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Endocrine and Metabolic Regulation of Renal Drug Transporters

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Abstract

Renal xenobiotic transporters are important determinants of urinary secretion and reabsorption of chemicals. In addition to glomerular filtration, these processes are key to the overall renal clearance of a diverse array of drugs and toxins. Alterations in kidney transporter levels and function can influence the efficacy and toxicity of chemicals. Studies in experimental animals have revealed distinct patterns of renal transporter expression in response to sex hormones, pregnancy, and growth hormone. Likewise, a number of disease states including diabetes, obesity, and cholestasis alter the expression of kidney transporters. The goal of this review is to provide an overview of the major xenobiotic transporters expressed in the kidneys and an understanding of metabolic conditions and hormonal factors that regulate their expression and function.

Keywords

kidney; transporter; diabetes; pregnancy; obesity; gender; sex hormones; cholestasis

INTRODUCTION

While some chemicals enter and exit cells by passive diffusion, others require carriers or transport proteins. Transporters are membrane-spanning proteins that assist in the uptake and efflux of a large variety of compounds into and out of the cell, respectively. Transporters are widely distributed throughout the body and have an affinity for a range of substrates including endogenous compounds and xenobiotics. Because of their location in the plasma membrane, broad substrate specificities, and diverse patterns of tissue distribution, transporters are essential proteins that influence the disposition of endogenous and exogenous substrates.

Two superfamilies of transporters are recognized in humans and rodents: the solute carrier (SLC) and ATP-binding cassette (ABC) families (Table 1). The SLC family predominantly consists of uptake transporters, but there are some examples of SLC proteins with efflux and bidirectional transport activity. SLC proteins translocate substrates by either secondary or tertiary active transport. Secondary active transport couples the movement of a substrate to a co-substrate (such as an ion), whereas tertiary active transport requires coordinated transport by multiple membrane proteins including an ATPase pump. Transporters that are members of the SLC family include organic anion transporters (Oats/OATs), organic cation

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transporters (Octs/OCTs), organic anion transporting polypeptides (Oatps/OATPs), organic cation/carnitine transporters (Octns/OCTNs), glucose transporters (Gluts/GLUTS) and peptide transporters (Pepts/PEPTs), along with multidrug and toxin extrusion transporters (Mates/MATEs). While most of these transporters are responsible for the influx of chemicals, Oatp1a4 mediates the bidirectional transport of chemicals in exchange with gluthathione (1). Similarly, Mate transporters utilize an antiport mechanism to efflux cationic drugs using energy from proton exchange (reviewed in (2)). Lowercase letters denote rodent species and uppercase letters refer to human isoforms. The ABC family consists exclusively of efflux transporters that require energy liberated from ATP hydrolysis to actively translocate substrates against concentration gradients, a process called primary active transport. Members of the ABC family include multidrug resistance-associated proteins (Mrps/MRPs), multidrug resistance proteins (Mdrs/MDRs), and the breast cancer resistance protein (Bcrp/BCRP).

Transport systems are abundant within the kidneys and facilitate the movement of toxicants and drugs from the blood to the urine (tubular secretion) and from the urine to the blood (tubular reabsorption). To accommodate transcellular movement of substrates, SLC and ABC transporters within the epithelial lining of proximal tubules are distributed on the apical (or brush border) membrane facing the tubule lumen and the basolateral membrane facing the peritubular capillaries and interstitium (Figure 1).

Work has been done to identify specific kidney transporters and their physiological roles in renal function. Additionally, multiple laboratories have elucidated the involvement of renal transporters in the disposition and urinary clearance of drugs and toxins. In recent years, research on transporters has begun to focus on regulatory mechanisms involved in their expression and function. Described below are key features of each transporter family, including localization within the kidneys and substrate profiles. Additional attention is placed upon a variety of regulatory mechanisms that alter SLC and ABC transporter expression and function, including gender and hormonal regulation as well as metabolic conditions such as diabetes, obesity, and cholestasis.

EXPRESSION AND REGULATION OF DRUG TRANSPORTERS

SLC Transporter Families

Organic Anion Transporters—Organic anions are removed from the systemic circulation by the kidneys through glomerular filtration and/or tubular secretion in part by the organic anion transporters (Oats/OATs). Within the *SLC22* family, the OATs (humans) or Oats (rodents) are a subfamily with seven members that differ in species and tissue distribution as well as substrate specificity. Five of these members (Oat1-5/OAT1-5) along with Urat1/URAT1 are strongly expressed in the kidneys. These transporters are found on both the apical and basolateral membranes of proximal tubule cells (3-10). Of note, OAT4 is expressed in human kidneys (11) but not in mouse kidneys. As organic anion/dicarboxylate exchangers, Oat/OAT transporters facilitate the uptake of substrates including *p*-aminohippurate (PAH), cyclic nucleotides, uric acid, and prostaglandins as well as antibiotics (cephaloridine), antivirals (cidofovir, tenofovir, adefovir), toxins (ochratoxin A), and antineoplastics (6,12-15). The substrates of Oat transporters include not only anionic compounds but also some cationic chemicals such as cimetidine and 1-methyl-4-phenylpyridium (MPP) (16) and the zwitterion trigonelline (17).

