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INVITED REVIEW

Gender differences in kidney function

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Abstract Sex hormones influence the development of female (F) and male (M) specific traits and primarily affect the structure and function of gender-specific organs. Recent studies also indicated their important roles in regulating structure and/or function of nearly every tissue and organ in the mammalian body, including the kidneys, causing gender differences in a variety of characteristics. Clinical observations in humans and studies in experimental animals in vivo and in models in vitro have shown that renal structure and functions under various physiological, pharmacological, and toxicological conditions are different in M and F, and that these differences may be related to the sex-hormone-regulated expression and action of transporters in the apical and basolateral membrane of nephron epithelial cells. In this review we have collected published data on gender differences in renal functions, transporters and other related parameters, and present our own microarray data on messenger RNA expression for various transporters in the kidney cortex of M and F rats. With these data we would like to emphasize the importance of sex hormones in regulation of a variety of renal transport functions and to initiate further studies of gender-related differences in kidney structure and functions, which would enable us to better understand occurrence and development of various renal diseases, pharmacotherapy, and drug-induced nephrotoxicity in humans and animals.

Keywords Androgens · Estrogens · Drug transporters · Organic anion transporters · Organic cation transporters · Renal transporters · Sex differences · Sexual dimorphism

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Introduction

Sex hormones are involved in various aspects of reproduction, differentiation, development, growth, and homeostasis. Primarily, sex hormones influence the development of female- and male-specific traits and affect structure and function of reproductive organs. However, a number of studies over the last two decades indicated an additional important role in regulating structure and/or function of nearly every tissue and organ, including brain, bones, liver, and kidneys, causing sexual dimorphism (gender differences, sex differences) in a variety of characteristics.

Renal secretory and reabsorptive functions are based on the polar epithelium lining the nephron. The epithelial polarity is determined by the apical and basolateral plasma membrane domains that represent highly selective permeability barriers between the cytoplasm and the extracellular space (tubule lumen and intercellular space, respectively). The selectivity is determined by transport systems that transfer selected molecules across the lipid bilayer. Working together, the transporters in the apical and basolateral cell membranes maintain proper transmembrane gradients for a variety of compounds and thus ensure a vectorial trans-

cellular transport of molecules that are either removed from the tubule fluid (reabsorption) or removed from the peritubular space and released into the tubular fluid (secretion).

A myriad of studies have shown that, dependent on metabolic and functional demands, renal reabsorptive and secretory functions are regulated at the level of cell membrane transporters by various hormones in a short-term and long-term pattern. These regulations include changes in activity and/or abundance of specific transporters. Most of these studies have been performed in animals in vivo and in various models in vitro (isolated kidneys, isolated tubules and tubule cells, isolated membranes, established cell lines). In former times, in vivo experiments have been mostly performed on male (M) animals to avoid the influence of hormonal cycle (oestrus) in females (F). Recent observation in humans and animals indicated that renal structure and functions under various physiological, pharmacological, and toxicological conditions are different in M and F and that these differences may be related to sex-hormone-regulated expression and action of transporters. In this review we have collected available data on gender differences in renal functions, transporters, and other related parameters, which were published over the last few decades. We also present our own microarray data on the messenger RNA (mRNA) expression for various transporters in the rat kidney cortex, with the aim to (1) indicate the presence of thus far unrecognized effects of sex hormones on the expression of renal transporters and (2) initiate further studies to better understand gender-related differences in renal structure and functions, occurrence and development of some renal diseases, pharmacotherapy, and drug-induced nephrotoxicity in experimental animals and humans.

Sex hormone receptors in the kidney

It is generally assumed that the actions of sex hormones in their target tissues are crucially dependent on the presence of high-affinity, low-capacity sex-hormone-specific receptor proteins, which can reside in the cell membrane, cytoplasm, and/or nucleus of target cells and, after binding the respective hormone, cause either various signaling-mediated nongenomic actions and/or genomic regulation of transcriptional processes (reviewed in [21, 57, 75, 81, 86, 127, 131, 156, 172, 183, 223]). However, while receptors for androgens and estrogens are largely specific for their respective ligands, it has been demonstrated that progesterone can bind to mineralocorticoid receptor and exert various actions in the kidneys that antagonize the aldosterone/dexamethasone/corticosterone-related functions (reviewed in [36]). Genomic actions of the sex-hormone-receptor complex include an interplay of the complex with various nuclear cofactors (coactivators and/or corepressors), binding to specific DNA sequences [steroid response elements (SRE)] in the target gene promotor, and modification of local chromatin architecture, with activation (derepression) or inhibition (repression) of the target gene transcription as the final result. These SRE include response elements for androgens (ARE), estrogens [ERE and ERR (estrogen-related response elements)], and progesterone (PRE), which in the target gene promotor can exist in one or more copies [21, 81, 127, 131].

Receptors for sex hormones in kidneys and kidney-derived cell lines have been studied with different methods that gave very heterogeneous findings. As summarized in Table 1, various isoforms of androgen (ARα, ARβ), estrogen (ERα, ERβ), and progesterone (PgR A, PgR B) receptors were demonstrated in mammalian kidneys, but in most cases, their affiliation with defined nephron segments was either not tested or not clearly demonstrated. While in F and M hamsters the ER receptors were immunolocalized only to the nontubular structures [18], in several other studies, the presence of sex hormone receptors was related to specific kidney zones or nephron cells/segments: (a) in rabbits, ERs were demonstrated by immunoprecipitation in primary cultured proximal tubule cells [82]. (b) In an autoradiographic study on rat kidney sections, the binding of radiolabeled estradiol and testosterone in nuclei and cytoplasm of proximal tubules convoluted (S1/S2) segments was stronger than in S3 segments, and scattered cells were labeled in distal tubules and collecting ducts, indicating the possible presence of ER and AR in these nephron parts; the binding was more abundant in the tubules of F animals [55]. (c) In the rat kidney cortex, AR were localized by various methods to the nuclei of undefined tubules; the abundance of receptors was higher in F [162], whereas the abundance of ER proteins, as determined in cortex homogenates by Western blotting, were found to be higher in F (ERα) or M (ERβ) [199]. (d) In microdissected tubules from the M rat kidney, ARs were studied at the mRNA level and found to be highly expressed in proximal convoluted tubules (S1/S2 segments), whereas the expression in S3 segments and cortical collecting tubules was much lower and very weak, respectively [27]. (e) By immunoelectron microscopy, ER were found in the nuclei of proximal tubule cells in both M and F rats [62], whereas in tissue sections of rat and mouse kidneys, AR were detected by immunocytochemistry in the nuclei of distal nephron [246]. (f) In the cytosolic fraction of mouse kidney cortex and cultured proximal tubule cells, AR were detected by binding assay of ^{3}H-dihydrotestosterone (DHT) [176], and (g) in human kidneys, ERβ were localized by immunocytochemistry to the collecting duct in M [255] or by in situ hybridization in the M and F cortex and medulla

Table 1 Intracellular receptors for sex hormones in the mammalian kidney

Species	Gender	Method	Sample	Receptor type	Localization	F vs M	References
Hamster	F & M	IC	Tissue sections	ER	Capillaries, arteries, interstitial cells, G (podocytes)	F > M	[18]
Oppossum	N.D.	RT-PCR	OK cells in culture, total cell RNA	ER	–	–	[235]
Rabbit	F	IP	Primary culture	ER	Proximal tubules	–	[82]
Rat	F & M	Autoradiography	Tissue sections	ER, AR	PT (S1/S2 ≫ S3), some cells in DT and CD (nuclei, cytoplasm)	F ≫ M	[55]
Rat	M	Autoradiography	Tissue sections	ER	PT cells (nuclei); negative: G, DT and macula densa	–	[236]
Rat	F & M	WB	Whole tissue lysate	AR	Various tubules in the cortex (nuclei)	F > M	[162]
		IC	Tissue sections				
		RT-PCR	Whole tissue RNA				
Rat	F & M	WB	Tissue homogenate	ERα	Cortex	F > M	[199]
				ERβ	Cortex	F < M	
Rat	M	RT-PCR	Microdissected tubules (RNA)	AR	PT (S1/S2 ≫ S3), CCD (weak)	–	[27]
Rat	F & M	Immuno-EM	Tissue sections	ER	PT cells (nuclei)	F = M	[62]
Rat	M	RT-PCR	Total tissue RNA	ERα (ERβ—negative)	–	–	[123]
Rat	F & M	bDNA	Total tissue RNA	AR	–	F > M	[138]
				ERα		F < M	
Rat, mouse	F & M	IC	Tissue sections	AR	G, PT, DT (nuclei)	–	[246]
Mouse	N.D.	DHT binding	Cultured PT cells, kidney cortex	AR	Cytosol	–	[176]
Mouse	F & M	RNAse protection	Total tissue RNA	ERα (weak) (ERβ—negative)	–	F = M	[50]
Mouse	F & M	RT-PCR	Total tissue RNA	ERα	–	F = M	[222]
		WB	Tissue homogenate	(ERβ—negative)			
Mouse	F	IC	Tissue sections	PgR	Capsular cells	–	[263]
Mouse	F	RT-PCR	Total tissue RNA	ERα, ERβ	–	–	[101]
Human	M	IC	Tissue sections	ERα, ERβ	Interstitial cells, CD	–	[255]
Human	F & M	ISH	Tissue sections	ERβ	Cortex > medulla, convoluted PT	–	[64]
Human	F & M	Ligand binding, IC, WB, RT-PCR	Cortex and medulla	PgR B (PgR A—negative)	Medulla > cortex, individual cells in G, DT and interstitium (nuclei)	F = M	[36]
Human	F & M	WB	Total tissue lysate	ARα > ARβ	–	F = M	[275]
Human	F & M	RT-PCR, WB	PT cell line, total tissue RNA	AR	–	F ≪ M	[187]
Human	F & M	IC	Tissue sections	AR	DT (nuclei)	–	[111]

AR Androgen receptors; *bDNA* branched DNA amplification; *CCD* cortical collecting duct; *CD* collecting duct; *DT* distal tubule; *EM* electron microscopy; *ER* estrogen receptors; *F* female; *G* glomerulus; ^{3}*H-DHT* ^{3}H-dihydrotestosterone; *IC* immunocytochemistry; *IP* immunoprecipitation; *ISH*, in situ hybridization; *M* male; *N.D.* not defined/not determined; *PrG* progesterone receptors; *PT* proximal tubule; *RT-PCR* semiquantitative reverse transcriptase-polymerase chain reaction; *S1*, *S2*, and *S3* the respective proximal tubule segments; *WB*, Western blotting

Table 2 Sexual dimorphism (gender differences) in various morphological and/or functional characteristics of the mammalian kidneys

