Drug Transporter Function—Implications in CKD

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Drug transporters typically move substrates, including drugs, in an intracellular to extracellular direction and thus are efflux transporters. There is a small subset of transporters that move substrates in the opposite direction and are classified as influx transporters. Collectively, drug transporters contribute to the pharmacokinetic profile of a wide variety of drugs and other molecules including xenobiotics, metabolites, and endogenous solutes. Identification of genetic variants in the genes that encode these transporters is an emerging area of pharmacogenomics. Many polymorphisms of the multitude of genes that code for the transporters within the 2 major superfamilies (ATP-binding cassette transporters and solute carrier transporters) have been identified. Studies have shown that many single-nucleotide polymorphisms are associated with changes in protein expression, functionality, and drug exposure; however, there are limited data for most single-nucleotide polymorphisms and impact on clinical end points. Preliminary data suggest that patients with CKD may have reduced transporter function that may have effects on exposure and toxicity profiles. Additional research translating the functional significance of polymorphisms on clinical pharmacokinetics and relevant disease-specific end points will provide further understanding of the role of genetic variations in transporter genes.

Key Words: ATP-binding cassette transporters, Organic anion transporters, Drug transporters, Pharmacogenomics

INTRODUCTION

Although it has been stated that the estimated glomerular filtration rate is the single best measure of kidney function in patients,[1] there are a multitude of other processes occurring in the nephron that contribute to the overall ability of the kidney to maintain homeostasis of the internal milieu. Specifically, for the purposes of this review, the discussion will focus on providing a general overview of drug transporters in the kidneys (and other relevant sites), which are involved in the secretion and reabsorption of drugs and their metabolites.

The concept that renal clearance of drugs in patients with kidney disease (and thus drug dosing) may involve more than the process of glomerular filtration, and that tubular secretory/reabsorptive capability may decrease in a nonparallel manner, has been recognized for more than 30 years now.[2,3] By quantifying tubular secretion of phenolsulfonphthalein along with creatinine clearance in patients with varying degrees of renal dysfunction, a modified dosing regimen for ampicillin and cephalexin (both extensively secreted in the tubules) was developed. This regimen produced plasma drug concentrations mirroring those in patients with normal renal function as opposed to a regimen based solely on creatinine clearance. This review will discuss the specific drug transporters that have been identified subsequently and the influence of CKD and pharmacogenomics on their function.

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Drug Transporters

Drug transporters are proteins located on barrier epithelial cell membranes throughout the body, including in the kidneys (proximal tubule), liver (hepatocytes), intestines (enterocytes), brain capillaries, choroid plexus cell, and many others (Fig. 1).[4] They play a crucial role in determining the pharmacokinetics of drugs, that is, absorption, distribution, metabolism and excretion, as well as other solutes such as metabolites, toxins, antioxidants, hormones, nutrients, neurotransmitters, and signaling molecules.[5] These transporters generally allow for transcellular movement of drugs either by uptake or efflux activity. Competition for transporter handling by 2 or more drugs/solutes may lead to drug interactions, leading to increased drug toxicity.[5,6]

ATP-Binding Cassette Transporters

There are 2 general families of transporters present in the kidney involved in drug/substrate handling. One family is the ATP-binding cassette (ABC) transporters. There are 49 members of the human ABC transporter superfamily, divided into 7 subfamilies, notated as ABCA to ABCG.[7] ABCB members are denoted as multidrug resistance proteins (MDR), whereas ABCC members are called multidrug-associated resistance proteins (MRPs).

The ABC transporters are mostly drug efflux pumps, which move drugs/solutes against a concentration gradient by using ATP hydrolysis and subsequent phosphorylation to drive active transport. They extrude drugs/solutes out of the cell and into the bile, urine, and intestinal lumen. The following transporters are the best characterized of the ABC transporters in the kidney.

P-Glycoprotein (Pgp, ABCB1, MDR1)

Also known as the MDR1, it is probably the best known and well-studied drug transporter. Tumor cells expressing this transporter were found to be insensitive to some neoplastic agents.[8] It is found in the apical side (luminal) of enterocytes, hepatocytes (canalicular side), and proximal tubule cells (luminal), and many other tissues,

including hematopoietic stem cells, endothelial cells of the blood-brain barrier and more, affecting drug bioavailability and tissue exposure. Thus, the bioavailability of many oral drugs is diminished, and it enables the secretion of drugs and xenobiotics into the bile and urine.