Organic Anion Transporting Polypeptides—Similar to the Oat family of transporters, the organic anion transporting polypeptides (Oatp/OATP) facilitate the influx of a number of organic anionic compounds such as bile acids, drugs (rifampin and digoxin), toxins (ochratoxin A), xenobiotic conjugates, and thyroid hormones (reviewed in (18)). In the

SLCO family, there are 11 human, 13 rat, and at least 11 mouse isoforms of the Oatp/OATP transporters (19). Numerous mouse Oatp mRNA isoforms have been identified, but only a few are expressed in the kidneys. Mouse renal Oatp transporters include Oatp1a1, 1a6, 2b1, 3a1, and 4c1 (20). Human isoforms of these transporters often differ from rodents in their tissue distribution. For instance, mouse Oatp2b1 mRNA is strongly expressed in kidneys (20) whereas human OATP2B1 is predominantly expressed in the liver (21). Therefore, when studying Oatp transporters in mice, it is crucial to take species differences into consideration when extrapolating to humans.

Organic Cation Transporters—Members of the *SLC22* family of transporters that enable the uptake of cationic compounds belong to the organic cationic transporter (Oct/OCT) family, of which there are three members. Like other SLC families, Oct1-3/OCT1-3 overlap in tissue distribution and substrate specificity. Each member of the Oct/OCT family is abundantly expressed in the kidneys (22-25). Expressed on the basolateral membrane of proximal tubule cells (26,27), Oct/OCT transporters facilitate the electrogenic uptake of substrates including antivirals (lamivudine and zalcitabine) as well as the antidiabetic drug metformin, antihypertensives, and neurotransmitters and the prototypical cations tetraethylammonium (TEA) and MPP (28-31).

Organic Cation/Carnitine Transporters—The organic cation/carnitine transporters (Octn/OCTN) are also members of the *SLC22* family and enable the uptake of cationic compounds as well as carnitine. Octn1/OCTN1 and Octn2/OCTN2 are highly localized to the apical membrane of the proximal tubules (32-34). Members of the Octn/OCTN family act as proton/organic cation antiporters or simple organic cation uniporters, which influx carnitine, TEA, pyrilamine, quinidine, and verapamil (35,36).

Multidrug and Toxin Extrusion Transporters—The SLC transporter class is mostly comprised of uptake carriers with the exception of the multidrug and toxin extrusion transporters (Mate/MATE) that belong to the *SLC47* subfamily and participate in the efflux of organic cations from the cell. In rodents, Mate1 mRNA is predominantly expressed in the kidneys, liver, heart, as well as placenta (rats only) (37,38). In humans, MATE1 mRNA is found abundantly in the kidneys, liver, and skeletal muscle, with lesser amounts in the heart, and no expression in placenta (39). In contrast, rodent Mate2 is found only in the testes while human MATE2/MATE2-K is found in the kidneys (37,39). Both Mate1/MATE1 and MATE2 are expressed on the apical membrane of renal proximal tubule cells (32,39). In order to transport substrates such as TEA, metformin, MPP, cimetidine, cephalexin, acyclovir, and anticancer drugs (oxaliplatin, topotecan), Mate transporters exchange protons for organic cations using energy generated from antiport transport (38-41).

Peptide Transporters—Additional members of the SLC family that influence renal chemical transport include the peptide transporters (Pept/PEPT) that facilitate the uptake of di- and tripeptides (42,43). Members of the *SLC15* subfamily, both Pept1/PEPT1 and Pept2/PEPT2 are ubiquitously expressed with high levels in the kidneys of rodents and humans. Pept1/PEPT1 has been identified along the apical surface of the S1 segment of proximal tubule cells whereas Pept2/PEPT2 is found on the S3 segment (44-46). The Pept/PEPT transporters utilize proton/peptide cotransport to transport substrates including valacyclovir, valganciclovir, and beta-lactam antibiotics (45,47-49).

Glucose Transporters—In addition to Urat1, the glucose transporter (GLUT) 9 (*SLC2A9)* is also involved in urate homeostasis in the liver and kidneys of mice (50) and humans (reviewed in (51)). In the kidneys, mouse Glut9 is expressed on the apical and basolateral membranes of distal tubules, and to a lesser extent proximal tubules (50).

Overexpression of GLUT9 in oocytes from *Xenopus* frogs demonstrates that GLUT9 mediates the efflux of urate using voltage-driven facilitated transport (52). Mice lacking Glut9 expression exhibit hyperuricemia, hyperuricosuria, and mild renal insufficiency (50).

ABC Transporter Families

Multidrug Resistance Proteins—Members of the ABC class of transporters participate in the active efflux of chemicals from renal tubules. ABC transporters possess ATP-binding domains that bind and hydrolyze ATP to remove substrates from cells. The first family of ABC transporters identified was the *ABCB1* family and included the multidrug resistance proteins (Mdr/MDR) or P-glycoprotein. There are several members of the Mdr/MDR transporters including human MDR1 and MDR3 and the rodent orthologs Mdr1a/Mdr1b and Mdr2, respectively. Of these transporters, only Mdr1b/MDR1 is highly expressed in the kidneys (53,54). Substrates of MDR1 include anticancer drugs (vinblastine, doxorubicin, paclitaxel), antihyperlipidemic drugs, digoxin, verapamil, and colchicine (55-61).

Breast Cancer Resistance Protein—An additional ABC transporter encoded by the *ABCG2* gene was identified in a human breast cancer cell line resistant to the anticancer agent mitoxantrone and thus was named the breast cancer resistance protein (Bcrp/BCRP) (62). Soon after its initial discovery in breast cancer cells, the Bcrp/BCRP transporter was identified in other tumor types and found to be ubiquitously expressed in normal tissues, including the apical membrane of proximal tubules (63). BCRP transports numerous substrates such as anticancer drugs (mitoxantrone, doxorubicin, daunorubicin, topotecan, imatinib), miscellaneous pharmaceuticals (albendazole, prazosin, and nitrofurantoin), and sulfated conjugates of estrogens, genistein, and biochanin A (62-70).