Characteristics	Species	F vs M	Cause, localization	References
Organ size and tissue morphology				
Kidney mass	Mouse, rat, human	F < M	Anabolic effects of androgens, hypertrophy of (mostly) PT and DT cells that appear after puberty	[100, 143, 161, 169, 177, 194, 219]
Size of kidney cortex	Rat	F < M	Androgen-induced hypertrophy of PT	[22, 177]
Size of PT cells	Rat	F < M	Androgen-induced hypertrophy of PT cells	[214]
Activity/expression of miscellaneous enzymes/proteins				
Alcohol dehydrogenase	Mouse	F < M	Androgen-induced stimulation of transcription, absent in AR-deficient mice; cortex (cytoplasm)	[58, 70, 174, 189, 201]
	Rat	F > M	Estrogen-induced stimulation of transcription; cortex (cytoplasm)	
Alkaline phosphatase	Rat	F > M	Estrogen-induced stimulation of Vmax, inhibited with actinomycin D; cortex (PT BBM)	[80]
Ornithine decarboxylase	Mouse	F < M	Stimulatory effect of androgens; PT (cytosol), upregulation of mRNA by androgens; whole kidney	[130, 207]
Ornithine aminotransferase	Mouse	F > M	Downregulation of mRNA by androgens; whole kidney	[129]
Deoxyribonuclease I and II	Mouse	F < M	Stimulatory effect of testosterone; whole kidney	[120, 121]
TGF-β1	Rat	F > M	GD appears in puberty; cortex and medulla	[125]
Bradykinin B2-receptor	Rat	F > M	Estrogen-stimulated expression of mRNA and protein; whole kidney	[144]
Carbonic anhydrase	Rat	N.D.	Cytosolic enzyme activity: (a) increased by castration and decreased by testosterone treatment, and (b) decreased by ovariectomy and increased by estradiol treatment	[240]
CYP1A1	Rat	F > M	Protein and mRNA level; whole kidney	[94]
CYP2A subfamily	Mouse	F < M	AR-mediated upregulation by androgens; whole kidney	[87, 136, 197]
CYP2E1	Mouse	F < M	AR-mediated upregulation by androgens; whole kidney (mRNA level)	[136, 180]
CYP2J5	Mouse	F < M	AR-mediated upregulation by androgens and ERα-mediated downregulation by estrogens; whole kidney (mRNA level)	[141]
CYP2D9	Mouse	F < M	DNA microarray and real-time PCR data; whole kidney	[197]
CYP3A9	Rat	F < M	Downregulation by estrogens; cortex (protein and mRNA level)	[5]
CYP4A2	Rat	F < M	Upregulation by androgens; PT	[136]
CYP4A12	Mouse	F < M	DNA microarray and real-time PCR data; whole kidney	[197]
CYP4F subfamily	Rat	F > M	Upregulation by estrogens; whole kidney (protein and mRNA level)	[104]
CYP7b1	Mouse	F < M	DNA microarray and real-time PCR data; whole kidney	[197]
Histamine-methyltransferase	Rat	F < M	Upregulation by androgens; kidney cortex (enzyme activity)	[231]
N-acetyltransferase	Mouse	F < M	Upregulation by androgens; downregulation by estrogens; whole kidney (enzyme activity)	[230]

Expression of antioxidant enzymes/proteins				
eNOS	Rat	F > M	Estrogen-induced stimulation of eNOS mRNA and protein; cortex, inner medulla	[102, 168, 192]
MnSOD	Rat	F > M	Cortex, medulla	[253]
Metallothionein	Rat, mouse	F > M	Induction/stimulation of protein expression by estrogens; whole kidney	[23, 24, 220]
Function/Process				
Inulin clearance	Rat	F < M	Androgen-induced hypertrophy of PT	[194]
Whole kidney GFR	Rat	F < M	Androgen-induced hypertrophy of PT; higher rate of renal plasma flow in M; higher vascular resistance in F kidney	[22, 44, 161]
SNGFR	Rat	F < M	Androgen-induced hypertrophy of PT; higher vascular resistance in F kidney	[22, 161, 194]
Urine production	Rat, mouse	F > M	Higher water consumption in F	[124, 216, 271]
Urine protein	Rat, mouse	F < M	Androgen-dependent production and secretion of α- and β-microglobulins in PT and, possibly, a higher rate of endocytosis in F	[4, 102, 194]
Urine angiotensinogen	Rat	F < M	Androgen-stimulated production and secretion of angiotensinogen (transport via exocytosis in PT?)	[270]
Urine vasopressin	Rat, human	F < M	Reflects the plasma vasopressin levels (F < M). In rats, GD abolished by gonadectomy and restored by treating M with androgens and F with ovarian hormones. In humans, GD higher in blacks than in whites	[53, 184, 221]
Sensitivity to antidiuretic activity of vasopressin (urine flow, osmolarity, water clearance, BP)	Rat, dog, human	F < M	Higher density of vasopressin V_2 receptors and greater stimulation of cAMP in the male CD; effects partially mediated by PGs in rats. In F rats, gonadectomy elevated the antidiuretic response to vasopressin to the level of that in intact M	[98, 154, 177, 182, 271, 273]
Sensitivity to antidiuretic activity of desmopressin (synthetic vasopressin)	Human	F > M	Prostaglandin PGE_2-mediated mechanism	[173]
Natriuretic response to furosemide	Human	F < M	N.D.	[72]
Diseases				
Compensatory kidney growth after uninephrectomy	Mouse	F > M	ERα-mediated cell proliferation and growth (absent in ERKO mice)	[239]
	Rat	F < M	Renotropic effects of testosterone with glomerular and tubular damage in the remnant kidney; protective effects of estrogens	[160]
Sensitivity to: acute and chronic renal injury, free radical injury, progression of renal disease, incidence of renal carcinoma	Rat, human mouse	F < M	Renoprotection by estrogens; acceleration of the disease by androgens via stimulation of AR-mediated apoptosis of PT cells and necrosis of proximal convoluted tubules; androgens stimulate production of renal ROS, RAS and telomere shortening, and decrease NO production	[56, 61, 67, 69, 110, 142,152, 166, 167, 193, 225, 245, 254, 269]

Table 2 (continued)

Characteristics	Species	F vs M	Cause, localization	References
Sensitivity to ochratoxin A	Rat	F < M	Neoplastic transformation and degeneration of epithelial cells in the PT S3 segment	[26, 191]
Urolithiasis	Human	F < M	Higher urine concentration (osmolality) in M	[182, 232]
Gout	Human	F < M	Lower serum urate concentration in F due to higher renal clearance	[6, 237]

All the data are valid for adult, intact (untreated) animals, and humans.
AR Androgen receptors; *BBM* brush-border membrane; *BP* blood pressure; *CCD* cortical collecting duct; *CD* collecting duct; *CYP* cytochrome P-450 enzymes; *DT* distal tubule; *eNOS* endothelial nitric oxide synthase; *ERα* estrogen receptors alpha; *ERCO mice* ERα-knock out mice; *F*, female; *GD* gender difference; *GFR* glomerular filtration rate; *M* male; *MnSOD* manganese superoxide dismutase; *MW* molecular weight; *N.D.* not determined; *PG* prostaglandins; *PT* proximal tubule; *RAS* renin-angiotensin system; *ROS* reactive oxygen species; *SNGFR* single nephron glomerular filtration rate; *TGF* transforming growth factor

(cortex > medulla), notably in convoluted proximal tubules [64], whereas PgR B were demonstrated by various methods in the M and F tissue (medulla > cortex) and individual cells in distal tubules (nuclei), with similar abundances in both sexes [36]. In other studies [50, 101, 123, 138, 187, 222, 235, 275], receptors for sex hormones were reported in kidney tissue or kidney-derived cell lines at the level of mRNA [by reverse transcription polymerase chain reaction (RT-PCR)] and/or protein (Western blotting), and their abundances in both sexes were either similar [50, 222, 275] or gender-dependent [138, 187], or undetermined [101, 123, 235] (Table 1).

Besides the classical ERα and ERβ receptors, the presence of the type II ER, which binds quercetin and some other bioflavonoids with an affinity higher than that for estradiol, has been demonstrated in the cytoplasm and nuclei of rat uterus [146, 147]. As quercetin and some other bioflavonoids are well-known protectors of the kidney damage after ischemia/reperfusion and cold injury [1, 103], some of these effects may be mediated by the type II ER. This type of ER may also mediate intracellular actions of some estradiol metabolites, generated by the action of cytochrom P-450 enzymes [148], that exhibit poor binding to classical ER but cause a variety of either positive or damaging effects in kidneys and other organs (reviewed in [61, 283]). However, the presence of type II ER in the mammalian kidney has not been explored. From all these data it is clear that (a) studying and finding receptors for sex hormones in the mammalian kidney is not an easy task, possibly due to a limited abundance of the receptor proteins and/or their mRNAs, and (b) correlation of their presence/abundance with the hormone-specific actions on nephron segments can presently not be established with certainty.

A generally assumed dogma says that sex hormones are released from gonads and/or adipose tissue and delivered to the target cells via circulation. However, at least the human kidney tissue expresses a set of enzymes capable of producing various androgens, including testosterone and 5α-DHT, from pregnenolone [188, 193, 266], suggesting the possibility of an autocrine and/or paracrine regulation of renal cell morphology and function by locally generated androgens. Furthermore, the cytochrome P-450 enzyme aromatase (CYP19), whose expression has been demonstrated in rat kidneys of both sexes, can convert androstenedione and testosterone into estradiol, which then may bind to ER and cause local autocrine and/or paracrine estrogenic actions even in the absence of circulating estrogens [223, 266]. Finally, a number of data indicate that, besides its ER-mediated actions, the estradiol molecule itself is a strong antioxidant, whereas its numerous metabolic products, particularly 2-hydroxyestradiol and 2-methoxyestradiol, which exhibit negligible affinity for ER, are more potent than estradiol in various aspects of the cell/

organ protection from oxidative and other damage (reviewed in [61]).

Gender differences in renal morphology and function

Numerous studies have indicated that sex hormones affect mammalian kidneys, causing sexual dimorphism in a variety of morphological and/or functional properties. Most of these data were obtained from experiments in animals, largely rats and mice; only a limited amount of data is from humans. Where studied, sexual dimorphism was found to be mediated by the relevant sex hormone receptors, but this was not a universal conclusion. As listed in Table 2, gender differences in the kidney mass were first described in mice and rats about 80 years ago [143, 219] and were later also proven for the human kidneys. The cause of the higher organ mass in M is not a different number of nephrons (the number of glomeruli per kidney in M and F is similar [161]), but the anabolic action of androgens largely affects growth (hypertrophy) of proximal tubule cells, so that the main morphological differences are localized in the kidney cortex. In rodents, the level of enzyme activity and/or expression of some key enzymes in the respective metabolic pathways (alcohol dehydrogenase, alkaline phosphatase, ornithine decarboxylase, ornithine aminotransferase, (deoxyribonuclease I and II), and proteins important for the cell growth (TGFβ1) and vasodilation (bradykinin B2-receptor), exhibited gender differences in favor of either M or F. Interestingly, the gender-related activity of the key cytoplasmic enzyme in alcohol metabolism, alcohol dehydrogenase, also showed species differences; in mice, the activity was stronger in M, whereas in rats, it was stronger in F. The opposite regulation of cytosolic carbonic anhydrase activity in rat kidneys, e.g., inhibition by androgens and stimulation by estrogens, indicates the possibility that, at least in rodents, sex hormones regulate renal homeostasis of protons and bicarbonate [240]. The activity of a few other enzymes and proteins of diverse functions, including β-glucuronidase, arginase, glutamate dehydrogenase, and glutamine-oxaloacetate transaminase, were found to be androgen-responsive in the mouse kidney, and their expression was accordingly gender-related [12, 151].

The expression of several enzymes of the cytochrome P-450 family (CYP) exhibited gender differences in mice and rats. These enzymes are localized largely in the proximal tubules and serve phase I biotransformation reactions of various endogenous and exogenous compounds, which involve oxidation, reduction, and hydrolysis, before being directed to the phase II conjugation reactions for producing more polar compounds with better solubility and excretory properties (reviewed in [137]). As shown in Table 2, M-prevalent gender differences in some CYP enzymes in rats and mice were largely caused by AR-mediated, androgen-driven upregulation, but CYP3A9 in rats was downregulated by estrogens, CYP2J5 in mice was both upregulated by androgens (AR-mediated) and downregulated by estrogens (ERα-mediated), whereas CYP1A1 and CYP4F members in the rat kidney were upregulated by estrogens. In a recent study by Rinn et al. [197], sex-specific expression of various genes were studied in mouse kidneys and other organs by DNA microarrays and real time PCR; a strong, M-dominant expression was detected in several members of the CYP family that are involved in drug and steroid metabolism, whereas a few other genes that may have specific roles in osmoregulation, were found to be either higher in F or in M (not listed in Table 2). Regarding the enzymes of the phase II biotransformation reactions, only a few of them exhibited gender differences in the rodent kidney (for review see [137]); for example, the activity of renal histamine-methyltransferase in rats was androgen-dependent and therefore higher in M [231]. The activity of renal *N*-acetyltransferase in mice was also higher in M due to both stimulation by androgens and inhibition by estrogens [230]. In humans, gender differences in the activity/expression of the CYP family members, and the corresponding differences in the clearance of various substrates from the blood, were demonstrated in liver (reviewed in [71, 74]), but similar information on the renal enzymes and their metabolic role could not been found in the literature.

