

Renal Tubular Drug Transporters

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Key Words

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Abstract

The kidney plays an important role in the elimination of numerous hydrophilic xenobiotics, including drugs, toxins, and endogenous compounds. It has developed high-capacity transport systems to prevent urinary loss of filtered nutrients, as well as electrolytes, and simultaneously to facilitate tubular secretion of a wide range of organic ions. Transport systems for organic anions and cations are primarily involved in the secretion of drugs in renal tubules. The identification and characterization of organic anion and cation transporters have been progressing at the molecular level. To date, many members of the organic anion transporter, organic cation transporter, and organic anion-transporting polypeptide families have been found to mediate the transport of diverse organic ions. It has also been suggested that ATP-dependent primary active transporters such as MDR1/P-glycoprotein and the multidrug resistance-associated protein family function as efflux pumps of renal tubular cells for more hydrophobic molecules and anionic conjugates. Tubular reabsorption of peptide-like drugs such as beta-lactam antibiotics across the brush-border membranes appears to be mediated by two distinct H⁺/peptide cotransporters: PEPT1 and PEPT2. Renal disposition of drugs occurs through interaction with these diverse se-

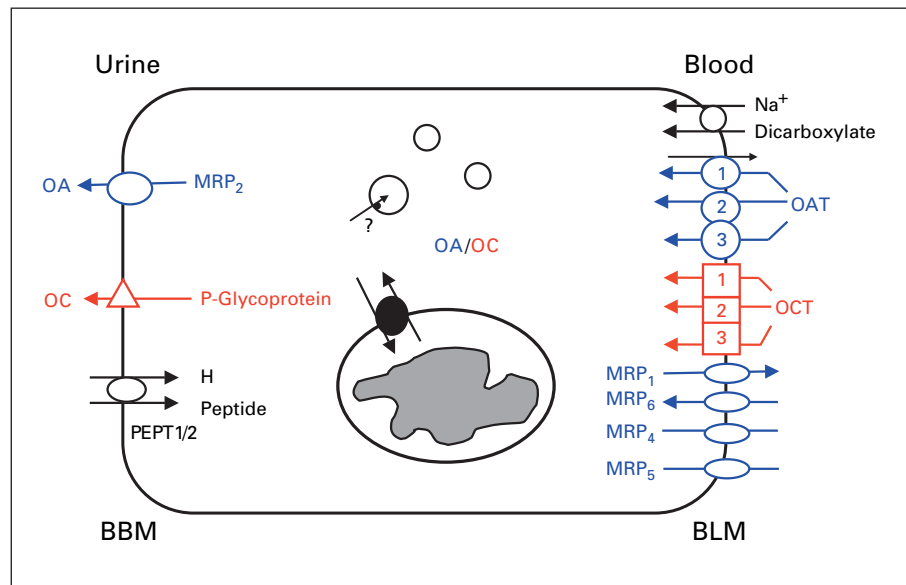
cretory and absorptive transporters in renal tubules. Studies of the functional characteristics, such as substrate specificity and transport mechanisms, and of the localization of drug transporters could provide information regarding the cellular network involved in renal handling of drugs. Detailed information concerning molecular and cellular aspects of drug transporters expressed in the kidney has facilitated studies of the mechanisms underlying renal disposition as well as transporter-mediated drug interactions.

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Introduction

In the early 20th century, Marshal and Vickers [1] and Schmith et al. [2] were the first to demonstrate the renal elimination of drugs with the observation that the phenol red administered as a collyrium was able to colorate urines. The first clinical application of this concept happened soon after World War II with penicillin. During the war, this antibiotic was widely used and physicians had difficulties with maintaining efficient blood levels of the drug because of its high-speed renal elimination. In 1951, probenecid was developed as a competitive inhibitor of penicillin renal secretion and allowed physicians to slacken the antibiotic renal elimination and thus to maintain adequate drug levels for a longer time [3]. In 1988, the racing cyclist Pedro Delgado was proved to use probenecid in order to inhibit the renal secretion and thus the urinary detection of steroids. More recently, probenecid has been used as a nephroprotective therapy against