Multidrug Resistance-Associated Proteins—The *ABCC* subfamily encodes the multidrug resistance-associated proteins (Mrp/MRP). Similar to their related ABC members, the Mrp/MRP family confers chemoresistance to multiple substrates. There are nine members in the MRP family, but only six (Mrp1-6) are expressed in mouse kidneys (71). Mrp3/MRP3 and Mrp6/MRP6 are basolaterally-located whereas Mrp2/MRP2 and Mrp4/MRP4 are apically-located within proximal tubules and some other kidney cell types (72-79). Mrp proteins transport substrates such as cephalosporin antibiotics, diuretics (furosemide), PAH, glutathione conjugates and free glutathione, glucuronide conjugates, chemotherapeutics (vincristine, cisplatin, methotrexate, and daunorubicin), and endogenous molecules (urate, leukotrienes, cyclic nucleotides, bilirubin glucuronides, and bile salts) (73,80-87) and are reviewed in (88,89).

Endocrine and Metabolic Regulation of Renal Transporter Expression and Function

Diabetes and Obesity—Since renal transporters play an important role in nutrient, toxin, and drug disposition, altered expression in disease states can change pharmacokinetics and susceptibility to adverse effects. Diabetes affects over 350 million individuals worldwide (90). Hyperglycemia resulting from diabetes has significant effects on the kidneys causing glomerular structural changes, increases in extracellular matrix of the mesangium, tubular atrophy, and expansion of basement membranes (91). Patients with diabetes produce higher amounts of urine, and in some cases, greater clearance of drugs. Research has begun to characterize the influence of diabetes on renal transporter expression. Initial studies exploring the effect of Type I (insulin-dependent or juvenile) diabetes (TID) on renal drug handling demonstrated altered renal transport of specific organic cations and anions. The clinical features of TID including hypoinsulinemia and hyperglycemia can be recapitulated in rodents using streptozotocin (STZ). STZ accumulates in the pancreas and causes selective destruction of beta islet cells (92). In renal cortical slices and proximal tubule cells isolated from male rats with STZ-induced TID, the cellular accumulation of the organic cation ^{14}C-

TEA was reduced in comparison to non-diabetic rats (93). Lower cellular levels of ^{14}C-TEA in diabetic kidney slices and proximal tubule cells suggested down-regulation of organic cation transport. Administration of insulin to TID rats restored ^{14}C-TEA accumulation in kidney slices and proximal tubule cells, suggesting preservation or up-regulation of organic cation transporters (93).

Additional mechanistic work by the same group focused on transporter expression in renal cortical slices from STZ-treated diabetic male rats. Protein expression of Oct1 and Oct2 was significantly decreased in kidneys of TID rats in comparison to non-diabetic controls and returned to normal levels following insulin treatment (Table 2) (94). Down-regulation of basolaterally-located Oct1 and Oct2 transporters during diabetes translates to reduced organic cation transport across proximal tubule epithelial cells (93,94). Subsequent work implicated glycation of Oct proteins as a mechanism for reduced expression and function in TID rats (95). In addition to reversal of Oct down-regulation by insulin, treatment of diabetic rats with the angiotensin converting enzyme inhibitor, ramipril, also preserved Oct1 and Oct2 protein expression and function possibly by altering angiotensin II signaling (96). Similarly, treatment of TID patients with a related drug, perindopril, preserves tubular organic ion clearance (97).

Expression and/or function of other transporters have been assessed in STZ-treated rodents (Table 2). Rats treated with STZ show increased expression of Mdr1b mRNA (but not protein) as well as Pept1 protein (98-101). Recently, Quezada et al. demonstrated up-regulation of Mrp1 expression and function in isolated glomeruli from STZ-treated rats (102). There were similar increases in Mdr1 levels in glomeruli although this did not translate to changes in function.

Type II diabetes (TIID), or noninsulin-dependent diabetes, is more prevalent than TID and is associated with impairment of insulin secretion as well as reduced insulin sensitivity of peripheral tissues. Because the incidence of TIID is increasing in Western countries, it is important to also investigate how this disorder influences renal transporter expression and/or function. Three rodent models have been used to recapitulate various clinical features of TIID such as increased food consumption and altered body composition, weight gain, hyperglycemia, and hypoinsulinemia. These models include ob/ob (obese) mice, db/db (diabetic) mice, and rats fed a high fat diet and administered a low dose of STZ (Table 2). Ob/ob and db/db mice have deficient leptin and leptin receptor signaling, respectively. In addition to excessive weight gain, ob/ob mice exhibit a 2.5-fold increase in circulating glucose levels (103). Analysis of kidney transporters in ob/ob mice revealed decreased mRNA and protein expression of Mrp3 in female mice, decreased Oatp1a1 and Oat2 mRNA expression, and increased Mrp4 mRNA and protein expression (103). In addition, the kidneys of ob/ob mice have increased expression of Bcrp, Urat1, and Glut9 protein and trends for elevated Bcrp and Glut9 mRNAs (104). This pattern of transporter regulation would favor enhanced secretion and reduced reabsorption of organic anions in TIID. Db/db mice are used as an alternate model of TIID because they also exhibit hyperglycemia, hyperlipidemia, and weight gain. Db/db mice have reduced expression of Oatp1a1 and Oatp1a6 mRNA as well as lower levels of Oat1, Oat2, and Oct2 mRNA (105). It should be noted that some changes in transporter expression were observed in only male or female db/db mice. For example, female db/db mice have reduced Mrp3 mRNA whereas male counterparts exhibit up-regulation of this transporter (105). The mechanism(s) for gender-divergent regulation of transporters in TIID models is currently unknown.

