L-carnitine (K_m 8.5 μM), D-carnitine (K_m 10.9 μM), and L-carnitine (K_m 4.34 μM), [12]	Amisulpride (K_m 185 μM) [126]; betaine [177]; butyryl-L-carnitine (K_m 0.4 μM) [178]; cephaloridine [179]; imatinib [180]; ipratropium (K_m 53 μM) [171]; mildronate (K_m 26 μM) [181]; pyrilamine, quinidine [182] spironolactone [183]; TEA^+, verapamil, and valproate [182]
hOCT6 (hCT2) (SLC22A16)		Sperm [176]	Carnitine (K_m 26 μM) [176]	

hMATE1 (SLC47A1)	570 [184]	Liver, kidney, skeletal muscles [184]	ADMA [143]; creatinine [13]; L-arginine [143]; *N*-methylnicotinamide (K_m 301 μM) [146]	Acyclovir (K_m 2640 μM) [13]; agmatine (K_m 240 μM) [125]; chloroquine (K_i for inhibition of metformin uptake 2.8 μM) [185]; cimetidine (K_m 8 [186] and 170 [13] μM); cisplatin [187]; DAPI (K_m 1.1 μM) [188]; estrone sulfate (K_m 470 μM) [13]; fexofenadine [189]; ganciclovir (K_m 5120 μM), and guanidine (K_m 2100 μM) [13]; imatinib (IC_{50} for inhibition of ASP^+ uptake 118 nM) [21]; MPP^+ (K_m 16 [184] and 100 [13] μM); metformin (K_m 780 μM); nitidine [95]; oxaliplatin [190]; paraquat [19]; procainamide (K_m 1230 μM); TEA^+ (K_m 366 μM) [186]; thiamine (K_m 3.5 μM) [13, 156]; topotecan (K_m 70 μM) [13]
hMATE2-K (SLC47A2)	566 [191]	Kidney [191]	Creatinine [13]; *N*-methylnicotinamide (K_m 422 μM) [146]	Acyclovir (K_m 4320 μM) [13]; cimetidine (K_m 370 [191], 120 [13] and 18 [186] μM); cisplatin, [187, 190]; DAPI (K_m 3.2 μM) [188]; estrone sulfate (K_m 850 μM) [13]; ganciclovir (K_m 4280 μM) [13]; guanidine (K_m 4200 μM) [13]; metformin (K_m 1980 [13] and 1050 [191] μM); MPP^+ (K_m 93.5 μM) [191]; oxaliplatin [187, 190]; procainamide (K_m 1580 [13] and 4100 [191] μM); TEA^+ (K_m 830 [191] and 375 [186] μM); thiamine (K_m 3.9 μM) [13, 156]; topotecan (K_m 60 μM) [13]

ADMA asymmetric dimethylarginine, *ASP*$^+$ 4-4-(dimethyl-aminostyryl)methylpyridinium, *DAPI* 4′,6-diamidino-2-phenylindol, *HPP*$^+$ 4-(4-chlorophenyl)-1-[4-(4-fluorophenyl)-4-oxybutyl]pyridinium, *MPP*$^+$ 1-methyl-4-phenylpyridinium, *phTCU* phenylthiophenecarboxamide ureas, *RHPP*$^+$ 4-(4-(chlorophenyl)-1-4-(fluorophenyl)-4-hydroxybutyl-pyridinium, *TEA*$^+$ tetraethylammonium, *YM155* 1-(2-methoxyethyl)-2-methyl-4,9-dioxo-3-(pyrazin-2-ylmethyl)-4,9-dihydro-1H-naphtho[2,3-d]imidazolium

Mouse Organic Cation Transporter 3 (mOct3)

The coding region of *Slc22a3* consists of 11 exons and 10 introns [199]. *Slc22a3* encodes a low-affinity transporter for the neurotransmitters 5-HT and histamine [15, 200]. Measuring mOct3 mRNA levels in different tissues, it was found that mOct3 was highly expressed in placenta, ovaries, and uterus [50], skeletal muscle and heart [201], and at low levels in most other tissues [50].