Breast Cancer Resistance Protein (BRCP, ABCG2)

Originally described as a mediator of doxorubicin resistance in the treatment of breast cancer, it is found in the liver, enterocytes, and many other tissues including the proximal tubular cell apical membrane where it causes the efflux of many xenobiotics as well as urate into the tubular lumen.[4,9]

Multidrug-Associated Resistance Proteins (MRP2, ABCC2, and MRP4, ABCC4)

Other efflux transporters located on the apical membrane of proximal tubular cells include MRP2 (ABCC2) and MRP4 (ABCC4) of the ABC superfamily.[4,8]

Solute Carrier Transporters

The second family of transporters that are active in the kidney are the solute carrier (SLC) superfamily of drug/SLCs. The SLC transporters most well characterized in the kidney include members of the SLC22A, SLCO, and SLC47 families.[10] In contrast to the ABC transporters, SLC transporters do not use ATP hydrolysis to drive drug/solute influx/uptake into the cell (although some cause efflux). Rather, they generally drive drug/solute down a concentration gradient across the cell membrane (or against their concentration gradient if coupled with a second solute, which moves down its concentration gradient).

CLINICAL SUMMARY

- Drug transporters are multispecific carriers of drugs, xenobiotics, metabolites, and endogenous solutes that mediate intestinal absorption, blood-brain barrier transit, enable hepatic metabolism/biliary secretion and urinary excretion of many substrates.
- Drug transporters are generally classified into 2 superfamilies, namely the solute carrier superfamily and the ATP-binding cassette superfamily.
- Many gene variants and single-nucleotide polymorphisms have been identified for drug transporters, a small proportion of which have been shown to have demonstrable effects of drug disposition clinically.
- More data are needed to translate identification of transporter gene polymorphisms to actionable clinical interventions.

SLC22A Transporters (OATs, OCTs)

Organic anion transporters (OATs) are located on the basolateral membrane (blood side) of the proximal tubule cells and are part of the SLC22A family.[10] They act to cause an influx of anionic drugs/substrates (and some cations) from the blood into the proximal tubule cell in exchange for dicarboxylates (α-ketoglutarate), which leads to eventual anion extrusion across the apical membrane.[11] Principal members of this family include OAT1 (SLC22A6) and OAT3 (SLC22A8).[10] OAT1 transports para-aminohippurate from the blood into the tubular cell, whereas probenecid inhibits OAT1 and OAT3 action, thus interfering with penicillin and uric acid excretion.[12,13] In addition, there is evidence that OAT1 and OAT3 mediate influx of thiazides and loop diuretics into the proximal tubule cell, with subsequent transport into the urine and eventually the loop of Henle and distal tubule, their site of action.[14] OAT1 and OAT3 are also capable of transporting some organic cations, for example, creatinine.[15]

There is also evidence that OAT3 acts to transport the dietary nephrotoxin aristolochic acid into the proximal tubular cell causing Balkan nephropathy.[16] Similarly, mercury conjugates are transported by OAT1 and OAT3, and this uptake can lead to nephrotoxicity.[17]

On the other hand, OAT4 (SLC22A11) is found on the apical membrane and is an efflux transporter of anions into the urine.[11]

OCT2 (SLC22A2) is a cation transporter located on the basolateral membrane, which causes influx of cations into the proximal tubule cell. Of note, it is a transporter of creatinine, allowing for intracellular entry and thus eventual secretion into the tubular lumen.[18]

SLCO Transporters (OATPs)

Organic anion–transporting polypeptides (OATP) such as OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3) are efflux transporters on the basolateral membrane of hepatocytes and are most commonly recognized as mediating hepatocellular uptake of statins from the blood.[10] In addition, OATP1B3 has been shown to be overexpressed in some tumor types (eg, prostate, lung, and so forth) and is a transporter of several antineoplastics (paclitaxel, docetaxel, irinotecan), which may influence therapeutic efficacy.[10] OATP4C1 (SLCO4C1) is located on the basolateral membrane of proximal tubular cells.

SLC47 A Transporters (MATEs)

Multidrug and toxin extrusion proteins (MATEs) such as MATE2K (SLC47A2) are present in the proximal tubular cell on the apical surface. They exchange luminal H+ ions with cations resulting in urinary excretion of drugs and endogenous solutes.[11] Examples of these substrates include creatinine (subsequent to OCT2-mediated influx)[19] and metformin.[20]

Transporters and Their Substrates

Drug transporters have been called multispecific drug transporters since they are typically capable of transporting more than one specific substrate (Table 1).[4] There are many varieties of substrates handled by transporters including drugs, drug metabolites, xenobiotics, endogenous metabolites (including uremic toxins), nutrients, microbiome products, bile salts, neurotransmitters, hormones and others. This multispecificity of drug transporters can lead to drug interactions, which may be beneficial (penicillin and probenecid) or detrimental (methotrexate and nonsteroidal anti-inflammatory drugs).[21] In addition, oftentimes drugs are handled by