Dietary models are also used in combination with diabetogenic chemicals to study TIID. In rats fed a high fat diet and administered a single low dose of STZ, protein expression of renal organic anion transporters Oat2, Mrp2, and Mrp4 was elevated (106). In addition, TIID

rats had reduced Oct2 protein levels similar to rats with TID. It is important to note that mice fed a high fat diet (no STZ) exhibit only mild hyperglycemia and relatively constant renal transporter expression, suggesting that disease severity may be critical in transcriptionally regulating ABC and SLC genes (107). When comparing the various rodent models of diabetes, there are some fairly consistent changes in renal transporter expression including down-regulation of Oct2 and up-regulation of Pept1 and Mrp4. There are currently no studies that have investigated the regulation of renal transporters in patients with TIID. Collectively, this work suggests enhanced organic anion secretion and impaired organic cation clearance in rodents with moderate to severely uncontrolled hyperglycemia.

Cholestasis—Cholestasis is a condition of slowed or blocked bile flow within the liver or bile ducts. Cholestasis can result from obstruction of the common bile duct (termed extrahepatic cholestasis) or from altered bile acid handling within the liver (called intrahepatic cholestasis). Extrahepatic cholestasis can result from stones or tumors and is recapitulated in rodents using surgical ligation of the common bile duct. Intrahepatic cholestasis can occur during pregnancy or from genetic disorders in bile acid transporters. Rodent models of intrahepatic cholestasis include feeding with toxic bile acids such as cholic acid or lithocholic acid or administration of chemicals such as alpha-naphthylisothiocyanate (ANIT) or the synthetic estrogen, ethinyl estradiol.

Most research in the field of cholestasis has focused on how defects in hepatobiliary transporters contribute to disease development as well as adaptive changes in transporter expression. Several previously identified bile acid transporters include the sodium taurocholate co-transporting polypeptide (Ntcp), Oatp1a1, and Oatp1b2 which are localized on the sinusoidal membrane and the bile salt export pump and Mrp2 located on the canalicular membrane (reviewed in (108)). Cooperative efforts between sinusoidal and canalicular transporters produce the directional flow of bile acids through hepatocytes and into the bile. When bile flow is impaired or decreased, bile constituents accumulate in the liver and spill over into the circulation. To model the cholestasis phenotype, rodents undergo ligation of the common bile duct (109). Livers from bile duct-ligated rodents have decreased mRNA expression of sinusoidal uptake transporters Oatp1a1 and Oatp1b2 and increases in efflux transporters Mrp1-5 over a 14 day period following surgery (109,110). Similarly, sinusoidal Oct1 protein and hepatic accumulation of TEA are reduced by bile duct ligation, reflecting a reduced uptake of cations into hepatocytes during cholestasis (111). Together, decreased expression of uptake transporters along with up-regulation of efflux transporters appears to be an adaptive mechanism to remove bile acids and other chemicals and protect the liver.

Retrograde transport of bile acids and bilirubin from hepatocytes to circulating blood during cholestasis has been shown to alter expression of transporters in other organs including the kidneys (Table 3). In kidneys from mice that have undergone bile duct ligation, the expression of Oatp1a1 mRNA was reduced and levels of Oatp1a4 and Mrp1-5 mRNA were increased (109). Additional work confirmed Mrp4 mRNA up-regulation as well as Bcrp protein down-regulation in the kidneys of mice during cholestasis (112). Because Mrp4 can transport bile acids, higher levels of this transporter should aid in reducing bile acid accumulation and enhancing urinary excretion (113). Extensive work has been done in bile duct-ligated rats revealing elevated urinary clearance levels of PAH, bile salts, and compounds such as bromosulfophthalein, glucuronidated acetaminophen, and cimetidine (114-119). In response to cholestasis in rats, the kidneys have elevated protein expression of Oct2, Oatp1a1, and Mrp2 (114,116-123). Treatment of rats with ANIT also results in cholestatic liver injury that is accompanied by up-regulation of renal Mrp2 protein and down-regulation of Oat1 and 3 proteins (124). Down-regulation of Oct2 mRNA and protein has also been observed in the kidneys of rats administered a cholestatic dose of ethinyl

estradiol (125). Furthermore, treatment of mice with cholic acid increases the renal expression of Mrp2 and Mrp4 mRNAs which correlates with increased urinary excretion of bile acids (126,127). The regulatory mechanisms underlying transporter regulation in the kidneys of rodents after cholestasis are unknown. Cumulatively, the up-regulation of basolateral uptake carriers and apical efflux transporters may enhance urinary clearance of bile acids and other chemicals. Therefore, renal transporters appear to be regulated in a fashion that would compensate for a loss in biliary secretion by enhancing urinary elimination.

Hormonal Influence: Sex Hormones, Growth Hormones, and Pregnancy—It is becoming increasingly evident that hormonal signaling is important in regulating transporters in the kidneys. Renal transporter expression and function has been explored in studies evaluating gender differences, pregnancy, disruption of growth hormone secretion, surgical removal of sex organs (gonadectomy) or the pituitary gland (hypophysectomy), and exogenous administration of hormones. Mechanisms likely involved in hormonal regulation of transporters include the activation of steroid and hormone nuclear receptors. As mechanisms of gene control continue to become better understood, additional levels of transporter regulation by hormones may be revealed.