In the placenta, mOct3 expression was shown to depend on embryonic development, dramatically decreasing toward the end of gestation [34], analogously to what observed for the expression of the intracellular enzyme monoamine oxidase A (MAOA), which inactivates monoamines after transport into the cell [202]. In the placenta, mOct3 and MAOA were found to co-localize in the labyrinth layer, where trophoblast cells are in contact with both the maternal and the foetal circulation to allow an exchange of nutrients, gases and waste products [202]. mOct3 has been identified as a component of the uptake 2 system, a transport system responsible for clearing extracellular monoamines, which is active in tissues with high mOct3 expression such as skeletal muscle, heart, and uterus [201]. In an attempt to establish the importance of mOct3 as part of the uptake2 system, the effects of deletion of the *Slc22a3* gene in mice (*Slc22a3*$^{-/-}$ mice) were evaluated. These mice were viable and fertile and showed no obvious physiological defect and no significant imbalance of NA and dopamine. However, uptake experiments with MPP^+ revealed that *Slc22a3* is an essential component for uptake-2 function in the adult heart and placenta but not in other adult organs [201]. Further experiments with *Slc22a3*$^{-/-}$ mice showed that these animals ingested an increased quantity of hypertonic saline under thirst and salt appetite conditions, and showed alterations of the neural response in the subfornical organ after Na^+ deprivation [203]. In mouse brain, mOct3 was demonstrated to be expressed in dopaminergic neurons of the substantia nigra compacta, non-aminergic neurons of the ventral tegmental area, substantia nigra reticulate (SNr), locus coeruleus, hippocampus and cortex [204]. However, mOct3 expression was also occasionally detected in astrocytes in the SNr, hippocampus and several hypothalamic nuclei. *Slc22a3*$^{-/-}$ mice showed a decreased intracellular content and increased turnover of aminergic transmitters in the brain, which resulted in subtle behavioral alterations, such as increased sensitivity to psychostimulants and increased levels of anxiety and stress [204]. In contrast with these findings, deletion of *mOct3* was found by another group to tendencially increase animal activity and diminish anxiety [205]. The reason for this discrepancy is not known.

Interestingly, it has been shown that mOct3 is able to transport 5-HT and that its expression is upregulated in the brain of mice with constitutively reduced 5-HT transporter [206]. Moreover, in these mice the OCT blocker decynium-22 diminished 5-HT clearance, exerting antidepressant-like effects. In this way, mOct3 may be an important transporter mediating serotonergic signaling when the expression or function of 5-HT transporters is compromised [206]. mOct3 has been found to be expressed also in basophils, cells able to synthetize and secrete huge amounts of histamine. Here, mOct3 seems to be involved in the control of histamine secretion [200].

Rat Organic Cation Transporter 3 (rOct3)

rOct3 encodes a 551 aa protein with a predicted molecular mass of 61 kDa and 48 % identity with rOct1 and rOct2 [207]. rOct3 is expressed most abundantly in the placenta and moderately in the intestine, heart, and brain [207, 208]. Its expression is comparatively low in the kidney and lung and is undetectable in liver [207]. In the brain, rOct3 is expressed widely in different regions, especially in the hippocampus, cerebellum, and cerebral cortex [208], in osmolarity-sensitive regions, and in relay regions. Discrete expression of rOct3 was observed in circumventricular organs such as area postrema and subfornical organ, which are located at the blood–brain interface [209]. In these two structures, rOct3 was found in neurons. In addition, ependymal cells of the subcommissural organ and the pinealocytes of the pineal gland express rOct3. The transporter is also expressed in the choroid plexus and in ependymal cells of some areas lining the ventricles and in ependymal and glial-like cells of the dorsomedial hypothalamus (DMH) of male rats [210].

DMH accumulates histamine and this uptake could be reduced by corticosterone, serotonine, estradiol, and the OCT inhibitor decynium22, supporting the hypothesis that corticosterone-mediated inhibition of rOct3 is responsible for stress-induced accumulation of serotonine in the DMH [210]. Also the toxicity of MPP^+, a metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, in cerebellar granule neurons is probably mediated by rOct3 [211].

In the placenta, rOct3 is expressed on the basolateral, i.e., fetus facing side of the placenta, while the rMate1 is expressed in the labyrinth area mainly on the apical (maternal) placenta region [212]. The OC metformin can be transported in the rat placenta in a fetal-to-maternal direction even against its concentration gradient [213] leading to the conclusion that rOct3 and rMate1 represent an "efficient transplacental excretory pathway" responsible for protection and detoxication of the fetus [213].