Fig. 1. Schematic model of organic anion and cation transporters in renal proximal tubule. Uptake of organic anions (OA) across the basolateral membrane (BLM) is mediated by the classic sodium-dependent OAT system, which includes -ketoglutarate (-KG2)/OA exchange via the OAT1 and sodium-ketoglutarate cotransport via the Na⁺/dicarboxylate cotransporter. The apical (brush-border) membrane (BBM) contains various transport systems for efflux of OA into the lumen or reabsorption from lumen into the cell. The multidrug resistance transporter, MRP2, mediates primary active luminal secretion. Cellular uptake of organic cation (OC) across the BLM is mediated by organic cation transporters (OCT) such as OCT1, OCT2 and OCT3. Exit of cellular OC across BBM is mediated by P-glycoprotein. PEPT1 and PEPT2 mediate luminal uptake of peptide drugs.



cidofovir renal tubular toxicity since it had been shown to inhibit the entry of cidofovir into the tubular cell [4]. This short story describes well that drugs are actively secreted into renal tubules, via transporters, and that several molecules may interact at this level.

There are many renal tubular drug transporters (RTDT). They belong to different families among which the main ones are the organic anion transporters (OATs) and the organic cation transporters (OCTs) families [5, 6]. Those transporters are expressed on both sides of the renal tubular cells. However, it is considered that OATs are mainly expressed on the basolateral membrane whereas OCTs are for the most of them found on the brush-border apical membrane. OATs thus carry drugs from the blood into the renal tubular cells (RTCs) and OCTs efflux the drug from inside the cells into the tubular lumen [7–9]. The localization of these transporters was made possible by the molecular characterization of OATs and OCTs that have been performed during recent years [10–13]. Other transporters families also exist such as the P-glycoprotein (Pgp) family and the multidrug-resistant associated proteins (MRP) [16, 17]. Furthermore, some peptide-like drugs such as betalactamines are known to be secreted and reabsorbed in renal tubules [18]. The reabsorption of these drugs happens through oligopeptidic transporters on the brush-border apical membrane of RTCs [18].

Those active secretion and/or reabsorption mechanisms are responsible for a significant part of drug excretion.

Alterations of this equilibrium between blood-into-cell and cell-to-lumen transports may result in intracellular accumulation of the drug that may in turn result in local toxicity. Furthermore, drug-drug interactions on one or several transporters may have similar consequences such as renal toxicity or systemic accumulation depending on which transport occurs the interaction. We thus herein review the data published in the international literature on RTDT.

Organic Compounds and the Kidney

The kidney is principally an excretory organ for drugs and their metabolites and has developed high capacity transport systems to rapidly eliminate the large quantities of foreign compounds delivered to it. To do so, filtration through the glomerular membrane is the main mechanism for drug and metabolites excretion into the urine. However, those compounds may also be excreted from the blood into the lumen of renal tubules via a transcellular active transport. Indeed, specific and selective transporters for organic cations and anions at the contraluminal and luminal membranes of renal tubular epithelial cells, also called basolateral and apical membranes, respectively. Uptake of those compounds is a tertiary active transport process which involves specific structures located on those membranes called ‘drug transporters’ (fig. 1).

Renal Tubular Transport of Organic Anions

The Organic Anion Transporters Family (OATs)

In 1997, the first *p*-aminohippurate (PAH)/dicarboxylate exchanger was isolated from rat kidney and was called OAT1 (rOAT1) by the researchers [19–22]. It is localized on the S2 segment of the proximal tubule, on the basolateral membrane of the cells [21]. OAT1 functional expression in *Xenopus* oocytes allowed identification of some of its substrates such as prostaglandins, cyclic nucleotides, uric acid and folates [19] as well as some xenobiotics such as betalactamine antibiotics [23], nonsteroidal anti-inflammatory drugs (NSAIDs) [22, 24], and antiviral agents [25, 26]. Furthermore, it has been demonstrated that rOAT1 was carrying ochratoxin A from the blood into RTCs thus potentially resulting in intracellular accumulation and toxicity [27].

