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Short-Term Regulation of Organic Anion Transporters

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Abstract

Organic anion transporters (OATs), which belong to the superfamily SLC22A, are key determinants in the absorption, distribution, and excretion of a diverse array of environmental toxins, and clinically important drugs, and, therefore, are critical for the survival of mammalian species. Alteration in the function of these drug transporters plays important roles in intra- and inter-individual variability of the therapeutic efficacy and the toxicity of many drugs. As a result, the activity of OATs must be under tight regulation so as to carry out their normal functions. This review article highlights the recent advances from our laboratory as well as from others in delineating the short-term regulation of OATs. These advances provide important insights into strategies to maximize therapeutic efficacy in drug development.

Keywords

Organic anion transporters; drug transport; regulation

1. INTRODUCTION

Organic anion transporter family (OATs) belongs to the amphiphilic solute carrier transporters family 22a (SLC22A), which transports a broad diversity of substrates including metabolites, toxins and clinical drugs such as β -lactam antibiotics, antivirals, ACE inhibitors, diuretics, and NSAIDs (You, 2004; Anzai et al., 2006; El-Sheikh et al., 2008; Srimaroeng et al., 2008). To date, ten members of the OAT family (OAT1-10) have been identified (Sekine et al., 1997; Sweet et al., 1997; Sekine et al., 1998; Kusuhashi et al., 1999; Cha et al., 2000; Youngblood and Sweet, 2004; Schnabolk et al., 2006; Shin et al., 2007; Bahn et al., 2008; Yokoyama et al., 2008), which differ from each other by their localization, expression level, and substrate specificity. As the first cloned OAT, OAT1 is expressed predominantly at the basolateral membrane of renal proximal tubular cells (Sekine

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et al., 1997; Sweet et al., 1997; Lu et al., 1999; Race et al., 1999) and at low levels in the cerebral cortex and hippocampus as well as in the choroid plexus (Alebouyeh et al., 2003; Bahn et al., 2005). OAT2 is primarily expressed in the liver (Sekine et al., 1998) and kidney (Kojima et al., 2002). In the liver, OAT2 is expressed at the basolateral membrane of hepatocytes (Hilgendorf et al., 2007). In the kidney, however, the cellular location of OAT2 seems to be species-dependent. Human OAT2 is expressed similarly as hOAT1 at the basolateral membrane of the proximal tubule (Enomoto et al., 2002b), while in rat and mouse, OAT2 is located at the apical membrane of proximal tubular cells (Ljubojevic et al., 2007). OAT3 is highly expressed at the basolateral membrane of renal proximal tubular cells (Cha et al., 2001; Hasegawa et al., 2002; Kobayashi et al., 2004) and at the apical membrane of choroid plexus (Sweet et al., 2002). OAT4 is expressed at the apical membrane of renal proximal tubular cells (Ekaratanawong et al., 2004), while in the placenta, OAT4 is expressed at the basal membrane of syncytiotrophoblast (Ugele et al., 2003). Expressed exclusively in kidney, OAT5, similar to OAT4, is located at the apical membrane of renal proximal tubular cells (Youngblood and Sweet, 2004). The unique feature of OAT6 is its complete absence in the kidney and its expression in olfactory mucosa (Monte et al., 2004). Discovered as a liver-specific OAT, OAT7 localizes at the sinusoidal membrane of the hepatocyte (Shin et al., 2007). Recently, three other OATs were identified in the kidney. Rat OAT8 is expressed in rat renal collecting duct and located at the apical membrane of renal intercalated cells (Yokoyama et al., 2008). OAT9 is expressed in the kidney and brain (Anzai et al., 2006). OAT10 is highly expressed at the apical side of renal proximal tubular cells (Bahn et al., 2008). The urate transporter URAT1 (SLC22A12), acting as an organic anion exchanger, is expressed at the apical membrane of the kidney proximal tubule and is believed to be responsible for renal urate reabsorption (Enomoto et al., 2002a).

In the kidney, OAT1 and OAT3 utilize a tertiary transport mechanism to move organic anions across the basolateral membrane into the proximal tubular cells for subsequent exit across the apical membrane into the urine for elimination (**Fig.1**). Through this tertiary transport mechanism, Na^+/K^+ -ATPase maintains an inwardly directed (blood-to-cell) Na^+ gradient. The Na^+ gradient then drives a sodium dicarboxylate cotransporter, sustaining an outwardly directed dicarboxylate gradient that is utilized by a dicarboxylate/organic anion exchanger, namely OAT, to move the organic anion substrate into the cell. This cascade of events indirectly links organic anion transport to metabolic energy and the Na^+ gradient, allowing the entry of a negatively charged substrate against both its chemical concentration gradient and the electrical potential of the cell.