Sex hormones: As early as 1955, it was demonstrated that the organic anion, PAH, accumulated in rat kidney slices in response to testosterone (128). This work was further supported by pharmacokinetic studies demonstrating comparable clearance of PAH between male and testosterone-treated female rats, which was higher than untreated female rats (129). Likewise, castration of male rats reduced PAH clearance, which could be reversed by administering testosterone (129). Preliminary studies depicting gender-specific patterns of renal transport and potential involvement of sex hormones set the stage for future mechanistic work.

By the 2000s, researchers began to speculate that the expression and/or activity of transporter proteins might explain gender differences in the renal clearance of organic ions. Gender-specific expression patterns have been demonstrated in rodents for many SLC and ABC transporters (Table 4). Messenger RNA and protein expression analysis have revealed rodent Oat1 as a male-predominant transporter and Oat2 and Oat5 as female-predominant transporters (8,130-137). As expected, Oat1 protein expression and uptake of PAH was lower in basolateral membrane vesicles prepared from kidneys of female rats compared to males (138,139). Furthermore, castration of adult male rats decreased Oat1 protein expression in kidney cortex that was reversed by treatment with testosterone (8). These findings suggest that testosterone is a stimulator of Oat1 expression in the kidneys.

Gonadectomy of rats and mice demonstrates that female-predominant Oat2 and Oat5 expression is dependent upon hormonal regulation. The mRNA and protein expression of both transporters are up-regulated in kidneys of castrated males (132,134-137). Moreover, the administration of estrogen to castrated males further increased Oat2 and Oat5 expression. Conversely, testosterone replacement decreases expression to match that of control or sham-operated males (132,134-137). Ovarectomized female rodents experience small reductions in Oat2 and Oat5 mRNA and protein. Treatment of gonadectomized females with testosterone further suppresses Oat5 expression while estrogen supplementation increases expression to that of control females (136). Collectively, data from rodents suggest that testosterone suppresses and estrogen weakly stimulates renal Oat2 and Oat5 expression.

Similar to organic anions, the renal uptake of the organic cation, TEA, occurs at a greater rate in male rats than females suggesting that testosterone may enhance basolateral organic

cation uptake or that estrogens may inhibit this process (140).The organic cation transporter Oct2 is expressed at a higher level in male rodents and rabbits compared to females (22,25,141). It has been suggested that elevated Oct2 levels enhance renal clearance of the nephrotoxicant cisplatin in male rodents (142). Gonadectomy of male rats and mice decreases Oct2 mRNA as well as renal clearance of the organic cation TEA (22,143). With testosterone treatment, renal Oct2 mRNA and protein expression and TEA uptake increase to control male levels while estrogen supplementation has no effect (22,143,144). Thus, gender differences in Oct2 expression have been attributed to testosterone stimulation. Subsequent work investigating a mechanistic link between testosterone regulation and rodent Oct2 expression analyzed the rat Oct2 promoter region and revealed two potential androgen response elements that may be transactivated by testosterone binding to the androgen receptor (145).

Efflux transporters also exhibit gender divergent regulation in the kidneys of mice (Table 4). Mdr1b, Mrp3, and Mrp4 are female-predominant transporter genes in kidneys of C57Bl/6 mice (53,146). Despite this similar gender predominance, different sex hormones are responsible for each of these ABC transporters. Gonadectomy causes Mdr1b and Mrp3 expression to decrease in female mice and increase in male mice. Estrogen treatment increases Mrp3 levels in castrated mice of both sexes whereas testosterone treatment has the opposing response (146). Thus, hormonal regulation of renal Mrp3 is balanced by testosterone (suppression) and estrogen (stimulation) (146). Interestingly, both estradiol and testosterone reduce Mdr1b mRNA in kidneys of gonadectomized male mice (53). In contrast, gonadectomy of male mice increases Mrp4 expression relative to that of female controls (146). While estrogen addition had no effect, testosterone replacement caused Mrp4 expression to decrease to control male levels. Testosterone, but not estrogen, appears to have a suppressive effect on renal Mrp4 expression and explains female-predominant expression of this transporter (146).

When considering gender divergence in transporter expression, it is important to acknowledge that sex differences occurring in one species or strain may not occur in another. Rabbits exhibit similar levels of Oat1 between the sexes, which contrasts with previous studies in rodents that indicated male-predominant Oat1 expression (130,131,133,138,141). Gender expression patterns may also differ between strains. For example, Oat3 mRNA is higher in kidneys of female 129J mice, but not C57Bl/6 mice (131). Considering the potential differences that may exist between species and strains, it is critical to exercise caution when attempting to extrapolate gender differences in transporter expression between species.

Growth hormone: Pituitary growth hormone secretion differs between genders resulting in distinct patterns of gene expression. In male rats, growth hormone is secreted in high-amplitude pulses at regular intervals, with periods of little to no growth hormone in between (147,148). On the other hand, female rats secrete growth hormone more frequently as low-amplitude pulses resulting in continuously detectable levels of hormone (148,149). As early as 1991, it was evident that gender divergent patterns of growth hormone secretion could explain differential expression of hepatic cytochrome p450 enzymes between males and females (130,150,151). As cytochrome P450 enzymes and transporters are often coordinately regulated by similar mechanisms, more recent studies have begun to explore whether growth hormone may participate in these differences. Several methods are used to assess the influence of growth hormone secretion on transporter expression including 1) hypophysectomy, which is the surgical removal of the pituitary that obliterates not only production of growth hormone but also luteinizing and follicle-stimulating hormones and 2) mutant lit/lit mice that have a spontaneous mutation in the growth hormone-releasing hormone receptor that prevents release of growth hormone (152).