Four human variants of OAT exist: hOAT1, hOAT2, hOAT3, and hOAT4 [28]. Two subclasses of hOAT1 have been further identified [30–32]. They both are PAH-dicarboxylate exchangers and they have the same affinity for PAH as rOAT1 [29, 31]. However, hOAT1-2 does not transport methotrexate, prostaglandin E2 and urate [31] and its affinities for cidofovir and adefovir are, respectively, 5 and 9 times those of hOAT1-1 [26].

rOAT2 was firstly called novel liver-specific transport protein (NLT) when it was isolated from rat liver. However, their expression remains mainly hepatic, rOAT2 and hOAT2 are also retrieved in the kidney [33, 34].

rOAT3 has been isolated from rat brain. It is, however, widely expressed in the organism and may be retrieved in the liver, the kidney and the eye [35]. Its substrates comprise PAH, ochratoxine A, estrone sulfate, and cimetidine. It is inhibited by probenecid, bumetanide, piroxicam, furosemide whereas guanidine, quinine or tetraethylammonium (TEA) do not appear to interact with it [35]. rOAT3 has been suggested to be involved in organic endogenous and exogenous anions detoxification, mainly on the blood-brain barrier. hOAT3 messenger ribonucleic acid (mRNA) is exclusively retrieved in the kidney [34, 36] and it is located on the basolateral membrane of proximal RTCs [36]. However, whereas hOAT1 expression is limited to S2, hOAT3 is expressed in all segments: S1 > S2 = S3 [36]. Furthermore, hOAT3 has a 20-fold lower affinity than hOAT1 for PAH but its affinity for anionic conjugates such as estrone sulfate, dehydroepiandrosterone (DHEA) and estradiol-17 β -*D*-glucuronide is higher [36, 37]. In patients with chronic renal insufficiency, OAT1 and OAT3 have significant importance since they carry some uremic toxins responsible for

uremic encephalopathy such as indoxyl sulfate (OAT1 and OAT3), 3-carboxy-4-methyl-5-propyl-2-furanpropionate (OAT3), indolacetate and hippuric acid (OAT1) [38].

hOAT4 mRNA is largely retrieved in the kidney [34, 36]. This transporter carries estrone sulfate and DHEA with a similar affinity as hOAT3 [36]. However, its exact localization remains unknown, it has been suggested to be mainly expressed at the apical membrane of RTCs [39].

The main difference between hOAT1 and hOAT2, hOAT3, and hOAT4 is that those latter carry organic anions independently to the sodium gradient. This thus suggests that endogenous ions different from dicarboxylates would exist in RTCs. Potential candidates are reduced glutathione (GSH) or sulfates.

The Organic Anion-Transporting Polypeptide Family (OATPs)

In all species, this subfamily of transporters comprises at least 14 members [40, 41]. OATP1 mRNA has been identified in the liver, the kidney, the brain, the lung, the skeletal muscle and the proximal colon of rats. In the kidney, rOATP1 is expressed at the brush-border apical membrane of the S3 segment of the proximal convoluted renal tubule and in the internal medulla [41, 42]. It has been suggested to participate in the excretion of glucocorticoids and spironolactone. Estradiol-17 β -*D*-glucuronide is one of the OATP1 substrates and it has been suggested that this transporter would be the main efflux route for steroids after conjugation in the tubule [43]. Furthermore, none of the cloned OATP appeared to be homologous to rOAT1 [44, 45] confirming the existence of this subfamily.

Two other OATP transporters have been isolated [46, 47]. OATP2 and OATP3 transport thyroxine and triiodothyrosine. OATP2 further carries digoxin and ouabain.

rOATP2 mRNA is expressed in the central nervous system cells, the retina, and the liver whereas rOATP3 is mainly localized at the apical membrane of RTCs and intestinal cells rather than in the eye [47, 48]. rOATP3 carries biliary acids and, as for rOATP1, it seems that no human form exist [45].

In 1996, one member of the OATP family was characterized and named OAT-K1. It is exclusively expressed in rat kidney at the basolateral membrane of RTCs, and it carries methotrexate independently to sodium, folates

but not PAH, prostaglandin E2 and leucotriene C4 [49]. OAT-K1 mRNA has been retrieved in juxtaglomerular proximal tubules [50]. In cells expressing OAT-K1, some NSAIDs such as ketoprofen competitively inhibit methotrexate transport through this pathway [51]. Other NSAIDs such as ibuprofen or flufenamate but not salicylates are also potent methotrexate OAT-K1 captation inhibitors. These results suggest that this transporter could be one site for drug-drug interaction between methotrexate and NSAIDs.