Structurally, all members of the OATs share some common features (**Fig. 2**) including 12 putative membrane-spanning segments, a cluster of potential glycosylation sites located in the first extracellular loop between transmembrane domains 1 and 2, and multiple presumptive phosphorylation sites in the intracellular loop between the sixth and the seventh transmembrane domains and in the carboxyl terminus.

One remarkable characteristic of OATs is their wide range of substrate recognition, from endogenous metabolites to xenobiotics and drugs including anti-HIV therapeutics, anti-tumor drugs, antibiotics, anti-hypertensives, and anti-inflammatories (You, 2004; Enomoto and Endou, 2005; Anzai et al., 2006; Srimaroeng et al., 2008). Given the critical role of

OATs in the control of distribution, elimination and retention of such a diverse array of chemicals within the body, the activity of these transporters must be under tight regulation in order to accomplish their normal task. This review article highlights the recent advances from our laboratory as well as from others in unveiling the regulation of OATs, especially the short-term regulation of these transporters, as well as their clinical implications.

2. Regulation of OATs

OAT activity is subject to long- and short-term regulation. The long-term regulation, also called chronic regulation, usually occurs at transcriptional as well as translational levels within a time frame of hours to days. Long-term regulation usually happens when the body undergoes massive change, such as during development or the occurrence of disease (Buist et al., 2002; Sakurai et al., 2004; Naud et al., 2008). The short-term regulation, also called acute regulation, usually occurs at post-translational levels within a time frame of minutes to hours and often takes place when the body has to deal with rapidly changing amounts of substances as a consequence of variable intake of drugs, fluids, or meals as well as metabolic activity (Kellett and Helliwell, 2000; Glatz et al., 2002; Zahniser and Sorkin, 2009). Key players involved in the regulation of OATs are hormones, protein kinases, nuclear receptors, scaffolding proteins, and disease conditions. In this review, we will focus on the short-term regulation of OATs.

2.1. Glycosylation

One of the early studies on the regulation of OATs demonstrated the importance of glycosylation. Glycosylation is a two-step process; first, a bulky sugar chain is covalently added to the NH₂ group on the side chain of an asparagine (Asn) residue (N-linked glycosylation) or to the OH group of serine (Ser) or threonine (Thr) side chains (O-linked glycosylation) of the proteins, and secondly, the added sugars undergo a series of modification. Glycosylation has been demonstrated to play critical roles in the regulation of membrane targeting (Lee et al., 2003; Tanaka et al., 2004), protein folding (Kameh et al., 1998; Zhou et al., 2005), the maintenance of protein stability (resistance to proteolysis) (Khanna et al., 2001; Buck et al., 2004), and providing recognition structures for interaction with diverse external ligands (Ott et al., 1992; Bernardo et al., 1997). For the OAT family, each step of glycosylation plays a distinct role in OAT function. Mutagenesis studies on OAT1 (Tanaka et al., 2004) and OAT4 (Zhou et al., 2005) in cultured cells revealed that although disrupting each individual N-glycosylation site in the first extracellular loop by replacing asparagine with glutamine had no effect on the transport activities of these transporters, simultaneous elimination of all these glycosylation sites resulted in these transporters being trapped in an intracellular compartment, suggesting that addition of sugars to the transporters, the first step in the glycosylation process, plays a critical role in the targeting of these transporters to the plasma membrane. The second step in the glycosylation process, modification of added sugars, has also proven to be important. With the use of mutant Chinese hamster ovary (CHO)-Lec cells lacking various enzymes required for glycosylation processing, it was shown that processing of glycosylation from a mannose-rich type to a complex type was associated with an increased affinity of OAT4 for its substrate (Zhou et al., 2005).