It has been observed that at low concentration inhibitors and substrates stimulated rOct3-mediated MPP^+ and noradrenaline, but not cimetidine transport. Basing on these observation, a kinetic model with two binding sites for substrate or inhibitor per transporter unit was proposed, where activation may serve to keep the transporter working for specific substrates in the face of inhibitors [214].

rOct3 has been identified in the luminal membrane of ciliated epithelial cells of the lung but it did not seem to be involved in the transport of ACh [75].

Human Organic Cation Transporter 3 (hOCT3)

The hOCT3 (also known as extraneuronal monoamine transporter, EMT) has been first cloned from Caki-1 cells, a human kidney carcinoma cell line [157]. The *SLC22A3* has been mapped to 6q27, the end of the long arm of chromosome 6 [157] and codes for a 556 aa long protein. Like in mouse *Slc22a3*, *SLC22A3* coding

regions consist of 11 exons and 10 introns [199]. The *SLC22A3* promoter is located within a CpG island and lacks a consensus TATA box, but contains a prototypical initiator element and a number of potential binding sites for the ubiquitous transcription factors Sp1 and NF-1 [119]. mRNA for hOCT3 was detected in liver, heart and brain cortex. HEK293 cells transfected with hOCT3 showed uptake of known substrates of the extraneuronal catecholamine transporter, such as tyramine, adrenaline, NA, 5-HT and the neurotoxin MPP^+. Adrenaline was taken up three times more efficiently than NA, while TEA^+, a prototypical substrate for the OCT proteins, was not accepted as a substrate by hOCT3 [15, 157]. The transport of the neurotransmitters dopamine, NA, and 5-HT by hOCT3 was determined to be of high-capacity and low-affinity [215]. Functionally, the hOCT3 has been proposed to be involved in the inactivation of released monoamine transmitters that escapes neuronal reuptake and thus in the prevention of uncontrolled signal spreading [157] and to be a new molecular target for the development of drugs that aim at an elevation of free monoamine transmitters [157, 216]. Loss of hOCT3 function may cause chronically elevation of sympathetic tone, which may induce vasoconstriction and vascular hypertrophy, leading to progressive increases in peripheral resistance and hypertension [157]. A genome-wide haplotype association study identified *SLC22A3-apolipoprotein*(*a*)*L2-apolipoprotein*(*a*) gene cluster as a strong susceptibility locus for coronary artery disease [217].

A recent study examined the relationship between catecholamine gene expression in peripheral blood and tic severity in Tourette syndrome (TS), a heritable disorder characterized by tics and by dysregulation of neurotransmitters (such as dopamine, histamine, 5-HT, and NA) [218]. *SLC22A3* was highly associated with TS severity, underlining the potential importance of hOCT3 in regulating neurotransmitter balance [218].

hOCT3 has been localized in the basolateral membrane of acinar and ductal cells of human submandibular salivary gland, where it is supposed to play a role in the secretion of histamine by such non-professional histamine-producing cells. Interestingly, hOCT3 expression in these cells is strongly reduced in Sjögren's syndrome patients, suggesting that impaired histamine transport may contribute to glandular pathology in these patients [158].

Also at the example of hOCT3 it has been shown that sensitivity of tumor cells to chemotherapeutic treatment with e.g. irinotecan, vincristine, melphalan [219], and oxaliplatin [220] depends on the expression of transporter proteins mediating specific drug accumulation into target cells [219].

hOCT3 is more widely expressed than its mouse ortholog [34].

A functional discrimination of the three hOCTs has been demonstrated to be attained using the following substances: hOCT1 is selectively inhibited by prazosin, reversibly inhibited by phenoxybenzamine (PbA) and it is not sensitive to inhibition by (9-fluorenyl)-*N*-methyl-beta-chloroethylamine (SKF550) and *O*-methyl-isoprenaline (OMI); hOCT2 is reversibly inhibited by SKF550, irreversibly by PbA and not by prazosin, ß-estradiol and OMI, whereas hOCT3 is selectively inhibited by corticosterone, OMI and decynium22 [221].