Another similar transporter (OAT-K2) has been isolated in rat RTCs and in the cortical collecting duct. It exhibits opposite effects compared to OAT-K1 since it facilitates hydrophobic anions captation such as methotrexate, folates and prostaglandine E2. Some other organic anions such as biliary acids, cardiac glycosides and steroids are potent OAT-K2 inhibitors.

The Multidrug Resistance-Associated Protein Transporters (MRPs)

The MRP family is the third subgroup of the ATP-binding cassette (ABC) transporters superfamily. It comprises 13 members (ABCC1 to ABCC13) named MRP (1 to 9), CRTR (cystic fibrosis transmembrane conductance regulator – ABCC7), and SUR1 or 2 (sulphonylurea receptors – ABCC8 and 9) [53].

MRP1 (ABCC1) was the first identified from a multi-resistant Eisai hyperbilirubinemic-resistant (EHBR) lung cancer. Mice homozygote for the gene coding for MRP1 exhibited high susceptibility to drugs [54, 55]. MRP1 mRNA is retrieved from several tissues including the kidney and the transporter is located at the basolateral membrane of Henle's loop and collecting duct cells [57, 58]. MRP1 carries in an ATP-dependent manner different substrates among which are found several conjugated derivatives, sulfates, and GSH [59, 62]. Carrying some non-conjugated drugs necessitates an exchange with GSH [63–65]. As a result, drug-resistance mediated by MRP1 may be counterbalanced by GSH synthesis inhibition [66].

MRP2 (ABCC2) is 48% homologous to MRP1. Formerly named cMOAT (canalicular multispecific organic anion transporter) and located at the apical membrane of hepatic duct cells, it is the main pathway for bile secretion [59]. In the kidney, it contributes to the detoxification of drugs and both endogenous and exogenous compounds, mainly under their conjugated form. It has been located at the brush-border membrane of S1, S2 and S3 segments

of proximal RTCs [58–71]. A lack of MRP2 leads to hyperbilirubinemia in Wistar IR and Sprague-Dawley EHPR rats. In humans, it is related to Dubin-Johnson syndrome [72]. Similarly to MRP1, MRP2 gives cells resistance to some anticancer drugs [73–75]. This is not a unique pathway since some in vitro studies demonstrated that the renal excretion of organic anions was not modified on TR-/EHBR rats proximal RTCs not expressing MRP2. This suggests that other routes may compensate the lack of MRP2 excretion. However, in some pathological situations or during a prolonged exposure to a drug, MRP2 plays an important role in proximal tubule protection. Indeed, MRP2 expression in the kidney, but not in the liver, 8 days following cisplatin administration is increased as compared with the time of administration [76]. Furthermore, subtotal nephrectomy induced a 200% increase in MRP2 mRNA in the remaining kidney [77].

MRP3 (ABCC3, 58% MRP1 homology) is expressed in the liver, the kidney, the small intestine and the colon [78, 79]. In human liver, MRP3 is located at the basolateral membrane of cholangiocytes and hepatocytes around the portal tractus [80, 81]. In the kidney, MRP3 is expressed at the basolateral membrane of distal RTCs [82] and carries glucuroconjugated compounds and other molecules from the internal tubular cell into the blood [83]. In opposition to MRP1 and MRP2, MRP3 has a lower affinity for anionic conjugates and does not carry GSH [80, 84].

MRP4 (ABCC4) mRNA has been detected in some tissues among them the kidney, at the brush-border membrane of proximal RTCs [78, 82]. Similarly to MRP1 and MRP3, MRP4's substrates comprise methotrexate, E2-17 β G and probenecid [85]. It also enhances cell resistance to some antiviral agents such as adefovir and zidovudine [86, 87]. It also seems to play an important role in antiviral drugs renal excretion. MRP4 is also the transporter for cyclic AMP and GMP through an ATP-dependent system and it constitutes the elective excretion pathway for cyclic nucleotides in renal epithelial cells [88–90].

MRP5 (ABCC5) is widely expressed in the organism, including the kidney [78, 91]. It is located at the basolateral membrane and carries GSH [92]. It is not known to induce cell resistance to anticancer drugs [91]. However, some resistance to adefovir, 6-mercaptopurine and thio-guanine have been identified [92]. It also carries some cyclic nucleotides [93–95].