2.2. Phosphorylation

Phosphorylation is a process in which a negatively charged phosphate group is added to the target protein, consequently influencing the conformation and charge of the target protein, thereby also its activity (either up or down), cellular location or association with other proteins. The phosphorylation state of a target protein is dynamically controlled by protein kinases and protein phosphatases acting in an exact opposite fashion. Reversible protein phosphorylation is responsible for regulation of cellular processes as diverse as mobilization of glucose from glycogen (Nuttall et al., 1988; Longnus et al., 2005), prevention of transplant rejection by cyclosporine (Erxleben et al., 2006), and development of a cancer form like chronic myeloid leukemia (Eriksson et al., 1994; Coppo et al., 2006).

Reversible phosphorylation has proven to be another important mechanism in regulation of OAT activity. It was shown (You et al., 2000) that treatment of OAT1-expressing LLC-PK1 cells with okadaic acid resulted in an increased level of phosphorylation in OAT1. Okadaic acid is a potent inhibitor of protein phosphatase 1 and protein phosphatase 2A, two of the four major serine/threonine protein phosphatases in the cytoplasm of mammalian cells, and it enhances the phosphorylation of many cellular proteins, presumably by preventing dephosphorylation. It was further shown (You et al., 2000) that okadaic acid induced phosphorylation of OAT1, which paralleled in time and concentration the decrease of OAT1-mediated transport of para-aminohippurate (PAH), a prototypical organic anion. Phosphoamino acid analysis indicated that phosphorylation occurred primarily on serine residues. These results suggest that the increase in serine phosphorylation of OAT1 by okadaic acid is, at least in part, responsible for the okadaic acid-induced decrease in basolateral PAH transport. OAT1 is a PAH/ α -ketoglutarate exchanger, with the divalent anion α -ketoglutarate being the intracellular counter-ion for exchanging the extracellular monovalent anion PAH. We hypothesize that phosphorylation of OAT1 may change its affinity for either α -ketoglutarate or PAH. If the phosphorylation sites are located on intracellular loops, addition of negatively charged phosphate groups on OAT1 could prevent intracellular α -ketoglutarate (also negatively charged) from being exchanged with extracellular PAH, via repulsion of negative charges on both the phosphate groups and α -ketoglutarate. On the other hand, since α -ketoglutarate is negatively charged, it is likely that the binding pocket for α -ketoglutarate consists of positively charged amino acid residues. Negatively charged phosphate groups on OAT1 could neutralize these positive charges, therefore, dampening the interaction between α -ketoglutarate and these residues. In addition to the two possibilities mentioned above, which affect the selectivity of OAT1 for its intracellular substrate α -ketoglutarate, a third possibility is that phosphorylation may cause a conformational change in OAT1, thereby affecting the affinity of OAT1 for its extracellular substrates such as PAH.

2.3. Membrane Trafficking

Although once considered static resident plasma membrane proteins, a growing body of evidence demonstrates that many transporters undergo internalization from and recycling back to the cell surface constitutively or in response to stimuli (Bose et al., 2002; Loder and Melikian, 2003). Abnormal membrane trafficking of the transporters is the key cause for many clinical syndromes (Muth and Caplan, 2003; Dugani and Klip, 2005). For example,