Organic Cation Transporter Novel 1

Mouse Octn1

Mouse Octn1 (mOctn1) has a low, Na^+-dependent, carnitine transport activity [222]. mOctn1 is expressed in kidney, smooth muscle, and hematopoietic tissues, such as spleen and bone marrow. Here, its expression was shown to be associated with myeloid cells of the erythroid-lineage at the differentiation stage from immature erythroid cells to peripheral mature erythrocytes [223]. In mouse kidney, mOctn1 is expressed predominantly in the luminal membrane of cortical proximal tubule cells [163]. Moreover, mOctn1 is expressed in inflammatory joints of mice with collagen-induced arthritis, a model of human arthritis, but not in the joints of normal mice [224]. Together with mOctn2 and -3, mOctn1 is widespread expressed across the mouse central nervous system with a distribution pattern indicating a role in modulating cerebral bioenergetics and in ACh production for neurotransmission in olfactory, satiety, limbic, memory, motor and sensory functions [225]. Indeed, mOctn1 has been demonstrated to play a role in neuronal differentiation and proliferation, which are required for brain development [226].

The mOctn transporters are also expressed in epithelial ducts, specialized myoepithelial cells and fatty stroma of mammary glands. In pregnant and lactating mice the expression of these transporters has been shown to be up-regulated compared with virginal females, and to be down-regulated 15 days after cessation of lactation, probably to provide the suckling infant with adequate carnitine [227]. Mice with genetic deletion of *mOctn1* (*Slc22a4*$^{-/-}$) developed normally and did not display any gross phenotypic abnormalities [228]. However, they developed an ergothioneine deficiency (for ergothioneine function see the paragraph human OCTN1 below) and were more prone to intestinal inflammation in the ischemia and reperfusion model. Moreover, using *Slc22a4*$^{-/-}$ mice it has been demonstrated that mOctn1 transports the antidiabetic drug metformin [229], being involved in its oral absorption in small intestine, and phenformin, influencing its accumulation in mitochondria [230].

mOctn1-mediated uptake of ergothioneine in neural progenitor cells was shown to inhibit cell proliferation while promoting cellular differentiation by regulating the expression of basic helix-loop-helix transcription factors through a still unknown process, which is different from antioxidant action [231].

Rat Octn1

Rat *Octn1* gene codes for a protein of 553 aa with a high homology to human OCTN1 (85 % identity) [232]. rOctn1 has been demonstrated to be a pH-dependent polyspecific transporter for organic cations, which is expressed in a wide variety of tissues in the rat, principally in the liver, intestine, kidney, brain, heart, placenta [232], choroid plexus [233], and testis Sertoli cells [234]. Renal rOctn1 mRNA

levels were shown to increase gradually from postnatal day 0 through day 45 in both genders [73]. Also rOctn1 was shown to be involved in the Na^+-dependent transport of ergothioneine [235]. rOctn1 and also rOctn2 accept oxaliplatin as a substrate and are functionally expressed in dorsal root ganglia neurons. rOctn1-mediated transport of oxaliplatin was suggested to contribute to its neuronal accumulation and treatment-limiting neurotoxicity [236].

Human OCTN1

Human *OCTN1* gene encodes a 551 aa protein with 11 transmembrane domains and one nucleotide binding site motif [162]. hOCTN1 works as a polyspecific, bidirectional proton antiporter [11], transporting several cationic compounds, including ACh, TEA^+, pyrilamine, quinidine, verapamil, donepezil, betonicine, ergothioneine and stachydrine [11, 168, 169]. Human OCTN1 is strongly expressed in kidney, trachea, bone marrow and fetal liver and in several human cancer cell lines, but not in adult liver [162]. A discrete expression of hOCTN1 has been also detected in cardiomyocites [164]. In the intestine, hOCTN1 is expressed at the same level in all gut sections [175]. hOCTN1 is highly expressed in ocular tissues, especially in the iris-ciliary-body [237] and in the apical membrane of human corneal and conjunctival epithelial cells [165]. hOCTN1 together with hOCTN2 is also expressed in human airway epithelia, with a predominant localization to the apical portion of epithelial cells [238]. Lactating mammary epithelial cells (MEC) express more than fourfold higher RNA levels of hOCTN1 relative to nonlactating MEC [166]. hOCTN1, together with hOCTN2 and hOCTN3 is expressed in sperm, where they possibly mediate carnitine uptake [176]. hOCTN1 is expressed in immunological and hematological organs and tissues, and expression of its mRNA is induced by proinflammatory stimuli [224], suggesting that SLC22A4 functions as a transporter in lymphoid organs or inflammatory milieu. Interestingly, polymorphisms of *hOCTN1* in a gene region, where the transcription factor RUNX1 binds, and polymorphisms of RUNX1 itself were suggested to be associated with susceptibility to rheumatoid arthritis [224]. However, these findings are strongly debated (see for example [239]). A localization of hOCTN1 in mitocondria has been also demonstrated [167]. Here, the transporter should mediate the uptake of L-carnitine [167]. Ergothioneine (ET), a substance that is biosynthesized exclusively by fungi and mycobacteria and is captured by plants through their roots, has been identified as key substrate of hOCTN1 ($K_m = 21$ μM) [169]. In humans, ET is of dietary origin (high levels of ET are present in mushrooms) and accumulates in erythrocytes, bone marrow, and seminal fluid [169]. ET is considered to be an intracellular antioxidant [169]. Indeed, epidermal keratinocytes express hOCTN1, which enables them to internalize and accumulate L-ergothioneine conferring to the cells a resistance to oxidative damage [240]. In blood cells, hOCTN1 is involved in the transport of physiological compounds that are important for cell proliferation and erythroid differentiation [241]. hOCTN1 mediates the cellular extrusion of ACh [168].