MRP6 (ABCC6) is a particular member of this family since only one substrate has been identified to date, BQ123 an endothelin antagonist, which is not a substrate

of other MRPs [96]. It is expressed in the kidney, at the basolateral membrane of proximal RTCs and in the liver [78]. Recently, some mutations have been noticed on the gene coding for MRP6 in patients with pseudoxanthoma-elasticum (PXE) [97, 98]. The PXE phenotype is characterized by alterations (calcifications) in the eye and the cardiovascular system but MRP6 was not expressed in those tissues [98]. It has thus been suggested that the loss of functional MRP6 in the kidney and the liver could induce the phenotype observed in PXE patients.

MRP7 (ABCC10) MRP8 (ABCC11) and MRP9 (ABCC12) have been recently identified and they do not seem to be expressed in the kidney [99].

Renal Tubular Transport of Organic Cations

The Organic Cations Transporters Family (OCTs)

In the kidney, OCTs play an important physiological and pharmacological role in the reabsorption and/or the secretion of endogenous and exogenous cationic compounds: choline, dopamine, epinephrine, histamine, TEA, cimetidine, procainamide, and quinidine, for example. They are mainly expressed in the proximal renal tubule and in the collecting duct [100–102].

The first identified was rOCT1, by Grundemann et al. [103] in 1994 on rats kidney. rOCT1 mRNA was detected in proximal tubules, glomeruli and collecting ducts but not in distal tubules. Immunohistochemical analysis revealed that it was localized at the basolateral membrane of proximal RTCs of S1 and S2 segments, in the intestinal wall and in the liver [103]. Human OCT1 is composed of 554 amino acids and has 78% homology with rOCT1. Its mRNA has been only detected in the liver [104].

rOCT2 is 67% homologous to rOCT1. rOCT2 mRNA has been mainly detected in the kidney and not in the liver, the lung or the intestine. In renal cortex, rOCT2 mRNA has been retrieved in proximal and distal tubules.

The mRNA of the third member (rOCT3) is largely expressed in placenta and moderately in intestine, heart and brain. Its renal and pulmonary expression is weak and it is not retrieved in the liver.

Three other members of the OCT family named hOCTN1, hOCTN2 and hOCTN3 have been cloned [105–107]. hOCTN1 mRNA has been retrieved in large amounts in kidney, trachea, bone marrow, fetal liver, and in some tumoral human cells. It has not been identified in adult human liver. Its activity depends on the pH. It is greater when pH is neutral or alkaline and weaker when pH is acid [108]. hOCTN1 may be inhibited by com-

pounds including drugs such as cimetidine, propianamine, quinidine and dopamine. However, the functional role of hOCTN1 in the renal excretion system remains unknown. hOCTN2 is 76% homologous to hOCTN1. It is expressed in kidney, trachea, spleen, bone marrow, skeletal muscle, heart, and placenta in adult humans. It has been reported that hOCTN2 could carry carnitine and that a mutation on the gene coding for this transporter could be responsible for a primary systemic carnitine deficit which is an autosomal-recessive disease characterized by low plasma and intracellular carnitine concentrations [109–111]. Very recently, hOCTN3 has been identified in patients presenting with Crohn's disease [112].

MDR1/P-Glycoprotein (P-gp)

MDR1/P-gp is the second subgroup (ABCB) of the ABC superfamily. Those transporters facilitate the active excretion of drugs such as alkaloids, anthracyclines, steroids, cyclosporine, tacrolimus and other hydrophobic organic cations from inside to outside a cell [113]. In the kidney, P-gp is expressed at the brush-border apical membrane of proximal RTCs. It acts like an effluent pump from inside the renal cell into the collecting duct [15]. More than 20 P-gp polymorphisms have been described to date. Among them, only two have been related to clinical effects (C3435T and 2677G). In those cases, the decrease in P-gp expression resulted in reduced digoxin and tacrolimus clearances [114]. Furthermore, the C3435T P-gp polymorphism has been associated with an increase risk for developing renal epithelial tumors [115]. However, transplant recipients patients with this polymorphism seem to be at a lower risk for femoral head fractures [116].