The expression of rat renal endothelial nitric oxide synthase (eNOS) that plays an important role in production of vasoactive nitric oxide (NO; reviewed in [61]) and manganese superoxide dismutase (MnSOD), a metalloenzyme responsible for metabolism and detoxification of various reactive oxygen species (ROS; reviewed in [15]), and of rat and mouse renal metallothionein, an efficient scavenger protein for free radicals and some heavy metals and regulator of intracellular redox potential (reviewed in [153]), was found to be higher in F due to estradiol-mediated upregulation processes in both species. Related to these data are also the findings in guinea pigs, where the treatment with estradiol, but not with progesterone or testosterone, upregulated the renal expression of NOS [274]. Although gender differences for these proteins in the human kidneys have not been documented, their antioxidative actions may play an important role in the well-known renoprotective effects of estrogens in experimental models of acute and chronic renal injury in rats and in human nephropathies associated with an increased production of ROS and decreased production of NO [61, 67, 110, 152, 166, 192, 225, 245, 254].

In rats, inulin clearance, the whole kidney glomerular filtration rate (GFR), and the single nephron GFR (SNGFR) were found to be higher in M, possibly due to higher renal plasma flow and lower vascular resistance that result in a

sustained higher glomerular ultrafiltration (hyperfiltration) in M [22, 161]. These conditions may be related to the androgen-driven higher metabolic and functional demands in the M kidneys due to higher whole-body metabolic rate, higher rate of excretion of nitrogenous waste products, and higher reabsorptive rates in the proximal tubule, which result in more concentrated urine in M rats [186, 226]. Although these differences occurred in puberty and were caused largely by the well-known anabolic actions of testosterone in proximal tubule cells [22, 194], the vascular resistance in F kidney was diminished by ovariectomy [161], indicating that hormones of both sexes contribute to generation of the observed gender differences. A higher glomerular capillary pressure due to lower vascular resistance in the M kidney may contribute to the hyperfiltration-induced damage to the nephron and exacerbate renal disease ([161], and references therein). In spite of having a lower GFR, F rats (and mice) exhibited higher urine production, possibly due to higher water consumption [124, 216], but the roles of various transporters of inorganic and organic substances and water channels in this sex-dependent urine volume excretion have not been well investigated. A few studies, however, point to a complexity of this problem. For example, in rats, this gender-dependent renal water excretion (F>M) may be related to higher plasma vasopressin levels in M [53, 184, 221], which could influence reabsorption of water in distal nephrons via affecting the expression of water channel AQP2 (reviewed in [171]). As shown by Share et al. [221], the plasma vasopressin in rats is influenced by sex hormones, showing a tendency to decrease in M and increase in F after gonadectomy, but in the study by Peysner and Forsling [184], both ovariectomy and the treatment of ovariectomized rats with high doses of estradiol decreased the plasma vasopressin concentration. Furthermore, several aminopepdidases with angiotensin II- and vasopressin-degrading activity showed gender differences in the membranes from rat kidney cortex (M>F) and medulla (F>M); these enzymes can affect the intrarenal concentration/activity of the ion- and water-regulating peptides and, consequently, fluid excretion [185]. In the scope of these data are also observations by Sardeli et al. [211] showing a significant increase in AQP2 abundance in kidneys of ovariectomized rats, which was associated with the reduction in urine excretion. In addition, our preliminary studies showed that the M-dominant gender differences may exist in the renal expression of water channel AQP1 in adult but not prepubertal rats, which may be driven by the inhibitory effects of female sex hormones [202]. All these data indicate that the observed sex differences in urine production in rats and mice (F>M) may have some more complex but poorly studied causes, not just/only "higher water consumption in F."

In humans, overall gender differences in GFR were not apparent in the age range of 20–50 years, yet a significant decline in GFR was observed in ageing M but not in F, indicating a protective nature of estrogens in the pre-menopausal period [14]. Furthermore, gender difference in the urine excretion of low MW protein (α- and β-microglobulins) are well known in rats and mice; the production and exocytotic excretion of these proteins in the cells along proximal tubules was androgen-dependent and resulted in twofold to threefold higher concentration of proteins in the M urine [4, 102, 194]. The excretion of angiotensinogen in the rat urine exhibited similar pattern (M>F) [270].

Besides rats (mentioned above), humans also exhibit M-dominant gender differences in the plasma vasopressin concentrations, and in both species, the renal clearance of vasopressin is also higher in M than in F [53, 221]. Furthermore, in rats, dogs, and humans, blood pressure, urine flow, osmolarity, and water clearance exhibit gender differences (M>F), possibly due to higher sensitivity of the M gender to vasopressin; M contain higher density of vasopressin V_2 receptors in the collecting duct cells and exhibit higher vasopressin-induced antidiuresis than F [182, 271–273]. However, another study on healthy men and women, who were treated with a synthetic vasopressin, desmopressin, revealed just opposite gender-dependent vasopressin action: F exhibited a more pronounced antidiuretic response than M [173].

The occurrence and development of various diseases in human and experimental animals seem to be gender-dependent. After unilateral nephrectomy in mice, F showed greater increase in kidney mass than M; this increase was absent in the ERα-deficient (ERKO) mice, indicating ER-mediated estrogen effects as being important for proliferation and growth of renal cells [239]. In rats, however, androgens seem to be the driving forces; the growth of the remnant kidney after uninephrectomy was stronger in M, but the remnant kidney exhibited glomerular and tubular damage which did not occur in F, indicating renoprotective effects of estrogens [160]. The renoprotective effects of estrogens were further demonstrated in various pathophysiological conditions and diseases in humans and experimental animals, including ageing [67, 254], diabetes and its complications [166, 225], nondiabetic renal diseases [167], polycystic kidney disease [51], acute and chronic ischemic renal failure [69, 110, 152, 245], and nephrotoxicity induced by iron chelate ferric nitrilotriacetate [56, 142] or by the mycotoxin ochratoxin A [26, 191]. In all these studies, F sex and/or supplementary treatment with estradiol were found to attenuate the progression of the disease and diminish damage to the renal tubules via suppressing production of endothelin and ROS and via stimulating production of NO. On the other side, ovariectomy in F, M sex, and treatment with androgens were associated with worsening of the disease and tubular damage via stimulating the activity of renin–angiotensin system (RAS) and

production of ROS, decreasing production of NO and promoting apoptosis of tubular cells [51, 186, 193, 269]. Furthermore, the recently described higher prevalence of kidney stones in men may be related to the excretion of a more-concentrated urine in this gender [182, 232]. However, the studies of experimental, ethylene glycol-induced calcium oxalate nephrolithiasis in rats showed that androgens may stimulate urinary stone formation by increasing oxalate excretion and decreasing the renal expression of osteopontin, a renoprotective glycoprotein secreted by the loop of Henle and distal tubule cells in rats and humans, whereas estrogens have just opposite effects [68, 95, 279, 280]. Finally, the prevalence of gout in adult men is about twice as high as in adult women [237]; the lower rate of urate excretion in the male kidney is responsible for higher level of uric acid in men's blood [6]. This gender-related advantage is lost after women enter menopause.

Gender differences in renal transport of specific organic compounds

Major roles of the kidneys in maintaining body fluid and electrolyte homeostasis are based on polarized localization of various transport proteins (transporters/carriers) in the apical (luminal) and basolateral membrane domains of the cells along the nephron. These carriers use adenosine triphosphate (ATP) or transmembrane ion gradients to drive vectorial transport of their substrates in the baso-apical direction, resulting in secretion, or in the apico-basal direction, resulting in reabsorption of the substances. Recent studies have recognized a paramount role of these transporters, termed *A*TP-*b*inding *c*asette transporters (Abc/ABC for animal/human transporters) and *so*l*u*te *c*arriers (Slc/SLC for animal/human carriers) for (a) handling of endogenous organic compounds that are produced during normal metabolism, such as organic anions and cations, peptides, nucleosides, and their products; (b) handling of exogenous (xenobiotic) organic compounds, such as food constituents (flavonoids, mycotoxins, pesticides, other alimentary organic substances) and drugs (various antibiotics and chemotherapeutics); (c) drug–drug interactions; and (d) development of nephrotoxicity and specific transporter-related diseases. The knowledge on various Abc/ABC transporters have been recently summarized [234], and thus far described solute carriers have been categorized [85], and their structure/function relationship as well as their physiological, pathological, toxicological, and therapeutic implications in humans and experimental animals were emphasized in numerous articles (reviewed in [8, 9, 17, 31, 37–40, 54, 71, 89, 96, 109, 118, 119, 126, 128, 132, 157, 198, 206, 217, 218, 238, 241, 242, 247, 257, 267]).

Because of their major importance in drug transport and drug-mediated nephrotoxicity relevant to humans, most of the current research in the field of renal carriers has been dedicated to the roles of organic anion (OA) and cation (OC) transporters (Oat for animal/OAT for human, and Oct for animal/OCT for human transporters, respectively). It appears that rats and mice exhibit the clearest gender-dependent transport of various organic compounds and, therefore, these animals and tissue samples from their kidneys (tissue slices, isolated tubules, isolated cells, isolated cell membranes) have been used as the most plausible models. The studies have shown that these transporters are more or less polyspecific, that the expression of some of them was gender-dependent, and that the final pattern of excretion of a specific compound in the urine resulted from the interplay of both gender-independent and gender-dependent transporters. Some of the relevant findings from these studies are summarized in Table 3.

The studies started 50 years ago by demonstrating an androgen-dependent gender difference (M>F) in accumulation of a model OA, *p*-aminohippurate (PAH), in in vitro incubated rat kidney cortex tissue slices [92]. As shown later, the PAH uptake in the renal cortical slices after gonadectomy and treatment of intact and gonadectomized rats with various sex hormones could be well correlated with (a) maximum rate of tubular transport of PAH [113], (b) rate of PAH elimination from blood [43, 44, 196], (c) renal clearance of PAH in isolated perfused kidneys [244], (d) PAH transport in isolated renal cortical basolateral membrane vesicles [42, 44], and (e) expression of Oat1, a major PAH transporter localized in the proximal tubule cell basolateral membrane [42]. Sex differences in renal PAH transport in rats were absent before puberty [30], which agrees well with the low expression of PAH transporters Oat1 and Oat3 [135]. The renal clearance of the diuretic furosemide, also a substrate for Oat1 and Oat3, exhibited a similar M-dominant pattern [43, 244]. The importance of Oat1 and Oat3 for PAH and furosemide transport/secretion in the mammalian kidney was recently demonstrated in Oat1 and Oat3 knockout (KO) mice; in comparison with the wild-type mice, the KO mice manifested (a) strongly diminished uptake of PAH in renal slices and decreased urinary excretion of PAH and furosemide, (b) impaired diuretic response to furosemide, and (c) increased levels of various OA in the plasma and lower concentrations of these compounds in the urine [66, 243]. Furthermore, the uptake of taurocholate in isolated rat proximal tubule cells, possibly via basolateral Oat3 and/or Oatp1, was found to be inhibited by estrogens, resulting in a similar gender-dependency (M>F) [215]; the functional role of Oat3 in the transport of taurocholate (and estrone sulfate) in the mammalian proximal tubules was shown in the Oat3 KO

Table 3 Gender differences in the renal transport of specific compounds in experimental animals and humans