Mouse Octn2

Because of the function of hOCTN2 as a carnitine transporter (see below), expression of Octn2 has been investigated in wild-type (WT)- and in the juvenile visceral steatosis (JVS)-mice, so called because of accumulation of fat in viscera due to defects in fatty acid oxidation caused by carnitine deficiency (for this reason this is an animal model of human systemic carnitine deficiency) [242]. In JVS mice, a missense mutation in *mOctn2* gene from CTG (Leu) to CGG (Arg) at codon 352 located within the sixth transmembrane transporter domain was identified, suggesting that *mOctn2* is a candidate gene responsible for the JVS and that JVS mice can be considered to be *mOctn2*$^{-/-}$ mice [242]. The JVS mice spontaneously develop intestinal villous atrophy, breakdown and inflammation with intense lymphocytic and macrophage infiltration, leading to ulcer formation and gut perforation [243]. Using this animal model, it has been demonstrated that the Na^+-dependent carnitine transporter Octn2 is responsible for carnitine transfer from the mother to the fetus and to supply the placenta with carnitine for its own metabolic needs [244] and that carnitine is necessary to maintain normal intestinal and colonic structure and morphology [243]. mOctn2 was found to be also expressed in pancreatic A-cells [245]. In mice, PPARα transcriptionally up-regulates mOctn2 and enzymes involved in hepatic carnitine biosynthesis [246]. Also fasting and caloric restriction were demonstrated to activate PPARα leading to an upregulation of mOctn2 in several tissues [247]. The pharmacological importance of mOctn2 has been suggested in studies with mice, demonstrating that the uptake of the organic cation ipratropium bromide, an anticholinergic drug used to treat chronic obstructive pulmonary disease, is mediated by mOctn2 expressed at the apical portions of ciliated epithelial cells of trachea [248].

Rat Octn2

Rat *Octn2* encodes a 557 amino acid protein with 12 putative membrane-spanning domains, which mediates the high-affinity, Na^+-dependent transport of L-carnitine ($K_m = 25$ μM) [249]. rOctn2 is expressed in the testis, colon, kidney (in the proximal and distal tubules and in the glomeruli), heart (in myocardium, valves, and arterioles) and liver and also in the skeletal muscle (where it is involved in the import of carnitine for fatty acid oxidation, especially in highly oxidative muscles [250]), in the labyrinthine layer of the placenta, small intestine, and brain (in the cortex, hippocampus, and cerebellum) [249, 251]. Rat Octn2 is also expressed in the basolateral membrane of epithelial cells in the distal caput, corpus, and proximal cauda epididymides, where it is likely to be responsible for the transport of L-carnitine into the cells of the epididymal epithelium [252] and also in the Sertoli cells, which are part of the blood-testis barrier [253]. Expression of rOctn2 has been also detected in astrocytes [254] and in brain capillary endothelial cells at the basolateral membrane and in the cytoplasmic region [255], suggesting an important role of rOctn2 in

removal of carnitine esters from the brain. Renal mRNA expression of rOctn2 increased by a factor of 1.7 in carnitine deficient rats, whereas rOctn2 mRNA expression remained unchanged in gut, liver or skeletal muscle [256]. Muscle contraction facilitated carnitine uptake in skeletal muscles, possibly via the contraction-induced translocation of rOctn2 to the plasma membrane [257]. Two splicing variants of rOctn2 have been identified in rats [258].