The influence of growth hormone on the endocrine regulation of rat renal Oat transporters (male-predominant Oat1 and female-predominant Oat2) has been assessed in hypophysectomized rats in the absence and presence of growth hormone supplementation (130). Messenger RNA expression of renal Oat1 in female rats was unchanged by hypophysectomy, suggesting little to no involvement of growth hormone in regulating this transporter. In contrast, hypophysectomy decreased renal Oat2 mRNA expression in female rats which could be reversed by restoration of growth hormone signaling (130). Based on gonadectomy and hypophysectomy studies, regulation of Oat1 appears to be more sensitive to sex hormone signaling while growth hormone secretion participates in Oat2 predominance in female rats along with sex hormones (130).

Contribution of growth hormone secretory patterns to female-predominant Mrp3 and Mrp4 expression in kidneys of mice was examined using hypophysectomized and lit/lit mice (146). In hypophysectomized female mice, Mrp3 mRNA expression was dramatically reduced. Treatment of these mice with growth hormone did not alter Mrp3 mRNA. Rather, the administration of 17β-estradiol increased Mrp3 expression significantly. These results suggest that female-predominant Mrp3 expression in the kidneys is dependent on sex hormones and not growth hormone (146). In contrast, in hypophysectomized and lit/lit mice, the absence of growth hormone increased Mrp4 mRNA expression in both genders. Testosterone replacement, as well as growth hormone addition (in a male-specific pattern) in hypophysectomized mice caused Mrp4 expression to decrease to levels observed in male control mice (146). Therefore, Mrp4 female-dominant expression is due to repression by testosterone and male-specific growth hormone secretion. Further analysis of the 5' flanking region of the mouse *Mrp3* promoter identified two estrogen response elements potentially responsive to estrogen regulation. Unlike Mrp3, the Mrp4 promoter region contains response elements that are responsive to androgens and growth-hormone secretory patterns suggesting this transporter is regulated by both hormones (146).

Regulation of Oatp transporters in the kidneys of mice is solely dependent upon sex hormones (153). Regulation of male-predominant renal Oatp1a1 and 3a1 transporters has been explored in gonadectomized, hypophysectomized, and lit/lit mice. In gonadectomized male mice, Oatp1a1 and Oatp3a1 mRNA expression was reduced. Treatment with testosterone caused Oatp1a1 and Oatp3a1 to dramatically increase while exogenous 17β-estradiol had no effect, suggesting testosterone acts as a stimulator of male-predominant Oatp1a1 and Oatp3a1 (153). Additional studies demonstrated that Oatp1a1 and 3a1 mRNA expression in male mice is independent of growth hormone signaling since hypophysectomy of male mice reduces renal Oatp1a1 and 3a1 mRNA, which is restored by testosterone but not growth hormone supplementation (153). Male lit/lit mice do have reduced Oatp1a1 mRNA, however growth hormone supplementation has no effect, further confirming a key role for androgens in regulating these two renal transporters. Taken together, individual transporter isoforms can be regulated by sex and/or growth hormones, which allows for different mechanisms to influence renal chemical secretion and reabsorption.

Pregnancy: Pregnancy causes both hormonal (progesterone, estradiol, prolactin, etc) and hemodynamic changes that influence maternal kidney function. Pregnancy-induced renal alterations include elevations in renal plasma flow and glomerular filtration rate resulting in an increased clearance of nutrients, toxins, and drugs (154-157). Studies exploring the influence of pregnancy on renal transport have largely focused on the accelerated excretion of drugs into urine. For instance, urinary elimination of the cardiac glycoside, digoxin, and the antidiabetic drug, glyburide, are elevated during human and rodent pregnancies, respectively (158,159). More recent work has begun to shed light on the role of transporters in pregnancy-induced renal clearance. In a pharmacokinetic study using Bcrp knockout mice and its known substrate glyburide, the absence of apical Bcrp in the kidneys had little to no

effect on the elevated renal clearance of glyburide during pregnancy (158). This was despite a modest increase in renal Bcrp protein expression in pregnant dams (160). This suggested that the glomerular hyperfiltration that accompanies pregnancy may be more important for enhanced glyburide elimination than changes in active tubular secretion. More recent unpublished work from our laboratory demonstrates down-regulation of apical renal transporters (Mrp2, Mrp4, Mate1, Mdr1b) in pregnant mice during mid-gestation that would favor retention of chemicals by the kidney and may in fact be a compensatory mechanism to the hyperfiltration that accompanies pregnancy. Further research is needed in this field to understand how fluctuations in sex hormones during pregnancy might participate in the altered expression of renal transporters.

CONCLUSIONS AND FUTURE PERSPECTIVES

Renal transporters are tubular proteins involved in the secretion and reabsorption of nutrients, drugs, and toxins. Sex hormones, pregnancy, and growth hormone secretory patterns as well as hyperglycemia, obesity, and cholestasis have a variety of effects on renal transporter expression and function. As a result of metabolic and endocrine regulation of renal transport, drug efficacy and toxicity may be altered. Although significant strides in this field have been made, much work is needed to understand the molecular signaling mechanisms as well as relevance between species.