Findings, species, possible transporter(s) involved	F vs M	References
Findings in experimental animals		
Cases where the renal transport was found to be higher in males		
PAH uptake in rat renal cortical slices in vitro: (a) higher in M, (b) inhibited by castration and stimulated by testosterone treatment of M, (c) unaffected by ovariectomy and estradiol treatment of F and M rats, and (d) low and similar in prepubertal F and M animals (transport mediated by Oat1 and Oat3 in the PT).	F < M	[28, 30, 92, 113, 196]
Maximum rate of tubular transport of PAH in rats (transport mediated by Oat1 and Oat3 in the PT)	F < M	[113]
Renal clearance of PAH in rats (studies in whole animals and isolated kidneys); the elimination half-time was (a) shorter in M, (b) inhibited by castration, and (c) stimulated by testosterone treatment in castrated rats (transport via Oat1 and Oat3 in the PT).	F < M	[43, 44, 196, 244]
PAH transport in isolated renal cortical BLM in rats; higher in M (transport via Oat1, Oat3 in the PT).	F < M	[42, 44]
Renal clearance of furosemide in rats (transport via Oat1 and Oat3)	F < M	[43, 244]
Taurocholate uptake in freshly isolated rat renal PT cells; it was higher in M, whereas the renal clearance of taurocholate was faster in F. Testosterone treatment had no effect, whereas estradiol treatment of intact M and ovariectomized F decreased taurocholate accumulation in the cells (possible transporters involved: Oat3 and Oatp1 in the PT).	F < M	[215]
Accumulation of mercury in the renal tissue of mice; mercury may be transported bound to glutathione/cysteine conjugates via Oat1 and Oat3 in the PT.	F < M	[31, 179]
Uptake of TEA in renal cortical slices and isolated BLM from the rat kidney; the TEA transport was mediated by Oct2 in the PT, which is more expressed in M.	F < M	[264, 265]
Transport capacity (uptake) for antiviral drug amantadine in the rat cortical tubules and renal clearance in the whole animals; it was higher in M—amantadine may be excreted via Oct2 in the PT, which is more expressed in M. However, GD in the amantadine uptake was observed only in the distal tubules, which do not express Oct2.	F < M	[25, 277, 278]
Renal clearance of cisPt in rats; transport of cisPt may be mediated by Oct2 in the PT	F < M	[281]
Urinary excretion of ascorbate (vitamin C) in mice. Sexual dimorphism may be related to the higher plasma ascorbate in F and to the renal tubular transport. However, the expression of vitamin C transporters SVCT1 and SVCT2 in the PT seem to be expressed in similar abundance in F and M mice.	F < M	[124]
Transepithelial transport capacity for Ca^{2+} and Mg^{2+} in microdissected mouse cortical TALH: (a) low in prepubertal animals, (b) higher in adult animals, and (c) greater in M (transporters undefined)	F < M	[276]
Cases where the renal transport was found to be higher in females		
Urinary excretion of *N*-acetylcysteine conjugates (pentachlorobenzenethiol, tetrachloro-1,4-benzenedithiol, pentachlorophenyl mercapturate) in rats; it was higher in F due to active secretion in PT (possibly via Oat1 in the PT).	F > M	[229]
Renal clearance of nilvadipine metabolites, a calcium antagonist, in rats; much higher in F and probenecid-sensitive (possibly transported by Oats in the PT)	F > M	[256]
Renal clearance of perfluorooctanoic acid (PFOA), a toxic industrial pollutant, in rats: (a) higher in F, (b) increased by castration and estradiol treatment of castrated M, and (c) decreased by testosterone treatment of castrated M. PFOA may be filtered and secreted by Oat2 in the PT, which is higher expressed in F. In humans, GD in renal clearance of PFOA was not observed.	F > M	[80, 122]
Urinary excretion of estradiol-17β-D-glucuronide in rats: (a) higher in F, (b) increased by castration, and (c) decreased by testosterone treatment of castrated animals. The compound may be filtered and then reabsorbed along the PT via Oatp1, which is higher expressed in M.	F > M	[77]
Renal clearance of 1-aminocyclohexanecarboxylic acid (metabolite of semisynthetic penicillin cyclacillin) in rats: (a) lower in M due to higher rate of reabsorption in PT, (b) increased by castration, (c) decreased by ovariectomy, (d) additionally increased by estradiol treatment in castrated M, and (e) unaffected by testosterone treatment, thus indicating an estrogen-dependent mechanism of transport (transport mediated by Pept1 in the PT?).	F > M	[99]
Excretion of carnitine in the urine in rats: (a) higher in F, (b) increased by castration, and estradiol treatment in castrated rats, and (c) decreased by testosterone treatment in castrated rats [possible transporters: carnitine transporters in the PT (Octn2?)].	F > M	[41]
Urinary excretion of egualen sodium, an antiulcer drug, in rats: (a) partially inhibited by probenecid, (b) higher in F, (c) increased by castration and unaffected by ovariectomy, and (d) decreased by testosterone treatment in gonadectomized rats (transporters undefined).	F > M	[209]

Table 3 (continued)

Findings, species, possible transporter(s) involved	F vs M	References
Renal clearance of organic anions taurocholate, dibromosulfophtalein and zenarestat in rats; it was higher in F, possibly due to higher reabsorption in M via Oatp1 in the PT, which is more expressed in M.	F > M	[107]
Urinary excretion of aldose reductase inhibitor, zenarestat, in rats and mice; probenecid-sensitive and higher in F, possibly due to lower reabsorption via Oatp1 in the PT. Dogs and humans exhibited no GD in the excretion of zenarestat.	F > M	[107, 249, 250, 251]
Urinary excretion of creatinine in mice (possible transporter involved—Oct2)	F > M	[124, 128]
Urinary excretion of the glucocorticoid tipredane in rats and mice; higher in F (transporters undefined)	F > M	[48]
Urinary metabolite profiles in M and F rats by NMR spectroscopy of urine; findings: *N*-acetylglycoprotein, *m*-hydroxyphenylpropionic acid (*m*-HPPA), cholate, estrogen metabolites, progesterone metabolites, trimethylamine-*N*-oxide, *N*,*N*'-dimethylglycine (transporters undefined).	F > M	[233]
Diuretic, natriuretic, and kaliuretic response to furosemide in rats; higher in F due to lower abundance of NKCC2 in the apical membrane of TALH.	F > M	[29]
Findings in humans		
Plasma levels of acetylsalicylic acid in humans is higher in F, possibly due to lower biotransformation activity in liver and lower renal clearance (possible transporters involved: OAT1-4 in the PT).	F > M	[88]
Renal clearance of urate in humans; the clearance is lower in M due to higher reabsorption of urate, possibly via URAT1 in the PT. The clearance was unaffected by estradiol treatment in F.	F > M	[6, 7]
Urinary excretion of antibiotic ciprofloxacin in humans; slower excretion in F (probenecid-inhibitable mechanism of secretion in renal tubules, possibly via OATs in the PT)	F < M	[188]
Renal clearance of anti-viral drug amantadine in humans (possible transporter involved: OCT2 in the PT)	F < M	[278]

F Female; *GD* gender difference; *M* male; *PAH*, *p*-aminohippurate; *PT* proximal tubule; *TALH*, thick ascending limb of Henle; *TEA*, tetraethylammonium

mice by greatly reduced accumulation of these molecules in renal slices [243]. Gender difference were also observed for renal accumulation of the injected mercury in mice (M>F) [179], possibly due to phenomenon of molecular mimicry, where mercury may bind to SH groups in cysteine/glutathione conjugates and enter the proximal tubule cell in a complex transported by Oat1 and/or Oat3, which are expressed in higher abundance in M mice [31, 35, 79, 241]. Furthermore, M-dominant gender differences were observed in renal handling of some OC, such as tetraethylammonium (TEA), amantadine, and cisplatin in rats [25, 28, 278, 281]; these compounds may be transported by Oct2 in the basolateral membrane of proximal tubule S3 segments, where its expression exhibited strong, androgen-driven gender differences (M>F) [264, 281]. However, using the model of tubule fragments isolated from the kidney cortex of M and F rats, amantadine transport (uptake) was stronger in the M distal but not proximal tubules [277]; as distal tubules do not express Oct2 [105], the reason for the M-dominant renal clearance of amantadine in rats is not clear. Also not clear is the observed higher urinary excretion of vitamin C in M mice, because the vitamin C transporters Svct1 and Svct2 that are localized in the mice proximal tubule brush-border exhibited no differences in their expression [124]. The observed M-dominant transepithelial transport capacity for Ca^{2+} and Mg^{2+} in microdissected cortical thick ascending limbs of Henle (TALH) that appears in mice after puberty [276] is most probably the consequence of an increased expression of the Na^+,K^+-$2Cl^-$ cotransporter NKCC2 in M. Such a male-predominant expression has at least been demonstrated for the rat [29]. NKCC2 is responsible for the generation of a lumen-positive transepithelial potential difference [60], which drives Ca^{2+} and Mg^{2+} through paracellin-1 (claudin 16), a protein localized to the tight junctions [210]. A part of Mg^{2+} absorption in the mouse distal nephron is transcellular and may be mediated by the transient receptor potential melastatin 6 (TRPM6), a protein whose expression was reduced by ovariectomy and normalized by estradiol treatment in F mice [78].

As further listed in Table 3, the renal excretion of some compounds is higher in F than in M animals. The urinary excretion of several *N*-acetylcysteine conjugates, which are substrates for Oat1 (reviewed in [37]), and nilvadipine metabolites (transporters unknown) was higher in F rats, possibly due to active, probenecid-sensitive processes mediated by Oats [229, 256]. Furthermore, several structurally unrelated xenobiotics [perfluorooctanoic acid (PFOA), estradiol-17β-glucuronide, cyclacillin, carnitine, egualen sodium] also exhibited a higher renal clearance in F rats. In general, the renal excretion of these compounds was increased by castration and estradiol treatment and de-

creased by ovariectomy and testosterone treatment [41, 77, 84, 99, 122, 209], indicating the involvement of both estrogen- and androgen-dependent mechanisms via specific transporters. PFOA may be secreted more in F rats via the highly abundant luminal Oat2 in the F proximal tubules [122, 134], whereas estradiol-17β-glucuronide may be reabsorbed more along the M proximal tubule via androgen-stimulated luminal Oatp1 [77, 122, 139]. The reason for F-dominant excretion of cyclacillin and its metabolites might be a lower reabsorption of this compound via Pept1 [261], which may be expressed in lower abundance in the F proximal tubule luminal membrane (see later). Carnitine may also be reabsorbed with higher rate in M proximal tubules via luminal Octn2, which may be expressed more in M rats (see later). The transport mode for egualen sodium in the rat nephron is not known but obviously includes a mechanism that is probenecid-sensitive and androgen-inhibitable [209]. In accordance with the observed taurocholate uptake in freshly isolated rat renal proximal tubule cells, which was higher in M and inhibited by estradiol treatment of rats [215], the renal clearance of taurocholate was lower in M rats, possibly due to the higher rate of reabsorption via more abundant luminal Oatp1 in M proximal tubules (S3), which is upregulated by androgens and downregulated by estrogens [16, 77, 107, 122, 139]. Similar mechanisms may account for the increased renal clearance of dibromosulfophthalein and zenarestat in F rats [107, 250]. However, the higher urinary excretion of creatinine in F mice [124], and tipredane [48] in F rats and mice, and of various other metabolites in F rats [233] could not be clearly correlated with specific carriers. Finally, the recently described gender differences in diuretic, natriuretic, and kaliuretic response to furosemide in rats (F>M) could be explained by the lower abundance of NKCC2 transporter in the apical membrane of F TALH [29]. Besides NKCC2, a few other transports/transporters of inorganic substances, which may contribute to dissimilar urine production in M and F rats and mice [124, 216], may be affected by sex hormones, but these transporters have not been well studied, and the relevant gender differences in their activity/expression have thus far not been reported (not listed in Table 3). For example, (1) ovariectomy in F rats resulted in increased urinary excretion of calcium (Ca^{2+}) [175], possibly due to downregulation of calbindin-D-28k, a putative Ca^{2+} ferry protein in the distal tubule cells [52]; this effect was ameliorated by estradiol treatment and thus may explain an increased loss of Ca^{2+} in the urine after menopause in women. As tested in isolated proximal and distal tubules from the rabbit kidney, however, Ca^{2+} reabsorption across the luminal membrane of the distal, but not proximal tubules, was enhanced by a short-term (5 min) incubation with testosterone, possibly due to signaling-mediated opening of Ca^{2+} channels [49]. In addition, the activity of ATP-dependent plasma membrane Ca^{2+}-pump (PMCA) in the rat distal tubule cell line was increased by testosterone and 5α-DHT but not by estradiol; the effect occurred without a change in protein expression and it was inhibited by anti-androgen flutamide, indicating an AR-mediated signaling effect [59]. (2) Treatment of rats with estradiol caused an inhibition of phosphate (P_i) uptake in isolated cortical brush-border membrane vesicles via Na^+/P_i cotransport [13]. In primary cultures of rabbit kidney proximal tubule cells, however, estradiol had just an opposite effect by stimulating the intracellular P_i accumulation; this stimulation was mediated by AR and blocked by the inhibitors of RNA and protein synthesis [83]. (3) Ovariectomy decreased, whereas estradiol treatment of ovariectomized females increased the expression of chloride channel ClC-2 mRNA and protein in the rat nephron [164], whereas in cultured MDCK cells, testosterone, but not estradiol treatment stimulated fluid secretion and chloride via increasing cAMP generation [208]. Finally, (4) treatment of rats with 5α-DHT for 10 days caused the angiotensin II-mediated increased expression of NHE3 and upregulation of sodium, bicarbonate, and fluid reabsorption in proximal tubules [186], whereas in human proximal tubule cell line HKC-8, testosterone treatment induced an AR-mediated upregulation of sodium channel (ENaC) mRNA [187]. These data indicate that sex steroids may have receptor-mediated both short-term and long-term effects on the nephron transport functions.