Human OCTN2

Human *OCTN2* encodes for a polyspecific, pH-dependent transporter for OCs of 557 aa with twelve putative transmembrane domains and with 75.8 % similarity to OCTN1 [12, 172]. The physiological importance of OCTN2 derives from its function as a high affinity Na^+-carnitine cotransporter [12]. Indeed, mutations, which produced a missfunctioning hOCTN2, have been associated with primary systemic carnitine deficiency, an autosomal recessive disease, whose manifestations are progressive cardiomyopathy, skeletal myopathy, hypoglycaemia and hyperammonaemia [259–261]. Importantly, Na^+ does not change the affinity of hOCTN2 for OCs, but it strongly increases the hOCTN2 affinity for carnitine [251, 262]. hOCTN2 showed a stereospecific transport activity: D-carnitine was transported with slightly lower affinity ($K_m = 10.9$ μM) than the L-isomer ($K_m = 4.3$ μM) [182]. The fluxes of L-carnitine and Na^+ have been demonstrated to be coupled with 1:1 stoichiometry and to be electrogenic processes [263]. The transmembrane domains 1–7 of hOCTN2 were shown to be responsible for organic cation transport and for Na^+ dependence in carnitine transport, with glutamines 180 and 207 as critical amino acids for the Na^+ dependence [264]. The hOCTN2 is physiologically glycosylated but glycosylation does not affect maturation of hOCTN2 to the plasma membrane. The three asparagines that have been demonstrated to be normally glycosylated are located in a region important for substrate recognition and turnover rate [265]. The C terminus of hOCTN2 has been shown to interact directly with PSD-95-Dlg-ZO-1 domain-containing protein K1 and 2 (PDZK1 and 2), which resulted to be functional regulators of hOCTN2 [266, 267].

hOCTN2 is strongly expressed in kidneys on the apical membrane of renal tubular epithelial cells, skeletal muscle, heart, and placenta in adult humans [12, 263]. Expression of hOCTN2 has been also detected in primary cultured brain capillary endothelial cells [173], on the apical side of nasal epithelium [174], in the brush-border membrane of intestinal Caco-2 cells [268] and in the colon [175]. In the intestine, hOCTN2 was shown to transport the "competence and sporulation factor" from *Bacillus subtilis* into intestinal epithelial cells, protecting these cells from oxidative stress [269]. The production of such a factor by *Bacillus subtilis* probably provides the host with the ability to respond or adapt to changes in the microbiome in order to maintain intestinal homeostasis [269].

Because of its expression in brain capillary endothelial cells, hOCTN2 is suggested to be involved in transport of L-carnitine and acetyl-L-carnitine from the circulating blood to the brain across the blood brain barrier [173].

hOCTN2 seems also to be expressed in sperm, where carnitine is important for spermatozoan maturation, motility, and fertility [176]. hOCTN2 is also present in brush border membranes from human term placentas, where it may mediate most maternofetal carnitine transport [270].

Insulin can acutely increase muscle total carnitine content in humans during hypercarnitinemia, which is associated with an increase in *hOCTN2* transcription [271].

hOCTN2 is expressed in the endothelial cells of human heart and its expression can be modulated by drug administration. Moreover, hOCTN2 can contribute to the cardiac uptake of cardiovascular drugs [183]. hOCTN2 is also expressed in cultured human limbal corneal and conjunctival epithelial cells, where it mediates carnitine uptake [272].

Therapeutic use of cephaloridine, a beta-lactam antibiotic, in humans is associated with carnitine deficiency. This fact has been explained by inhibition of hOCTN2-mediated carnitine transport by beta-lactam antibiotics such as cephaloridine, cefoselis, cefepime, and cefluprenam. These antibiotics possess a quaternary nitrogen as carnitine does. Several other beta-lactam antibiotics that do not possess this structural feature did not interact with hOCTN2 [179]. Even though hOCTN2 is a transporter for organic cations, it is highly specific for carnitine and closely related molecules, such as the cardioprotective agent mildronate [181].

The high carbohydrate consumption observed in vegetarians was associated with a significant stimulation of hOCTN2 expression in oral mucosa, probably to compensate lower carnitine levels in the alimentation [273].