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Non-Standard Abbreviations

Abc	ATP-binding cassette
Bcrp	breast cancer resistance protein
BDL	bile duct ligation
Glut	glucose transporter
HFD	high fat diet
Mate	multidrug and toxin extrusion transporter
Mdr	multidrug resistance protein
Mrp	multidrug resistance-associated protein
MPP	1-methyl-4-phenylpyridium
Oat	organic anion transporter
Oatp	organic anion transporting polypeptide
Oct	organic cation transporter
Octn	organic cation/carnitine transporter
PAH	p-aminohippurate
Pept	peptide transporter
Slc	solute carrier
STZ	streptozotocin

TEA	tetraethylammonium
TID	type I diabetes
TIID	type II diabetes
Urat	urate transporter

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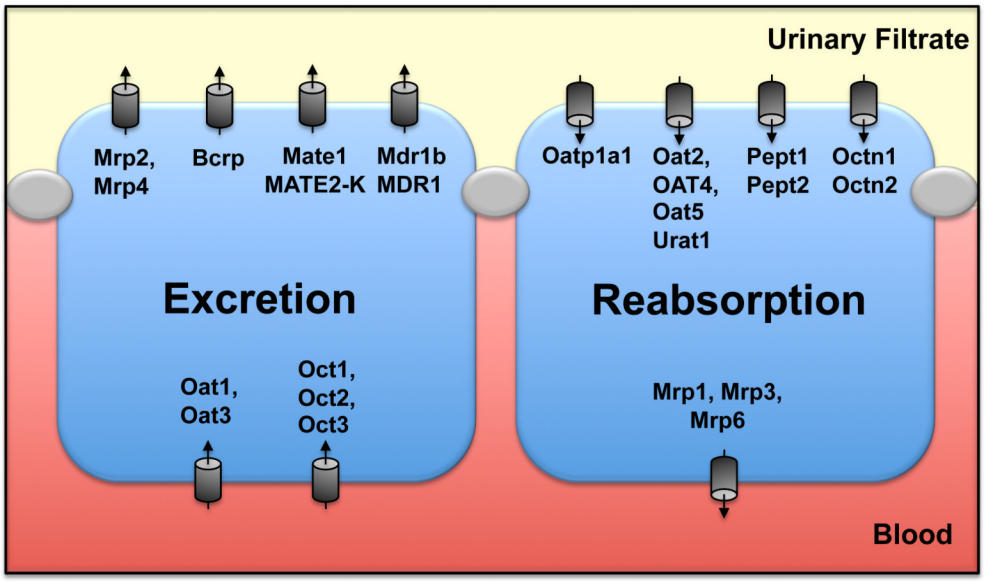

Figure 1. Transporters in kidneys

The tubule cell on the left illustrates the proposed and demonstrated localization of basolateral uptake and apical efflux transporters involved in tubular secretion or excretion. The tubule cell on the right illustrates the apical uptake and basolateral efflux transporters involved in tubular reabsorption. It has been proposed that Oatp1a4, 1a6, 2a1, 2b1, and 3a1 are localized to the luminal surface with Oatp4c1 on the basolateral membrane (136).

Table 1

Transporter nomenclature.[a]

SLC Transporters		*ABC Transporters*	
Gene	**Protein**	**Gene**	**Protein**
SLC22A6	OAT1	*ABCB1*	MDR1 (human), Mdr1a and 1b (rodent)
SLC22A7	OAT2	*ABCB4*	MDR3
SLC22A8	OAT3		
SLC22A11	OAT4	*ABCC1*	MRP1
SLC22A10/19	OAT5	*ABCC2*	MRP2
SLC22A12	URAT	*ABCC3*	MRP3
		ABCC4	MRP4
SLCO1a1	Oatp1a1 (rodent)	*ABCC5*	MRP5
SLCO1A2	OATP1A2 (human)	*ABCC6*	MRP6
SLCO1a4	Oatp1a4 (rodent)		
SLCO1a5	Oatp1a5 (rodent)	*ABCG2*	BCRP
SLCO1a6	Oatp1a6 (rodent)		
SLCO2B1	OATP2B1		
SLCO3A1	OATP3A1		
SLCO4A1	OATP4A1		
SLCO4C1	OATP4C1		
SLCO5A1	OATP5A1		
SLCO6A1	OATP6A1		
SLC22A1	OCT1		
SLC22A2	OCT2		
SLC22A3	OCT3		
SLC22A4	OCTN1		
SLC22A5	OCTN2		
SLC2A9	GLUT9		
SLC15A1	PEPT1		
SLC15A2	PEPT2		
SLC47A1	MATE1		
SLC47A2	MATE2-K (human), Mate2 (rodent)		

[a]The gene and protein names are listed for the solute carrier (SLC) and ATP-binding cassette (ABC) transporters. This is not intended to be a complete list, rather highlights transporters expressed in the kidneys. Transporters with different human and rodent isoforms are indicated.