Contrary to the numerous cases of gender-related transport of specific organic compounds described in experimental animals (largely rodents), very few reports have been related to humans. In general, humans and animals exhibit a similar set of renal transporters [9, 128, 132, 198, 218]. However, the presence, localization along the nephron, and intracellular localization of some carriers seem to be different from those in experimental animals. For example, (a) Oat2 in rats and mice was localized to the proximal tubule (S3 segment) brush-border membrane [116, 134], whereas in humans, OAT2 was localized to the proximal tubule basolateral membrane [65]; (b) Oct1 was localized in the rat kidney largely to the basolateral membrane of proximal convoluted tubules [105], whereas in the human kidney, OCT1 was not detected [76]; (c) Oct2 in the rat kidney was localized predominantly to the basolateral membrane of proximal tubule S3 segment [105], whereas OCT2 in the human kidney was localized to the basolateral membrane along the entire proximal tubule [159]; and (d) OAT4 in the human kidney was localized to the proximal tubule brush-border membrane, whereas a similar protein was absent from the rat nephron [11, 63]. These species differences in the expression and/or cellular localization of some transporters may influence the secretory and/or reabsorptive direction of renal transport of their substrates

and thus may affect their urinary excretion. Accordingly, gender differences in urinary excretion of zenarestat and PFOA in rats and mice (F>M) could not be confirmed in humans and dogs [84, 107, 122, 250], the F-dominant renal excretion on clentiazem in rats could not be observed in dogs [163], and the well-known gender differences in the transport of PAH and TEA in the proximal tubules in rats (M>F) could not be found in rabbits [79].

As shown in Table 3 (Findings in humans), studies in humans showed that the plasma level of the OA acetylsalicylate, which is a substrate of several OATs (OAT1–4; reviewed in [39, 132]), was higher in F, partially due to lower biotransformation of the compound in liver and due to lower renal clearance [88]. Similarly, the renal clearance of urate in women was found to be higher than in men, possibly due to lower reabsorption of urate via URAT1, which was localized to the proximal tubule brush-border membrane [6, 7]. Furthermore, the renal clearances of ciprofloxacin, which may be a substrate of OATs [178], and of the organic cation amantadine [278], a substrate of OCT2 [reviewed in 132], were found to be higher in men. However, possible gender-related expression of the respective carriers in the human nephron has not been reported. A number of other therapeutic drugs in humans (calcium channel blocker verapamil, antibiotic metronidazole, muscle relaxant vecuronium, etc.) exhibited gender differences in their blood clearance, but a possible contribution of renal excretion is not known (reviewed in [74, 150]).

Gender differences in nephrotoxicity

Numerous reports revealed gender-related differences in humans and experimental animals in pharmacokinetics (bioavailability, distribution, metabolism, excretion) and pharmacodynamics (pharmacological response) of various drugs or other organic substances that enter the body via the food (reviewed in [71, 74, 89, 128, 132]). Many drugs cause adverse, sometimes gender-dependent, reactions in humans; it has been reported that in human patients, women have a twofold to threefold higher risk than men for the development of adverse drug reactions [259]. Some of these reactions may be induced by general toxicity of a drug and/or its metabolite(s) in the cells due to different rates of detoxification/metabolism via gender-dependent activity/expression of CYP enzymes in liver and other organs, whereas toxicity in specific organs may result from the transport-mediated accumulation of a drug and/or its metabolite(s), or because of drug–drug interactions at the level of transporting mechanism(s). Eventually, these effects/interactions can generate damage to the cell/organ structure and function and may be life threatening. Due to complex non-carrier- and carrier-mediated cellular mechanisms of handling endogenous and xenobiotic substances along the nephron, a number of substances that are filtered, reabsorbed, and/or secreted may represent potential nephrotoxins (reviewed in [71, 74, 89, 118, 128, 132, 198, 238, 241, 257]). Gender differences in the expression and/or activity of membrane transporters in the cells along the nephron thus represent a base for gender-related development of nephrotoxicity of specific substances [89, 241].

As listed in Table 4, experiments in rats have indicated several, structurally unrelated substances that exhibited gender differences in nephrotoxicity due to their transporter-mediated accumulation in, and damage to (mainly) proximal tubules. However, cyclacillin, which is a substrate of Pept1/PEPT1, was nephrotoxic in rats but not in monkeys, dogs, and humans; Pept1 is a brush-border transporter along the rat proximal tubule S1 and S2 segment, which may be expressed in higher abundance in M rats (see later) and may reabsorb the filtered compound to high, toxic levels [132, 261, 262]. Regarding nephrotoxicity of hexachlorobutadiene in rats, in one report, the damage in proximal tubules was stronger in M [20], whereas in another report, F were more sensitive [260]. The sensitivity of proximal tubules to toxic effects of acetaminophen, a drug that is secreted in proximal tubules via several Oats/OATs (reviewed in [39]), was much stronger in F, and this difference is lost in old animals, possibly due to age-dependent downregulation of the transporter [253]. Toxicity of adriamycin/doxorubicin, which is a substrate of Oat1/OAT1 (reviewed in [217]), was much stronger in M rats; toxicity was diminished after castration, which is known to downregulate the expression of renal Oat1 in rats [135, 205].

Gender differences in renal transporters

Hormonal regulation of the activity and/or expression of various Oats and Octs in the nephron of experimental animals and (much less) of humans, and in various in vitro systems, has been reported in numerous studies (reviewed in [8, 9, 37–39, 54, 74, 118, 126, 128, 157, 198, 217, 218, 241, 242, 257, 267]). These studies revealed the existence of short-term and long-term regulation of carrier-mediated renal transport of specific substrates. Studies in isolated proximal tubules or cells, and studies in the in vitro expression systems (transporters expressed in Xenopus oocytes or cultured cells), showed that some hormones, such as catecholamines, dopamine, bradykinin, parathyroid hormone, endothelin, and epidermal growth factor, can induce a short-term, receptor-mediated regulation (inhibition or stimulation) of OA and OC transport via activating or inhibiting one of the protein kinases (PKA, PKC, MEK, TRK). It seems that this regulation involves processes of

Table 4 Gender differences in nephrotoxicity induced by organic anions or cations

Nephrotoxin	Species	Nephrotoxic effects/symptoms	F vs M	Putative mechanism or transporter(s) involved	References
Cyclacillin (semisynthetic penicillin)	Rat	Degenerative nephropathy, damage of the tubules and interstitium	F ≪ M (absent in Rhesus monkey, beagle dogs, and humans)	Higher accumulation in the M kidney due to lower rate of excretion, possibly via Pept1 in PT	[132, 261, 262]
N-(3,5-dichlorophenyl)-succinimide (agricultural fungicide)	Rat	Diuresis, proteinuria, glucosuria, hematuria, elevated BUN, damage of PT (S3 in M, and S2 and S3 in F)	F > M	?	[190]
Hexachlorobutadiene (a solvent, used in rubber industry)	Rat	Necrosis of PT S3	F < M	No GD in the rate of excretion; possible GD in the rate of biotransformation	[20]
	Rat	Decreased PAH uptake in renal cortical slices, damage of the PT S3	F > M	?	[260]
Acetaminophen (NSAID)	Rat	Nephrotoxicity in adult animals; old rats are more sensitive, but exhibit no GD	F ≫ M	Oat1 ≫ Oat2, Oat3, Oat4 (loss of relevant transporters by ageing)	[39, 253]
Adriamycin/Doxorubicin (anti-neoplastic)	Rat	Proteinuria, decreased renal function, glomerulosclerosis	F ≪ M	Ameliorated by castration; Oat1	[205, 217]
Etoxyquin (synthetic antioxidant)	Rat	Papillary necrosis	F ≪ M	?	[165]

BUN Bound urea nitrogen; *F* female; *GD* gender difference; *M* male; *NSAID* nonsteroid anti-inflamatory drug; *PAH* *p*-aminohippurate; *PT* proximal tubule; *S1*, *S2*, and *S3* respective PT segments.

endo- and exocytosis of the transporters that change protein abundance in the plasma membrane with concomitant change in the rate of transport. On the other side, studies in experimental animals in vivo indicated that growth hormone, thyroid hormones, testosterone, estradiol, and dexamethasone largely affect (stimulate or inhibit) the renal transport of OA and OC via upregulating or downregulating the expression of specific transporters at the level of transcription or translation (long-term mechanism). However, as estrogen and androgen hormones can also act via fast, receptor-mediated, nongenomic intracellular actions by activating various kinases [21, 81, 86, 131, 156, 189], possible short term effects of these hormones upon the activity and/or expression of Oats and Octs in the renal tubules cannot be excluded.

Available data predominantly describe gender differences and effects of sex hormones upon the renal transporters for OA and OC in rodents; only a very few studies were related to some other transporters, and none of the studies was related to the transporters in humans. As summarized in Table 5, gender differences and effects of sex hormones on the expression of renal transporters have been studied in surgically and hormonally manipulated experimental models in vivo and in vitro, and with different methods looking for (a) expression of mRNA by branched DNA (bDNA) amplification, RT-PCR, Northern blotting, and in situ hybridization; (b) abundance of transporters in tissue homogenates and isolated membranes by Western blotting; (c) distribution of transporters along the nephron and their cellular localization by immunocytochemistry in tissue cryosections; and (d) transport of specific substrates in intact animals, tissue slices, suspensions of isolated tubules and cells, isolated plasma membranes from whole kidneys or specific tissue zones, or in the established cell lines.