patients with Liddle's syndrome exhibit profound hypertension caused by renal sodium retention. The excessive sodium retention is a result of a sodium channel that is unable to internalize from the cell surface and, therefore, is constitutively active at the cell surface to absorb sodium (Snyder et al., 1995; Schild et al., 1996). Another example underscoring the importance of transporter trafficking is type II diabetes. Patients with type II diabetes are unable to respond to insulin to take up glucose from the blood into muscle and adipose tissues. This insulin resistance and, therefore, the inability of the cells to take up glucose are, in part, due to defective recycling of glucose transporter GLUT4 from intracellular compartments to the cell surface (Garvey et al., 1998). Using a biotinylation approach in conjunction with a functional assay, Zhang et al. (Zhang et al., 2008b) have recently shown that under basal conditions, OAT1 robustly internalized from and recycled back to the cell surface in order to maintain a steady-state cell surface level of the transporter. The rates for both internalization and recycling were ~10%/5 min, similar to that observed for the transferrin receptor, a protein that undergoes rapid internalization and recycling (Hao and Maxfield, 2000). Why would the cells expend energy to constantly cycle OAT1? The best explanation would possibly be that when OAT1 is in a dynamic rather than a static state, it would be more effective for the transporter to initiate trafficking in response to stimuli such as activation of protein kinases and, therefore, to provide quick and efficient fine-tuning in response to environmental changes. Indeed, Zhang et al. (Zhang et al., 2008a) further showed that activation of protein kinase C (PKC) by phorbol 12-myristate 13-acetate down-regulated OAT1 activity, mainly due to reduced expression of OAT1 at the cell surface. Such reduced surface expression of OAT1 could be caused by either an accelerated OAT1 internalization, or a decreased OAT1 recycling or a combination of both. Zhang et al. demonstrated that accelerating OAT1 internalization without significantly affecting its recycling was the main reason for PKC-induced inhibition of OAT1 activity. Several physiological hormones such as angiotensin II, progesterone, and parathyroid hormone have been shown to affect OAT activity through activation of PKC (Nii-Kono et al., 2007; Zhou et al., 2007; Li et al., 2009). In a recent study, Li et al. (Li et al., 2009) showed that treatment of OAT1-expressing COS-7 cells with angiotensin II inhibited OAT1 activity. Similarly, in another study, Zhou et al. (Zhou et al., 2007) showed that treatment of OAT4-expressing placenta BeWo cells with progesterone inhibited OAT4 activity. In both studies, the inhibition of OAT activity mainly resulted from a decrease of OAT1 at the cell surface and was reversed in the presence of a specific inhibitor for PKC. It is likely that modulation of membrane trafficking of OAT plays a role in such regulation. In contrast to the effect of angiotensin II, progesterone and parathyroid hormone, and other physiological signaling molecules such as epidermal growth factor (EGF) and insulin, have been shown to up-regulate OAT activity (Dantzler and Wright, 2003; Sauviant et al., 2003; Sauviant et al., 2004; Sauviant et al., 2006). The up-regulation of OAT induced by EGF is dependent on the activation of mitogen-activated/extracellular-signal regulated protein kinase through phospholipase A2, prostaglandin E2, and protein kinase A (PKA) activation, whereas the up-regulation of OAT induced by insulin is dependent on the activation of PKA and a PKC isoform ζ (Barros et al., 2009). Again, such up-regulation can be speculated to occur through altering the trafficking kinetics of an already existent OAT population.

2.4. Protein-protein Interactions

Many drug transporters have been shown to be associated with other proteins. The formation of such protein complexes gives the transporter an additional level of regulation for its activity. Often, heteromeric compositions of protein complexes are tissue-specific or development-specific and multiple genes can control the activity of a single heteromeric protein complex. The first example of such protein-protein interaction is that between members of the OAT family and PDZ (PSD-95/Discs Large/ZO-1) proteins. PDZ proteins contain multiple PDZ domains and bind typically to proteins containing PDZ consensus binding sites, the tripeptide motif (S/T)X (X = any amino acid and = a hydrophobic residue) at their C termini (Biber et al., 2005). Through such interaction, PDZ proteins modulate the function of the proteins by which they associate (Perego et al., 1999; Kato et al., 2006). PDZ protein PDZK1 has been shown to interact with urate-anion exchanger URAT1 and hOAT4. Through a yeast two-hybrid screening, *in vitro* binding assay, co-immunoprecipitation and surface plasmon resonance analysis, it was revealed (Anzai et al., 2004) that the wild-type URAT1, but not its mutant lacking the PDZ consensus-binding site, directly interacted with PDZK1. The association of URAT1 with PDZK1 enhanced urate transport activity in HEK293 cells stably expressing URAT1 and co-transfected with PDZK1. The deletion of the URAT1 C-terminal PDZ consensus-binding site abolished this effect. The augmentation of the transport activity was accompanied by a significant increase in the maximum transport velocity $V_{\max}$ of urate transport and was associated with the increased surface expression level of URAT1 protein. By similar analyses as that used in the study of URAT1 and PDZK1 interaction, it was shown (Miyazaki et al., 2005) that OAT4 wild type but not a mutant lacking the PDZ consensus-binding site interacted directly with both PDZK1 and NHERF1 (Na/H exchanger regulatory factor 1). OAT4, PDZK1, and NHERF1 proteins were co-localized at the apical membrane of renal proximal tubules. The association with PDZK1 or NHERF1 enhanced OAT4-mediated transport activity in HEK293 cells stably expressing OAT4 transfected with PDZK1 or NHERF1. Deletion of the OAT4 C-terminal PDZ consensus-binding site abolished this effect. The increased transport activity was accompanied by an increase in maximum transport velocity $V_{\max}$ of estrone sulfate transport, and was associated with the increased surface expression level of OAT4 protein. More interestingly, a recent study by Zhou et al. (Zhou et al., 2008) showed that the interaction between hOAT4 with PDZK1 or NHERF1 and the associated increase in OAT4 activity were only observed in kidney-derived LLC-PK1 cells, but not in placenta-derived BeWo cells. In kidney, OAT4 is expressed exclusively at the apical membrane of proximal tubular cells. while in the placenta, OAT4 localizes at the basolateral membrane of the syncytiotrophoblast. Therefore, the interaction of OAT4 with PDZ proteins such as PDZK1 and NHERF1 might be tissue-specific. In placenta, OAT4 might interact with a different set of proteins rather than PDZK1 or NHERF1.