Lactating mammary epithelial cells (MEC) express more than fourfold lower RNA levels of hOCTN2 relative to nonlactating MEC [166].

Mouse and rat Octn3, Human OCT6

An *Octn3* clustered on mouse chromosome 11 with *mOctn1* and *mOctn2* has been identified in the mouse brain (mainly in the grey matter, specifically in anterior horn cell bodies) [225], kidney and testis, where carnitine is required to maintain sperm cell motility [222]. The mouse Octn3 mediates a specific, Na^+ *independent* uptake of carnitine with a K_m of 3 μM [222] in peroxisomes [274], suggesting a role of carnitine in peroxisomal lipid metabolism. PPARα mediates transcriptional upregulation of mOctn3 [246]. In the rat, Octn3 protein is mainly expressed in the basolateral membrane of enterocytes [275], in the apical membrane of the kidney epithelia [276], and in astrocytes [277]. In humans, Octn3 has not been found. However, another high-affinity carnitine transporter called hCT2 or hOCT6 has been identified in sperm, where it mediates the uptake of carnitine with a K_m of 26 μM [176].

Multidrug and Toxin Extrusion Transporters (MATEs)

Multidrug and toxic compound extrusion (MATE) proteins are widely distributed in all kingdoms of living organisms. Plant MATE-type transporters are involved in the detoxification of secondary metabolites, including alkaloids [278]. Human and mouse MATE1 have been identified as the transporters involved in the H^+-coupled electroneutral exchange of endogenous and exogenous OCs as their final excretion step in the luminal membranes of the renal tubules and bile canaliculi [184].

MATE1 (SLC47A1)

Mouse Mate1

In addition to the localization in kidneys and liver, mMate1 is also expressed in other cells, including brain glia-like cells and capillaries, pancreatic duct cells, urinary bladder epithelium, adrenal gland cortex, α cells of the islets of Langerhans, Leydig cells, and vitamin A-storing Ito cells [279]. The expression of mMate1 mRNA in the kidneys of both male and female mice has been shown to increase steadily from prenatal day −2 to 45 days of age. Pregnancy significantly reduced mMate1 renal expression by 20–40 %. At day 30 appeared a gender difference, with higher expression in kidneys from male than female animals [280]. Pyrimethamine has revealed as a potent and specific inhibitor of mMate1 ($K_i = 145$ nM) and can be useful to discriminate transport of OCs by this transporter [281]. mMate1 was suggested to play an important role for cisplatin nephrotoxicity, since its genetic deletion (*Slc47a1*$^{-/-}$) or inhibition by pyrimethamine in mice increases renal toxicity of cisplatin, probably because of decreased cisplatin efflux from the tubular cells into the urine [282]. Since the treatment with the antidiabetic drug metformin can cause the fatal adverse effect lactic acidosis, and since metformin is an organic cation, which is substrate for mOct1 and also mOct2, it has been investigated whether mMate1 is linked to lactic acidosis. Indeed, treatment of *Slc47a1*$^{-/-}$ mice with metformin resulted in a high hepatic metformin concentration and in lactic acidosis, suggesting that the homozygous *mMate1* variant could be one of the risk factors for metformin-induced lactic acidosis [283]. [^{11}C]metformin has been synthesized as a positron emission tomography (PET) probe and used to study the role of mMate1 for its hepatobiliary transport in mice treated or not with pyrimethamine. Indeed, an increased concentration of [^{11}C]metformin was observed in the livers of mice pretreated with pyrimethamine, confirming the importance of mMate1 for hepatic secretion of metformin [284].

A variant of mMate1, mMate1b, with a long carboxyl terminal hydrophobic tail, but with similar transport characteristics, organ and cell distribution has been identified [285]. The carboxyl terminal hydrophobic tail seemed not to determine transport properties of mMate1b.

Rat Mate1

The rat Mate1 has been demonstrated to be abundantly expressed in the renal proximal convoluted and straight tubules, and in the placenta and to a lower level also in the spleen, while it is not expressed in the liver [286]. Also rMate1 works as a pH-dependent transporter and accepts organic cations such as cimetidine ($K_m = 3$ μM) [287] and metformin but also the zwitterionic compound cephalexin as substrates [286]. The Cys-62 and Cys-126 residues of rMate1, which are located in the first and the third transmembrane domain, respectively, were shown to play an important role as substrate-interaction sites, while the His-385 residue in the fifth extracellular loop functions as an H^+-binding site [288].