From the data in Table 5 we can draw the following conclusions: (1) except for the M-dominant expression of NKCC2 in rats, a transporter localized to the apical membrane of the thick ascending limb of Henle [29, 158], for the F-dominant expression of Mdr3, an ATP-driven transporter localized basolaterally in various polar epithelia (nephron segments unknown) [212], and for the M-dominant expression of ATP-driven efflux pump BCRP (breast cancer resistance protein; localization unknown) in rats [252], all other studies described gender differences for transporters localized in the proximal tubules. (2) With the exception of sodium-glucose cotransporter type 1 (Sglt1), all other studied gender-dependent transporters in proximal tubules were related to transport of OA and OC. (3) Gender differences and effects of sex hormones on the activity/expression of Abc family of transporters have been poorly studied [46, 145, 252]. (4) Gender differences were demonstrated for transporters localized in both basolateral (Oat1, Oat3, Oct2) and apical (Oat2, Oat5, Oatp1, Urat1,

Sglt1, Mrp4) cell membrane domains in the proximal tubules of various experimental animals ([42, 46, 79, 105, 135, 203, 264, 265, 268] and our unpublished data), whereas the cellular localization of Oatp3a1, Oat-K, Mrp3, and BCRP proteins in the mammalian nephron is unclear [149, 204, 212, 252]. (5) Several well-characterized transporters that exhibited strong androgen-driven upregulation (Oct2, Oatp1) or downregulation (Oat2, Oat5, Sglt1), and an opposite regulation by estrogens, are predominantly or exclusively localized in the proximal tubule S3 segment, indicating this segment as the most sensitive target of sex hormones; this is at odds with the data on expression of AR in microdissected tubules from the M rats, which showed a high expression of AR in the proximal convoluted (S1/S2) tubule segments and very low expression in the S3 segments [27]. (6) Most of the shown data were obtained by studying the expression of transporter-specific mRNA under the tacit assumption that mRNA levels reflect the expression of respective transporting proteins in the cell membrane and their function. These data, however, have to be interpreted cautiously; as shown recently by Groves et al. [79] in adult rabbits, gender differences in Oct2 mRNA expression (M>F) did not translate at the protein level. (7) Where studied in rats and/or mice, the expression of renal transporter proteins and/or their mRNAs (Oat1, Oat2, Oat3, Oat5, Oct2, Mrp3, Mrp4) were low and similar in M and F before the puberty; gender differences occurred after the puberty ([33, 134, 135, 145, 227] and our unpublished data). However, in rabbits, the expression of Oat1, Oat2, and Oat3 (mRNA and/or protein) in the proximal tubules significantly increased after the puberty without exhibiting sex differences. The expression of Oct1 mRNA remained unchanged after maturation in both sexes, whereas the expression of Oct2 mRNA was high and similar in M and F before the puberty, and gender differences in the expression of its mRNA (M>F) but not of protein, developed in adult rabbits [79]. This further indicates that the findings regarding gender differences and effects of sex (and, possibly, other) hormones upon renal transporters in one species cannot simply be regarded as relevant for other species. Furthermore, it has been shown that the mRNA expression of some renal OA transporters in rats (Oat1, Oat2) [34] and mice (Oatp1a1, Oatp3a1) [47] may be also under control of growth hormone because hypophysectomy downregulated the mRNA expression and abolished gender differences. However, the treatment of hypophysectomized animals with growth hormone caused only a partial and treatment with 5α-DHT a strong upregulation of the transporters, indicating that androgens have a major, direct effect in controlling the expression of their mRNA [47]. (8) Positive and negative data for the presence of gender differences were reported for the same transporters and species; the examples listed in the second part of Table 5, showing the data from the studies in which gender differences in renal transporters of Slc family have not been observed, the absence of gender differences for some Oats and Octs were demonstrated nearly exclusively at the mRNA level, particularly when using the method of bDNA amplification, indicating that some methods may not be sensitive enough to detect subtle differences in the transporter mRNA expression. (9) Only in a few cases the expression of mRNA in renal tissue samples, protein abundance by Western blotting in isolated membranes, immunolocalization of the transporter in tissue cryosections, and rate of substrate transport in tissue sections or membranes isolated from the same tissue were positively correlated. This largely applies to Oat1, Oat2, Oatp1a1, Oat5, Oct2, and Sglt1 in rats, whereas similar data for other transporters in rats and other species are heavily deficient. (10) Where studied in more detail, the gender-dependent expression of rat renal Oat1 and Oat3 mRNA and their proteins (M>F) was driven by both stimulatory effects of androgens (and, weakly, progesterone) and inhibitory effects of estrogens. The expression of Oat1 was downregulated by castration, upregulated by ovariectomy, upregulated by testosterone (strongly) and progesterone (weakly), and downregulated by estradiol treatment of castrated or ovariectomized rats. The expression of Oat3 exhibited a comparable pattern except that ovariectomy and progesterone treatment had no effect [34, 135]. On the other side, the gender-dependent expression of rat renal Oat2 and Oat5 mRNA and their proteins in the proximal tubule brush-border membrane (F>M) was driven by androgen inhibition and estrogen stimulation; Oat2 expression was upregulated by castration and downregulated by ovariectomy, strongly downregulated by testosterone treatment and weakly upregulated by estrogen and progesterone treatment in castrated males [34, 122, 134], and our unpublished data indicated a similar pattern for Oat5. The facts that the kidney mass in M and F rats differs 15–20% (M>F) and changes in the same range after castration and testosterone treatment [177], whereas the abundances of Oats in the membranes isolated from the kidneys of intact M, F, and hormone-treated rats differ up to 11-fold ([134, 135] and our unpublished data), indicate that the expression of specific transporters is not a mere reflection of the cell size in proximal tubules but rather that sex hormones actively regulate the number/density of these transporters in the respective membrane domains. (11) In the proximal tubules of M rats (and mice), an overall M-dominant, androgen-driven pattern of expression at the level of mRNA and protein exists for basolateral (secretory) transporters Oat1, Oat3, and Oct2, whereas the apical (reabsorptive) transporters Oat2, Oat5 (and Sglt1; see later) are weakly expressed, indicating that proximal tubules in M rats and mice may functionally operate in a secretory mode for

Table 5 Gender differences in renal transporters

Transporters	Species	Methods	Sample tested (localization)	F vs M	Sex hormone/effect	References
Slc/SLC family of transporters						
Studies in which gender differences in renal transporters of Slc family have been observed						
Oat1 (Slc22a6)	Rat	WB, PAH-transport	Isolated BLM	F < M	N.D.	[42]
		bDNA, NB	Whole kidney	F < M	N.D.; low before puberty (F = M)	[33]
		bDNA	Whole kidney	F < M	Downregulation by castration in M (strong) and by ovariectomy in F (weak)	[34]
		WB, IC	Isolated BLM, tissue cryosections (PT: S2 > S3, BLM)	F < M	Upregulation by A (strong) and P (weak); downregulation by E (strong); low before puberty (F = M)	[135]
	Mouse	bDNA	Whole kidney	F < M	N.D.; low before puberty (F = M)	[35]
		bDNA	Whole kidney	F < M	N.D.	[79]
Oat2 (Slc22a7)	Rat	RT-PCR	Whole kidney	F > M	Downregulation by A; upregulation by E	[122]
		NB	Whole kidney	F > M	Downregulation by A and E	[115]
		bDNA, NB	Whole kidney	F > M	N.D.; low before puberty(F = M)	[33]
		bDNA	Whole kidney	F > M	Downregulation by ovariectomy	[34]
		WB, IC	Isolated BBM	F > M	Downregulation by A (strong); upregulation by E and P (weak); low before puberty (F = M)	[134]
		RT-PCR	Tissue zones, tissue cryosections (PT: S3, BBM)			
	Mouse	bDNA	Whole kidney	F > M	N.D.	[79]
		WB, IC	Isolated BBM, tissue cryosections (PT: S3, BBM)	F > M	N.D.	[134]
Oat3 (Slc22a8)	Rat	WB, IC	Isolated BLM, tissue cryosections (Various cortical tubules, BLM)	F < M	Upregulation by A (strong); downregulation by E (strong); no effect of P; low before puberty (F = M)	[135]
Oat5 (Slc22a19)	Rat	WB, IC	Isolated BBM	F > M	Downregulation by A (strong); upregulation by E and P (weak); low before puberty (F = M)	[unpublished]
		RT-PCR	Tissue zones, tissue cryosections (PT, S3 > S2, BBM)			
Urat1 (Slc22a12)	Mouse	NB, WB	Whole kidney, crude PM	F < M	N.D.	[90]
	OK cells	–	Promotor activity (human URAT1)	–	Stimulation by A	[133]

Oatp1a1 (Slc21a1)	Rat	NB	Whole kidney	F < M	Upregulation by A (strong); downregulation by E (weak)	[139]
		WB	Whole kidney PM	F < M	Upregulation by A	[77]
		E17ßG clearance	Whole animal			
		NB, WB	Whole kidney, crude PM	F < M	N.D.	[107]
		RT-PCR	Whole kidney	F < M	Upregulation by A; downregulation by E	[122]
	Mouse	NB	Whole kidney	N.D.	Upregulation by A	[97]
		bDNA	Whole kidney	F < M	Upregulation by A	[47]
Oatp3a1 (Slc21a11)	Mouse	bDNA	Whole kidney	F < M	Upregulation by A	[47]
Oct2 (Slc22a2)	Rat	WB, IC, ISH, NB, TEA uptake	Isolated BLM, cortical slices, whole kidney (PT: S3 > S2, BLM)	F < M	Upregulation by A (strong) downregulation by E (weak);	[105, 264, 265]
		bDNA	Whole kidney	F < M	Upregulation by androgens; low before puberty (F = M)	[211]
		WB	Whole kidney PM	F < M	Upregulation by A	[261]
	LLC-PK1 cells	–	Promotor activity (rat Oct2)	–	AR-mediated stimulation by A	[10]
	Mouse	bDNA	Whole kidney	F < M	Upregulation by A	[2]
		bDNA	Whole kidney	F < M	N.D.	[79]
	Rabbit	WB, bDNA, TEA uptake	SPT	F < M (mRNA) F = M (protein)	N.D.	[79]
Oat-K (Slc21a4)	Rat	RT-PCR	Whole kidney	F < M	N.D.	[122]
NKCC2 (Slc12a1)	Rat	WB	Homogenate (renal medulla)	F < M	N.D.	[29]
Sglt1 (Slc5a1)	Rat	WB, IC, NB	Isolated BBM	F > M	Downregulation by A; no effect of E and P	[203]
		Uptake of ^{3}H-galactose	Tissue zones Tissue cryosections (PT: S3, BBM)			
Studies in which gender differences in renal transporters of Slc family have not been observed						
Oat1 (Slc22a6)	Rat	NB	Whole kidney	F = M	No effect	[115, 264]
		NB	Whole kidney	F = M	N.D.	
	Rabbit	WB, bDNA, PAH uptake	SPT	F = M	No effect	[79]
Oat2 (Slc22a7)	Mouse	bDNA	Whole kidney	F = M	N.D.; low before puberty (F = M)	[35]
		NB	Whole kidney	F = M	N.D.	[117]
	Rabbit	bDNA	SPT	F = M	No effect	[79]
Oat3 (Slc22a8)	Rat	NB	Whole kidney	F = M	N.D.	[33, 115]
		bDNA	Whole kidney	F = M	N.D.; low before puberty (F = M)	
	Mouse	bDNA	Whole kidney	F = M	N.D.; low before puberty (F = M)	[35]
	Rabbit	WB, bDNA ES uptake	SPT	F = M	No effect	[79]
Oat5 (Slc22a19)	Rat, mouse	RT-PCR	Whole kidney	F = M	N.D.	[282]
Oct1 (Slc22a1)	Rat	NB	Whole kidney	F = M	No effect	[264, 265]
		bDNA	Whole kidney	F = M	No effect	[227]
	LLC-PK1 cells	–	Promotor activity (rat Oct1)	–	No effect	[10]
	Mouse	bDNA	Whole kidney	F = M	No effect	[2, 79]
		bDNA	Whole kidney	F = M	N.D.	