As mentioned above, Zhang et al. (Zhang et al., 2008b) recently demonstrated that OAT1 underwent constitutive internalization from and recycling back to the cell surface and that activation of PKC inhibited OAT1 activity through accelerating OAT1 internalization. A requisite step for transporter internalization is its interaction with the cellular internalization machinery. So far, three different internalization pathways have been described for other transporters, (i) clathrin-mediated internalization, (ii) caveolae-mediated internalization, and

(iii) clathrin- and caveolae-independent internalization. Clathrin-dependent internalization normally occurs at specialized membrane sites, where a complex structure, called a coated pit, is assembled in order to concentrate surface proteins such as transporters for internalization (Mousavi et al., 2004). During internalization, transporter-containing clathrin-coated pits pinch off from the membrane and move as internalization vesicles into the cytoplasm. Dynamin is the main structural component of the coated pits. Three dynamin isoforms have been identified: Dynamin-1 is exclusively expressed in neurons, dynamin-2 is ubiquitously expressed, and dynamin-3 is expressed in testes and to a lesser extent in neurons and lung. Caveolae-mediated internalization is an alternative to clathrin-mediated internalization (Pelkmans and Helenius, 2002; Williams and Lisanti, 2004). Caveolae are flask-shaped invaginations of plasma membranes of many cell types, rich in cholesterol and sphingolipids as well as a structural protein called caveolin. During internalization, transporter-containing caveolae detach from the membrane and move as internalization vesicles into the cytoplasm. It has been shown that caveolin-1 and caveolin-3 colocalizes with OAT3 and OAT1, respectively, in rat kidney (Kwak et al., 2005a, 2005b). Caveolin-1 was also found to co-localize with OAT4 in primary cultured human placental trophoblasts (Lee et al., 2008). The transport activity of OAT1, OAT3 and OAT4 was up-regulated by caveolin through functional studies in *Xenopus* oocytes or CHO cells. These studies suggest that in addition to the clathrin-dependent pathway through which OAT1 internalizes in COS-7 cells (Zhang et al., 2008b), other pathways such as the caveolae-dependent pathway may also contribute to OAT internalization.

Using a combination of yeast two-hybridization, co-immunoprecipitation and functional assay in tissue slices, Barros et al. (Barros et al., 2009) recently identified atypical PKC ζ as an OAT3-associated protein in the kidney. They further showed that activation of PKC ζ enhanced OAT1 and OAT3 function and that insulin and epidermal growth factor regulated OAT activity through the PKC ζ -mediated pathway. The up-regulation of OAT activity by PKC ζ is in contrast to the down-regulation of OAT1 activity by PKC α (Li et al., 2009). Therefore, it is through these different protein-protein interactions, OAT activity can be either enhanced or inhibited.

3. CLINICAL IMPLICATIONS

Members of the OAT family are known for their broad substrate specificity, including many drugs in clinical use. Therefore, the activity of OATs plays critical roles in determining the therapeutic efficacy and the toxicity of these drugs. Abnormal OAT expression and function have been associated with poor drug/toxin elimination in several pathophysiological conditions. Some of the abnormality in organic anion transport is due to an altered expression of OAT genes and proteins, which was observed in a rat model for ischemic acute renal failure (Schneider et al., 2007; Kwon et al., 2008), and in rat models for cholestasis (Chen et al., 2008), whereas other abnormalities in organic anion transport is due, at least in part, to a redistribution of OAT between the cell surface and the intracellular compartment, which was observed in a rat model for bilateral ureteral obstruction (BUO) (Villar et al., 2005). BUO is a common clinical disease characterized by the development of hemodynamic and tubular lesions. Obstruction of the urinary tract results in adverse effects on renal blood flow, glomerular filtration rate (GFR), tubular function and renal parenchyma