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Table 2

Transporter expression in kidneys from hyperglycemic and obese rodents.[a]

	Type I Diabetes Models			Type II Diabetes Models		
Model:	STZ	STZ	STZ	Db/Db	Ob/Ob	HFD/STZ
Species:	Rat	Rat	Mice	Mice	Mice	Rats
Tissue:	Glomeruli	Total	Total	Total	Total	Total
Gender:	Male	Male or Female	Female	Male & Female	Male & Female	Male
Uptake						
Oatp1a1	ND	ND	ND	↓(M)	↓	ND
Oatp1a4	ND	ND	ND	ND	ND	ND
Oatp1a6	ND	ND	↔	↓(F)	ND	ND
Oatp2b1	ND	ND	↑	ND	ND	ND
Oatp4c1	ND	ND	↑	ND	ND	ND
Oat1	ND	ND	↔	↓(M)	ND	ND
Oat2	ND	ND	↓	↓	↓	↑
Oat3	ND	ND	↔	ND	ND	ND
Oat5	ND	ND	↓	ND	ND	ND
Urat1	ND	ND	↔	ND	↑ (M)	ND
Glut9	ND	ND	↑ *b*	ND	↑ (M)	ND
Oct1	ND	↓ (M)	↔	↔	ND	ND
Oct2	ND	↓ (M)	↔	↓ (M)	ND	↓
Oct3	ND	↓ (M)	↔	ND	ND	ND
Octn1	ND	ND	↔	ND	ND	ND
Octn2	ND	ND	↔	ND	ND	ND
Pept1	ND	↑ (F,M)	↑	ND	ND	ND
Pept2	ND	↔ (F)	↔	ND	ND	ND
Efflux						
Mate1	ND	ND	↔	ND	ND	ND
Mdr1a	↔	↑ (F)	ND	ND	ND	ND
Mdr1b	↑	↔ (F)	↓↔	↓ (M)	ND	ND
Bcrp	ND	ND	↔	ND	↑ (M)	↔

	Type I Diabetes Models			Type II Diabetes Models		
Mrp1	↑	ND	↑↔	ND	ND	↔
Mrp2	↔	ND	↑↔	↔	ND	↑
Mrp3	ND	ND	↓	↓ (F) ↑ (M)	↓ (F)	ND
Mrp4	↔	ND	↑	↑ (M)	↑	↑
Mrp5	ND	ND	↑	ND	ND	↔
Mrp6	ND	ND	↓↔	ND	ND	ND

[a]The mRNA and/or protein expression of transporters in kidneys of mice or rats after streptozotocin (STZ) treatment alone or in combination with high fat diet (HFD). Studies are also included from transgenic obese (ob/ob) and diabetic (db/db) mice. Species, tissue (either isolated glomeruli or total tissue), and gender (M: male or F: female) are noted. ↑ denotes up-regulation, ↓ denotes down-regulation, and ↔ denotes no change. ND denotes transporter expression that was not determined. Type I diabetes references include (94-96,100-102,161,162). Type II diabetes references include (103-106).

[b]The gender was not included in the Methods of this paper (162).

Table 3

Transporter expression in kidneys from rodents with cholestasis.[a]

Model:	BDL	BDL	ANIT
Species:	Rat	Mouse	Rat
Uptake			
Oatplal	↑	↓	ND
Oatp1a4	ND	↑	ND
Oatp1a5	ND	↑↓	ND
Oatp1a6	ND	↔	ND
Oatp4a1	ND	↑	ND
Oat1	↓↑	ND	↓
Oat3	↑	ND	↓
Oct1	↔↓↑	ND	ND
Oct2	↑	ND	ND
Efflux			
Mate1	↔	ND	ND
Bcrp	ND	↓	ND
Mrp1	↑	↑	ND
Mrp2	↑	↑	↑
Mrp3	↔	↑	ND
Mrp4	↓	↑	ND
Mrp5	ND	↑	ND

[a]The mRNA and/or protein expression of transporters in kidneys of male rats or mice after bile duct ligation (BDL) after varying time points. ↑ denotes up-regulation, ↓ denotes down-regulation, and ↔ denotes no change. ND denotes transporter expression that was not determined. Rat BDL references include (110,111,114-119,122,123). Mouse BDL references include (109,112). The ANIT reference is (124).

Table 4

Sex differences in renal transporter expression between male and female rodents.[a]

Transporter	Mice	Rats	References
Uptake			
Oatplal	M > F	M > F	(153,163,164)
Oatp1a6	M = F	M = F	(163,164)
Oatp2b1	M = F	N.D.	(163)
Oatp3a1	M > F	N.D.	(153,163)
Oatp4c1	M > F	N.D.	(136,163)
Oatl	M > F	M > F	(8,130,131,133,141)
Oat2	F ≥ M	F > M	(130-133,141)
Oat3	F ≥ M[b]	M ≥ F	(8,130,131,133,141)
Oat5	F > M	F > M	(135,136)
Urat1	M > F	N.D.	(136)
Oct1	M = F	F > M	(22,25)
Oct2	M > F	M > F	(22,25,141,144)
Oct3	M = F	M = F	(22,25)
Octn1	M = F	M = F	(22,25)
Octn2	M = F	M = F	(22,25)
Pept1	M = F	M = F	(165)
Pept2	M = F	F > M	(165)
Efflux			
Mate1	M > F	N.D.	(37)
Mdr1b	F > M	N.D.	(53)
Bcrp	M = F	M > F	(166)
Mrp1	M = F	N.D.	(71)
Mrp2	M = F	N.D.	(71)
Mrp3	F > M	N.D.	(71,146)
Mrp4	F > M	N.D.	(71,146)
Mrp5	M = F	N.D.	(71)
Mrp6	M = F	N.D.	(71)

[a]The mRNA and/or protein expression of transporters in kidneys of adult male (M) and female (F) rats or mice. ND denotes transporter expression that was not determined.

[b]Compared to male counterparts, elevated Oat3 mRNA was higher in female 129 J mice, but not female C57BL/6 mice.