Table 5 (continued)

Transporters	Species	Methods	Sample tested (localization)	F vs M	Sex hormone/effect	References
Oct3 (Slc22a3)	Rat	NB	Whole kidney	F = M	No effect	[264]
		bDNA	Whole kidney	F = M	No effect	[227]
	LLC-PK1 cells	–	Promotor activity (rat Oct3)	–	No effect	[10]
	Mouse	bDNA	Whole kidney	F = M	No effect	[2]
Octn1 (Slc22a4)	Rat, Mouse	bDNA	Whole kidney	F = M	No effect	[2, 227]
Octn2 (Slc22a5)						
Octn3						
Abc/ABC family of transporters						
Studies in which gender differences in renal transporters of Abc family have been observed						
Mrp3 (Abcc3)	Mouse	bDNA	Whole kidney	F > M	N.D.; low before puberty (F = M)	[145]
Mrp4 (Abcc4)	Rat	bDNA	Whole kidney	F < M	N.D.; low before puberty (F = M)	[46]
	Mouse	bDNA	Whole kidney	F > M	N.D.; low before puberty (F = M)	[145]
Bcrp (Abcg2)	Rat	bDNA	Whole kidney	F < M	Downregulation by E	[252]
Studies in which gender differences in renal transporters of Abc family have not been observed						
Mrp1 (Abcc1)	Mouse	bDNA	Whole kidney	F = M	N.D.; high before puberty	[145]
Mrp2 (Abcc2)	Mouse	bDNA	Whole kidney	F = M	N.D.; low before puberty	[145]
Mrp5 (Abcc5)	Mouse	bDNA	Whole kidney	F = M	N.D.; low before puberty	[145]
Mrp6 (Abcc6)	Mouse	bDNA	Whole kidney	F = M	N.D.; high before puberty	[145]
Mrp7 (Abcc7)	Mouse	bDNA	Whole kidney	F = M	N.D.	[145]

A Androgens; *Abc/ABC* ATP-binding cassette; *AR* androgen receptor; *BBM* isolated brush-border membrane; *bDNA* branched DNA amplification; *BLM* isolated basolateral membrane; *E* estrogens; *E17βG* estradiol-17β-glucuronide; *ES* estron sulfate; *F* females; *GD* gender differences; *IC* immunocytochemistry; *ISH* in situ hybridization; *M* males; *NB* Northern blot; *N.D.* not determined; *P* progesterone; *PM* plasma membranes; *PT* proximal tubule; *RT-PCR* semiquantitative reverse trancriptase-polymerase chain reaction; *S1*, *S2*, and *S3* various PT segments; *SPT* suspension of isolated proximal tubules; *WB* Western blot; *TCM* total cell membranes; *TEA* tetraethylammonium

various OA and OC. In a functional concert with these basolateral transporters may be the M-dominant expression of Mrp4, an ATP-driven efflux pump, which is in rats localized to the renal proximal tubule brush-border membrane and which shares similar substrate specificity with Oat1 and Oat3 [46, 89, 128, 228, 268]. Possible other androgen-stimulated apical transporters in the M rat tubules that could mediate the exit of accumulated organic compounds into the tubule fluid have yet to be defined. If similar phenomena are present in humans, they could explain the excretion of a higher concentrated urine and, in case of malfunctions, they may generate predispositions for higher prevalence of kidney stones in men [182, 232]. However, the expression of renal Mrp4 in mice exhibited just opposite gender difference (F>M), precluding any common conclusion due to possible species differences. On the other side, in the proximal tubules of F rats, the estrogen-driven low expression of basolateral transporters Oat1, Oat3, and Oct2, and a concomitant high expression of brush-border transporters Oat2 and Oat5 (and Sglt1; see later) and low expression of Mrp4, indicate that the F proximal tubules may principally operate in reabsorptive mode for the respective substrates. These two, gender-related opposing modes of OA and OC transport in the rat proximal tubules, e.g., the secretory mode of transport in M and the reabsorptive mode of transport in F, are schematically shown in Fig. 1. We have to emphasize, however, that for now this scheme may be valid only for rats, as the gender-dependent expression of various renal transporters appears to be also species-dependent. Moreover, the phenomenon that in rats, the brush-border (reabsorptive) anion transporter Oatp1a1 (and, possibly, Urat1) was also upregulated by androgens [77, 122, 139], and that both basolateral and apical Oats are polyspecific exchangers that may operate in both directions dependent on driving forces and substrate availability, indicates that the simple explanations are not possible.

Our recently published study showed the presence of gender differences (F>M) in the expression of high-affinity,

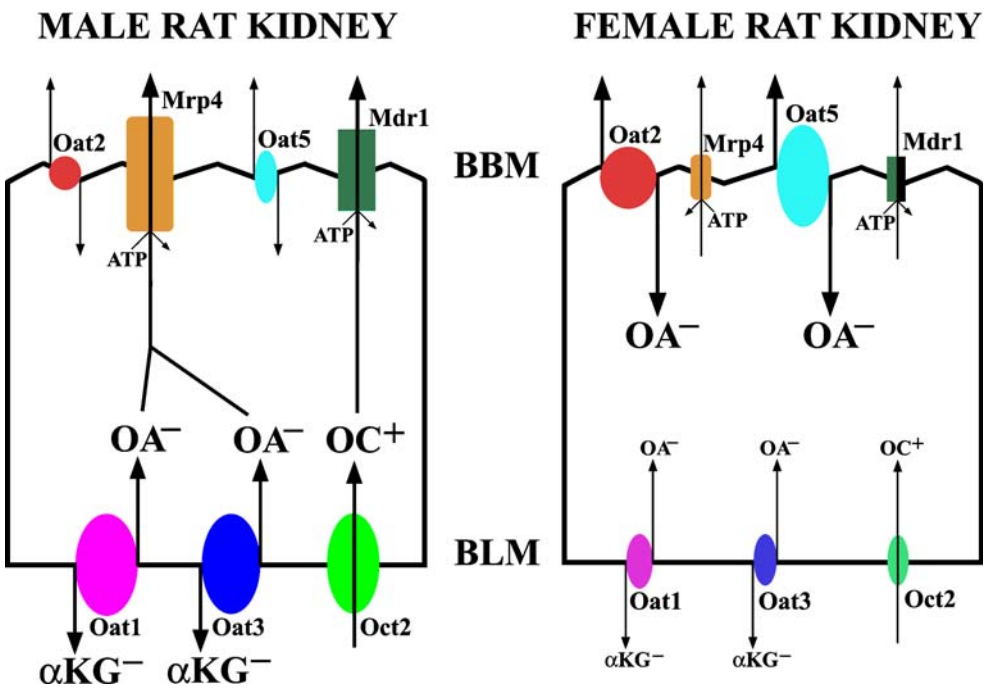

Fig. 1 A model of OA and OC transport in the proximal tubule of M and F rat kidneys based on the gender-dependent expression levels of relevant transporting proteins in the basolateral (*BLM*) and brush-border membrane (*BBM*). *MALE RAT KIDNEY*, in M rats, proximal tubules exhibit a high expression (mRNA/protein) of secretory transporters Oat1, Oat3, and Oct2 in the BLM, and Mrp4 and (possibly) Mdr1 in the BBM, whereas the abundance of reabsorptive transporters Oat2 and Oat5 in the BBM is low. These secretory transporters, being upregulated by androgens and downregulated by estrogens, may mediate an increased secretion of relevant OA and OC. *FEMALE RAT KIDNEY*, in F rats, proximal tubules have low expression of secretory transporters for OA and OC but exhibit high expression of the reabsorptive transporters Oat2 and Oat5 (mRNA/protein) in the BBM. The F-dominant Oats in the BBM are downregulated by androgens and upregulated by estrogens and indicate that the F proximal tubules may overall operate in reabsorptive mode for the respective substrates. The M-dominant expression of Mdr1, as shown in this model, is only tentative and based on our microarray study; the relevant gender difference in protein expression (M>F) has yet to be confirmed. The model may not be completely valid for: a) mice, which exhibit similar, M-dominant expression of Oat1, Oat2, Oat3, Oat5, and Oct2 (mRNA/protein), however with the F-dominant expression of mRNA for Mrp4; b) rabbits, which exhibit no gender differences in the expression of Oat1, Oat2, and Oat3 (mRNA/protein); and c) humans, where Oat2 is localized to the BLM and Oat4 in the BBM and where information on gender-dependent expression of any transporter is not available

low-capacity glucose/galactose transporter Sglt1 in the rat kidney [203]. This carrier was immunolocalized predominantly to the brush-border of proximal tubule S3 segment in the renal outer stripe and medullary rays, and its F-dominant gender difference was manifested in mRNA expression, immunostaining intensity in tissue cryosections, protein abundance in isolated cell membranes, and rate of galactose uptake in isolated brush-border membrane vesicles. The protein abundance was upregulated by castration, downregulated by testosterone treatment, and remained unaffected by estradiol and progesterone treatment of castrated rats. Although the significance of this finding for hexose transport in the rat kidney is not known (discussed in [203]), these data indicated that gender differences in renal transporters are not restricted to Oats, Octs, and Mrps.

As gender differences in the expression of various renal transporters listed in Table 5 seem to result largely from the gene regulation at the level of transcription, resulting in upregulation or downregulation of mRNA abundance in the tissue, the action of sex hormones my be related to the presence of specific responsive elements in the target gene promotor. In Table 6 we show selected renal transporters for inorganic (NKCC2) and organic anions (Oat1, Oat2, Oat3, Oat5, Urat1, Oat1a1, Oatp3a1, Oat-K1), glucose (Sglt1), organic cations (Oct2), and ATP-driven transporters (Mrp3, Mrp4, Bcrp) for which we searched in silico for androgen (ARE), estrogen (ERE), estrogen-related (ERR), and progesterone (PRE) responsive elements within a 3 kb promotor regions upstream of the translation start. It is evident that the promotor regions of rat, mouse, and human transporters harbor several AREs and relatively few EREs and ERRs. The promotors of Oatp1a1 and Oat-K1 contained 15 PREs, whereas for other transporters, PREs were less abundant than AREs. An M-dominant expression appears to be related to a surplus of AREs over EREs for most (Oat1, Oat3, Urat1, Oct2, Oat-K1, Mrp4) transporters. An F-dominant expression, however, is found either with more AREs than EREs (Oat5, Mrp3) or with no obvious difference between AREs and EREs (Oat2). Presently, it is unknown which of the sex SRE are active in driving gene expression of renal transporters in rodents and in humans.

To test if gender differences are present for other renal transporters in rats, we have isolated total RNA from the kidney cortex of six M and six F rats and performed hybridization studies on an established microarray chip (evanescent resonance-based NovaChip, Novartis, Switzerland), which contained oligonucleotides representing approximately 450 rat genes as recognition elements [32, 170]. The relevant data for renal transporters, which exhibited significant M-dominant or F-dominant differences, were extracted and summarized in Table 7. Some of the transporter families were not present on the chip and were labeled with "Not represented," whereas the families containing members that did not exhibit gender differences were labeled with "None." These and other members of Slc family of transporters, as well as the members of Abc family of transporters, that did not exhibit gender differences in our study are listed in Fig. 2 (see later). In addition, we have to

Table 6 Androgen, estrogen, estrogen-related, and progesterone responsive elements in the promotor regions of renal transporters in M and F rats, mice, and humans

Transporter	Gender-dependency	ARE			ERE			ERR			PRE		
		r	m	h	r	m	h	r	m	h	R	m	h
Oat1	(M > F)	3	4	3	–	1	–	3	2	2	1	1	2
Oat2	(F > M)	1	2	2	1	2	3	–	1	–	1	1	–
Oat3	(M > F)	2	4	1	2	1	1	3	2	1	1	2	–
Oat5	(F > M)	3	4	no	2	–	no	–	1	no	2	3	no
Urat1	(M > F)	4	2	1	–	–	1	1	–	1	1	2	–
Oatp1a1	(M > F)	4	4	4	1	1	–	–	2	2	15	2	2
OATP3A1	(M > F)	no	no	7	no	no	3	no	no	–	no	no	–
Oct2	(M > F)	5	1	3	3	3	2	1	2	–	3	2	2
Oat-K1	(M > F)	4	no	no	1	no	no	–	no	no	15	no	no
NKCC2	(M > F)	2	2	2	–	–	2	1	–	2	3	–	2
Sglt1	(M > F)	4	4	4	1	2	–	1	1	3	1	2	5
Mrp3 (ABCC3)	(F > M)	2	5	1	1	2	–	3	2	5	3	–	–
Mrp4 (ABCC4)	(M > F)	4	5	–	1	1	–	–	1	2	2	–	–
Bcrp (ABCG2)	(M > F)	1	2	2	1	4	2	–	2	–	1	2	1

Three kb of the proximal promotor regions were analyzed in silico by MatInspector (Release professional 7.4.8, May 2007), Genomatrix (München).