(Dal Canton et al., 1980). A lower renal excretion of PAH was found in BUO rats, which was partly due to a redistribution of OAT1 from cell membrane to intracellular compartments, suggesting a possible enhanced internalization of OAT1. In BUO rat, angiotensin II (Ang II) expression is elevated (Klahr, 1998; Klahr and Morrissey, 2002), and indeed, the recent results by Li et al. (Li et al., 2009) confirmed the inhibition of OAT1 activity by Ang-II treatment in COS-7 cells through the PKC signaling pathway. Therefore, it is likely that Ang II accelerates OAT1 internalization through activation of PKC in BUO rats, which leads to a reduced expression of OAT1 at the cell surface and subsequently, a reduced organic anion transport.

4. CONCLUSIONS

OATs are key players in the body's disposition of a diverse array of environmental toxins and clinically important drugs. Alteration in the function of OATs plays important roles in intra- and inter-individual variability of the therapeutic efficacy and toxicity of many drugs. Although significant progress has been made in understanding the regulation of OATs (Table 1), this is just the beginning. We now know that OATs are subject to regulation by phosphorylation, yet the protein kinase(s) involved in this process has (have) not been identified. We now know that OATs is subject to regulation by membrane trafficking, yet the interaction of OATs with its trafficking machineries has not been fully explored. We now know that OATs exist in a complex with scaffolding proteins and protein kinases, yet the cross-talk between these kinases needs to be elucidated, and more of the OAT-interacting partners are waiting to be discovered. Putting all pieces of the puzzles together about the complicated regulation mechanisms of OATs is a forthcoming mission for future studies of OATs.

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Abbreviations

BUO	Bilateral ureteral obstruction
NHERF1	Na/H exchanger regulatory factor 1
OATs	Organic anion transporters
PDZ	PSD-95/Discs Large/ZO-1
PKC	Protein kinase C

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Fig. 1.

Model for basolateral OAT pathway. SDCT₂: Na^+ -coupled dicarboxylate cotransporter-2. OAT1/3: organic anion transporters 1 and 3. OA^- : organic anion. $\alpha\text{-KG}$: α -ketoglutarate.

Fig. 2.

Predicted transmembrane topology of OAT family. Twelve transmembrane domains are numbered from 1-12. Potential glycosylation sites are denoted by tree-like structures. Potential phosphorylation sites are labeled as "P".

Table 1

Regulation of OATs

Type of regulation	Transporter	Details	References
Glycosylation	OAT1	Disruption of all of the glycosylation sites by mutagenesis results in mOAT1 or hOAT1 trapped in the intracellular compartment without targeting to the plasma membrane.	Tanaka et al., 2004
	hOAT4	Disruption of the glycosylation sites by mutagenesis and the inhibition of glycosylation by tunicamycin treatment results in hOAT4 trapped in the intracellular compartment without targeting to the plasma membrane. Disruption of processing of added oligosaccharides from mannose-rich type to complex type in CHO-Lec1 cells decreases the affinity of hOAT4 for its substrates.	Zhou et al., 2005
Phosphorylation	mOAT1	Promoting phosphorylation of mOAT1 by okadaic acid treatment inhibits mOAT1 transport activity.	You et al., 2000
Membrane trafficking	hOAT1	Activation of PKC by PMA enhances hOAT1 internalization from plasma membrane into endosomes.	Zhang et al., 2008a
Protein-protein interaction	OAT1	Interaction of rOAT1 with caveolin-3 enhances rOAT1 transport activity. Interaction of hOAT1 with PKC ζ enhances hOAT1 transport activity.	Kwak et al., 2005a Barros et al., 2009
	OAT3	Interaction of rOAT3 with caveolin-1 enhances rOAT3 transport activity. Interaction of hOAT3 with PKC ζ enhances hOAT3 transport activity.	Kwak et al., 2005b Barros et al., 2009
	hOAT4	Interaction of hOAT4 with caveolin-1 enhances hOAT4 transport activity. Interaction of hOAT4 with PDZK1 or NHERF1 enhances hOAT4 transport activity.	Lee et al., 2008 Miyazaki et al., 2005, Zhou et al., 2008