Transport of Peptides

Peptides (PEPT) carry di- and tripeptides in epithelial renal and intestinal cells. Some studies performed on small intestine cells and proximal RTCs demonstrated that this transport was located at the brush-border membrane and that it was dependent on the hydrogen gradient. In addition, those transporters play a role in oligopeptides absorption and they are thus important in preserving the proteic nutrition [117]. There are two PEPT in humans: PEPT1 and PEPT2 with 50% homology. In rats, rPEPT1 is localized at the brush-border membrane of S1 RTCs and at the brush-border intestinal cells [119]. Contrarily, rPEPT2 has been retrieved at the brush border of S3 RTCs [118]. PEPT1 and PEPT2 substrates com-

prise some anticancer drugs [120–122], angiotensin-converting enzyme inhibitors [123, 124], and betalactam antibiotics [124–127]. Aminopenicillins and anionic cephalosporines without an α -amine radical are efficient cellular inhibitors of rPEPT1 [128]. Other betalactamines such as cefalexin, cefadroxine and cefradine are weak PEPT1 inhibitors. Contrarily, rPEPT2 has greater affinity for these antibiotics. Astonishingly, valacyclovir, which is not a peptide, has also been shown to be transported by PEPT with a higher affinity for rPEPT2 [129]. However, the real participation of PEPT in the transport of drugs remains to be studied.

Other Transports

Renal tubular secretion of drugs is a very active field of research. Investigations are ongoing on different aspects of those mechanisms such as other transporters (NPT1) or particular regions where protein-protein interactions occur (PDZ domains).

PDZ Domains

PDZ domains are responsible for the stabilization and regulation of proteic linkage. At least three domains have been identified in the proximal tubule [130, 131]. Their role in drug transport has not been clearly elucidated yet.

Type 1 Sodium/Phosphate Co-Transport (NPT1)

NPT1, also named Na-PI-1, belongs to the sodium/phosphate transporters. It is expressed at the brush-border apical membrane of RTCs [132]. Mice and human NPT1s are known to transport different organic anions via chloride-dependent systems [133–135]. Some differences exist between species. For example, human NPT1 transports PAH whereas rabbit NPT1 does not [133].

Clinical Consequences of Drug-Drug Interactions on Transporters

Renal OATs and OCTs play a major role in the excretion of drugs and their metabolites. Alterations in their expression and/or activity as well as competition between several drugs substrate of the same transporter may induce significant modifications of their pharmacokinetics. Clinical consequences may be significant.

It is well-known that probenecid inhibit the renal secretion of some anionic drugs via OAT. For example,

ciprofloxacin serum concentrations increase when this drug is associated with probenecid [136].

Cimetidine and trimethoprim are potent inhibitors of the renal tubular secretion of some cationic compounds such as procainamide and its active metabolite N-acetylprocainamide. The toxicities of the latter are increased when those drugs are associated [137]. Similarly, H₂-antagonists such as ranitidine may inhibit triamterene renal excretion, potentially resulting in an increased toxicity [137].

Digoxin has often been associated with drug-drug interactions resulting in toxicities that may be severe. The responsibility of renal drug transporters has been early evocated and P-gp has been suggested to be the site of interaction for digoxin and quinidine [138]. Furthermore, clarithromycin, which is a potent inhibitor and/or a substrate of P-gp, may reduce digoxin excretion and thus increase its intracellular and systemic accumulation [139, 140].

Finally, the main clinical application of drug-drug interactions on renal tubular drug transporters consists of associating probenecid with other treatments in order to enhance or prolong their activity (penicillins) [141] or to protect the kidney from their local toxicity (cidofovir) [142, 143]. For the latter, it is recommended that probenecid 2 g orally should be administered 3 h prior to infusing cidofovir and 1 g orally should be given at 2 and 8 h after the end of cidofovir infusion. For penicillins, the usual dose in adults is 2 g daily orally in divided doses.

Conclusion

Renal tubular transporters play an essential role in drug urinary excretion. As a result, any alteration of their expression and/or activity may influence drugs pharmacokinetics as well as their tolerance and efficacy profiles. Such modifications may result from gene polymorphism as demonstrated for carnitine. However, such alterations may also occur during the course of a disease. That is the case in patients with chronic renal insufficiency for which Laouari et al. [100] reported an overexpression of MRP2 in the kidney and the liver without any modifications on P-gp. Those modifications have not been clearly elucidated to date. Further studies are mandatory to determine the substrates of these transporters and the factors that may affect their expression/activity. The pharmacokinetic and clinical consequences of such alterations will also need to be studied.

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