Transcriptional regulation of the human and rat *MATE1* gene is mediated by binding of Sp1 to the gene regions spanning −65/−25 and −146/−38 [289]. rMate1 is also expressed in the rat placenta in the labyrinth area predominantly on the apical, i.e., maternal side of the placenta, where it can mediate the efflux of OCs from placenta to the maternal circulation [212].

Human MATE1

In human kidney, hMATE1 is expressed at the brush-border membranes of proximal tubular epithelial cells and in human liver on the apical membrane of hepatocytes [184, 290]. As already proposed for rOct1 [195], also the hMATE1 seems to interact with its ligands at multiple sites within a larger binding surface [291]. It has been suggested that the kinetics of interaction between inward-facing hMATE1 and intracellular H^+ are not significantly different from the kinetics of the interaction between outward-facing hMATE1 and extracellular H^+ [292]. In hMATE1, the conserved Glu273, Glu278, Glu300, and Glu389 of transmembrane regions seem to be involved with different individual roles in binding and/or transport of TEA^+ and cimetidine [293]. hMATE1 and also hMATE2 (K_m 3.5 and 3.9 μM, respectively) are responsible for the renal efflux of thiamine and perhaps carnitine as well as drugs into the urine [156]. Immunofluorescence analysis suggested that hMATE1 is primarily expressed in the plasma, endoplasmic reticulum, and peroxisomal membranes in cultured hepatocytes, hMATE1 cells, and both mouse and human liver tissues [294].

MATE2 (SLC47A2)

Mouse Mate2

mMate2 mediates a pH-dependent transport with substrate specificity similar to, but distinct from that of mMate1 [295]. In male mice, mMate2 is specifically expressed in testicular Leydig [295] and Sertoli [280] cells. In female mice, mMate2 mRNA levels are expressed most highly in the colon [280].

Human MATE2

hMATE2 is a kidney-specific isoform of *hMATE1* [184], which has a splicing variant, *hMATE2K*, where an exon of *hMATE2* is deleted [191]. Both hMATE2 and hMATE2K are expressed in the kidneys, with hMATE2K having the higher expression level [296]. *hMATE2K* cDNA encodes a 566 aa protein, which shows 94, 52, and 52 % identity with the hMATE2, hMATE1, and rat MATE1, respectively [191]. The affinities of several OCs for hMATE1, hMATE2, and hMATE2K are similar [13, 296]; however, the zwitterionic cephalexin and cephradine are specific substrates of hMATE1, but not of hMATE2K [13]. Pyrimethamine is a potent competitive inhibitor also of the uptake by hMATE2K with an inhibition constant (K_i) of 56 nM [146].

In conclusion, OCTs play an important physiological role for neurotransmitter balance in the body. Moreover, they are also important uptake routes for intracellular drug delivery and, considering their high expression in excretory organs, together with MATEs are responsible for drug excretion. For this reason, OCTs and MATEs can be important determinants of drug efficacies and also toxicities. OCTNs are transporters involved in the cellular uptake of substances, which are important in cell metabolism and in signal transmission, such as the antioxidant ergothionein and the neurotransmitter ACh (substrates of OCNT1) and the quaternary ammonium compound L-carnitine (substrate of OCNT2), which is of pivotal importance for cell energy production. Even though the expression and function of orthologs of transporters for OCs is generally similar, still there are important differences (e.g. hOCT1 is not expressed in the basolateral membrane of renal proximal tubules, in contrast with what observed for mOct1 and rOct1) that have to be considered for a proper interpretation of translational studies. Paralogs of transporters for organic cations often display similar characteristics, however they show also important differences e.g. with regard to interaction with substrates and to regulation. Other important functional aspects of transporters for organic cations, such as the molecular correlates of polyspecificity, regulation, interaction with drugs, genetic variations, role in the central nervous system, and distribution in the plants are discussed in the other sections of this book.

Acknowledgments The support of the Deutsche Forschungsgemeinschaft (DFG CI 107/4-1 to 3), of the "Innovative Medizinische Forschung" (CI 120437) and of the "Interdisziplinäres Zentrum für Klinische Forschung (IZKF)" (CIA02/013/13), both at the Medical Faculty of the University of Münster for the studies of G.C. and E.S. mentioned in their respective chapters is also acknowledged.

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