ARE Androgen responsive element; *ERE* estrogen responsive element; *ERR* estrogen-related responsive element; *PRE* progesterone-responsive element; *M* males; *F* females; *r* rat; *m* mouse, *h* human; *no* no ortholog.

Table 7 Gender differences in the expression of various transporters of Slc family in rat renal cortex: the microarray data

Slc family (description)	Slc member (protein name/alias)	Predominant substrate(s)	Mean±S.E.M.(A.F.U.)		M / F
			M	F	
Slc1 (High affinity glutamate and neutral aa transporters)	a1 (EAAC1/System X^-_{AG})	L-Glutamate, D/L-Aspartate	7,180±490	4,796±362	1.5
Slc2 (Facilitative GLUT transporters)	a1 (Glut1)	Glucose, galactose, mannose, glucosamine	1,089±47	1,437±61	0.8
	a4 (Glut4)	Glucose, dehydroascorbic acid, glucosamine	158±18	246±18	0.6
Slc3 (Heavy subunits of the heteromeric aa transporters)	None (cf. Fig. 2)				
Slc4 (Bicarbonate transporters)	a1 (AE1/Band 3)	Chloride, bicarbonate	313±20	509±53	0.6
Slc5 (Na^+-glucose cotransporters)	a6 (SMVT)	Biotin, lipoate, pantothenate	8±0,5	16±0,5	0.5
Slc6 (Na^+ and Cl^--dependent neurotransmitter transporters)	None (cf. Fig. 2)				
Slc7 (Cationic aa transporters/glycoprotein-associated aa transporters)	a7 (y^+LAT1)	Cationic aa (Na^+-independent) Large neutral L-aa (Na^+-dependent)	23,731±1,414	17,441±1,102	1.4
Slc8 (Na^+/Ca^{2+} exchangers)	a3 (NCX3)	Sodium, calcium	4,834±482	6,864±327	0.7
Slc9 (Na^+/H^+ exchangers)	a1 (NHE1/APNH)	Na^+, H^+, Li^+, NH4	231±13	272±9	0.8
	a2 (NHE2)	Na^+, H^+, Li^+, $NH4^+$	230±8	433±35	0.5
Slc10 (Na^+-bile salts cotransporters)	None (cf. Fig. 2)				
Slc11 (H^+ coupled metal ion transporters)	None (cf. Fig. 2)				
Slc12 (Electroneutral cation-Cl^- cotransporters)	a1 (NKCC2/BSC1)	Na^+, K^+, Cl^-	4,721±115	7,070±176	0.7
	a3 (NCC/TSC)	Na^+, Cl^-	7,645±433	10,385±738	0.7
Slc13 (Human Na^+-sulfate-carboxylate cotransporters)	None (cf. Fig. 2)				
Slc14 (Urea transporters)	None (cf. Fig. 2)				
Slc15 (H^+-oligopeptide cotransporters)	a1 (Pept1)	Dipeptides, tripeptides, H^+	1,283±64	959±55	1.3
	a2 (Pept2)	Dipeptides, tripeptides, H^+	1,329±210	2,873±144	0.5
Slc16 (Monocarboxylate transporters)	a1 (MCT1)	Lactate, pyruvate, ketone bodies	7,497±544	4,643±538	1.6
	a2 (MCT8)	T3, T4	341±22	214±14	1.6
Slc17 (Vesicular glutamate transporters)	None (cf. Fig. 2)				
Slc18 (Vesicular amine transporters)	None (cf. Fig. 2)				
Slc19 (Folate/thiamine transporters)	a1 (RFT/RFC/FOLT)	N^5-methyltetrahydrofolate	3,524±124	2,423±243	1.5
Slc20 (Type III Na^+-phosphate cotransporters)	None (cf. Fig. 2)				
Slc21 (Organic anion transporters (Slco1a1, Slco3a1)	a1 (Oatp1/Oatp1a1)	Bile salts, organic anions, organic cations	1,118±274	18±2	63
	a11 (Oatp3a1/MJAM)	Estrone-3-sulfate, prostaglandin	12,997±621	9,155±808	1.4
Slc22 (Organic cation/anion/zwitterion transporters)	a2 (Oct2)	Organic cations	2,995±364	1,418±151	2.1
	a5 (Octn2/CT1)	L-Carnitine, organic cations	8,730±583	5,443±215	1.6
	a7 (Oat2)	Organic anions	68±19	2,153±83	0.03
	a8 (Oat3)	Organic anions	47,627±2,625	38,334±1,476	1.2
Slc23 (Na^+-dependent ascorbic acid transporters)	not represented				
Slc24 ($Na^+/(Ca^{2+}$-$K^+)$ exchangers)	None (cf. Fig. 2)				
Slc25 (Mitochondrial carriers)	a21 (ODC)	Oxodiadepate, oxoglutarate	93±11	146±5	0.6
Slc26 (Multifunctional anion exchangers)	a1 (Sat-1)	SO^{2-}_4, oxalate	4,281±306	2,825±193	1.5
	a4 (Pendrin)	Cl^-, HCO^-_3, I^-, formate	2,439±235	4,205±260	0.6
Slc27 (Fatty acid transport proteins)	None (cf. Fig. 2)				
Slc28 (Na^+-coupled nucleoside transporters)	None (cf. Fig. 2)				

Table 7 (continued)

Slc family (description)	Slc member (protein name/alias)	Predominant substrate(s)	Mean±S.E.M.(A.F.U.)		M / F
			M	F	
Slc29 (Facilitative nucleoside transporters)	None (cf. Fig. 2)				
Slc30 (Zinc efflux transporters)	None (cf. Fig. 2)				
Slc31 (Copper transporters)	None (cf. Fig. 2)				
Slc32 (Vesicular inhibitory aa transporters)	Not represented				
Slc33 (Acetyl-CoA transporters)	Not represented				
Slc34 (Type II Na^+-phosphate cotransporters)	None (cf. Fig. 2)				
Slc35 (Nucleoside-sugar transporters)	Not represented				
Slc36 (H^+-coupled aa transporters)	Not represented				
Slc37 (Sugar phosphate/phosphate exchangers)	Not represented				
Slc38 (System A and N, Na^+-coupled neutral aa transporters)	a1 (SNAT1/ATA1)	Glutamine, alanine, asparagine, cysteine, histidine, serine	819±42	529±34	1.5
Slc39 (Metal ion transporters)	None (cf. Fig. 2)				
Slc40 (Basolateral iron transporters)	Not represented				
Slc41 (MgtE-like magnesium transporters)	Not represented				
Slc42 (Rh ammonium transporters)	Not represented				
Slc43 (Na^+-independent, system L-like aa transporters)	Not represented				

Shown are the statistically significant ($P<0.05$) microarray data (arbitrary fluorescence units; A.F.U.) for the expression of mRNA from six male (M) and six female (F) rats.
Methods: Total RNA from the rat kidney cortex homogenate was isolated using TRIzol Reagent (Invitrogen) and Phase Lock Gel (Eppendorf) following recommendations by the manufacturers. The isolated RNA was cleaned up using RNeasy Mini Kit and DNase set (QIAGEN), quantified, and quality checked by agarose gel electrophoresis. The total RNA was then used for hybridization on an evanescent resonance (ER)-based NovaChip microarray chip (ER-microchip, Novartis). Details on the characteristics, preparation, cleaning, and use of these slides were published previously [32, 170]. RNA was labeled with the fluorescent probe Amersham CY5 using Ambion kit (q753) starting from 500 ng total RNA. A Tecan HS 4800 Hybridization station (Tecan, Inc.) was used for prewash/hybridization/postwash of the microarrays. Prewash consisted of three cycles with wash buffer at RT/75°C/50°C (each 20 sec) followed by an additional 10 sec wash with hybridization buffer at 50°C. One hundred microliter sample (100 ng labeled RNA) in hyridization buffer was then injected into the flow chambers at 50°C and agitated for 1 min. Subsequently, after 10 min at 75°C, the temperature was adjusted to 42°C for 16 h (agitation). The postwash consisted with four cycles wash buffer at 42°C followed by an additional wash at 23°C (each 20 s). Finally, the slides were washed three times with diluted wash buffer at RT, dried in N_2 stream, and scanned immediately with an Tecan fluorescence laser scanner (gain 80%). Scanning was carried out with 10-μ resolution, the "pixels" of the spots were averaged and the signal of a particular gene was the mean of three replicates. The fluorescence images were analyzed by means of Array Pro (Mediacybernetics, Inc., USA). Net signals (arbitrary fluorescence units) were calculated by subtracting the mean of local corner background from mean of each spot. Individual samples were processed on separate slides in single color mode (Cy5). The net mean value of each microarray was used for normalization. The image analysis was configured in a way that allowed exclusion of individual spots based of their quality (criteria: local fluorescence background, spots morphology). Only microarays with >95% qualified spots were used for further analysis.
aa Amino acids. *Not represented* genes not represented on the microarray chip. *None* members that exhibited no significant gender differences.

emphasize that F rats in this study were not tested for their hormonal status (oestrus cycle), which may influence the expression of some genes via modulating the blood levels of sex hormones; the expression pattern of Oats, Octs, or other renal transporters in the oestrus cycle has not been studied thus far.

From the data in Table 7 we can learn the following: (1) A number of transporters in Slc family exhibited gender differences at the level of mRNA expression. (2) Glut4 (Slc2a4) is not specific for kidney and probably originated from the contaminating adipocytes, SMVT (Slc5a6) was negligibly expressed, whereas ODC (Slc25a21) is a carrier in mitochondria and is not a topic of this review. (3) In general, the renal carriers that mediate Na^+-dependent and Na^+-independent (including exchangers) transports of organic compounds [neutral and cationic amino acids, oligopeptides (via Pept1), monocarboxylates and thyroid hormones, folate, various organic anions and cations, zwitterions, oxalate] and sulfate exhibited an M-dominant pattern, whereas transporters of inorganic substances (chloride, bicarbonate, iodine, some monovalent and divalent cations) but also some Na^+-independent carriers of organic compounds (hexoses, oligopeptides (via Pept2), and some organic anions) exhibited an F-dominant pattern. (4) The strongest gender differences were observed in the expression of M-dominant Oatp1 (Slc21a1; 63-fold higher in M than in F) and the F-dominant Oat2 (Slc22a7; 32-fold higher in F than in M). These microarray data for Oatp1 mRNA are in a good agreement with the previous findings in Western blot studies of isolated renal membranes, in which the respective protein band was strong in M and negligible in F [77], whereas the data for Oat2 mRNA perfectly match the recently published RT-PCR, Western blot, and immunocytochemical data in rats, where the respective mRNA expression, protein band density, and immunostaining intensity were strong in the brush-border of proximal tubule S3 segment in F and hardly visible in M [134]. (5) The previously observed M-dominant expressions of Oatp1 (Slc21a1) in rats, Oatp3a1 (Slc21a11) in mice, Oct2 (Slc22a2) in rats, and Oat3 (Slc22a8) in rats, and F-dominant expression of Oat2 (Slc22a7) in rats and mice (cf. data in Table 5) were confirmed in this study in rats. However, the mRNA expression for Oat1 (Slc22a6), Oat-K (Slc21a4), and Sglt1 (Slc5a1) exhibited no gender differences (their expression is shown in Fig. 2), whereas Oat5 (Slc22a19) and Urat1 (Slc22a12) were not represented in our study. The reason for the lack of gender differences in Oat1 and Oat-K mRNA expression in our study is not known; previous studies of gender differences in Oat1 mRNA in the rat kidney provided positive [33, 34] and negative results [115, 264]. This is also at odds with the fourfold to fivefold difference (M>F) in the abundance of Oat1 protein observed in isolated membranes from the renal cortex in M and F rats [135] and indicates that the expression of mRNA and protein is not always in parallel and can be independently regulated at the level of mRNA and/or protein synthesis and/or degradation. Regarding Sglt1, the strongest F-dominant gender difference in its expression was observed in the proximal tubule S3 segment in the outer stripe, and

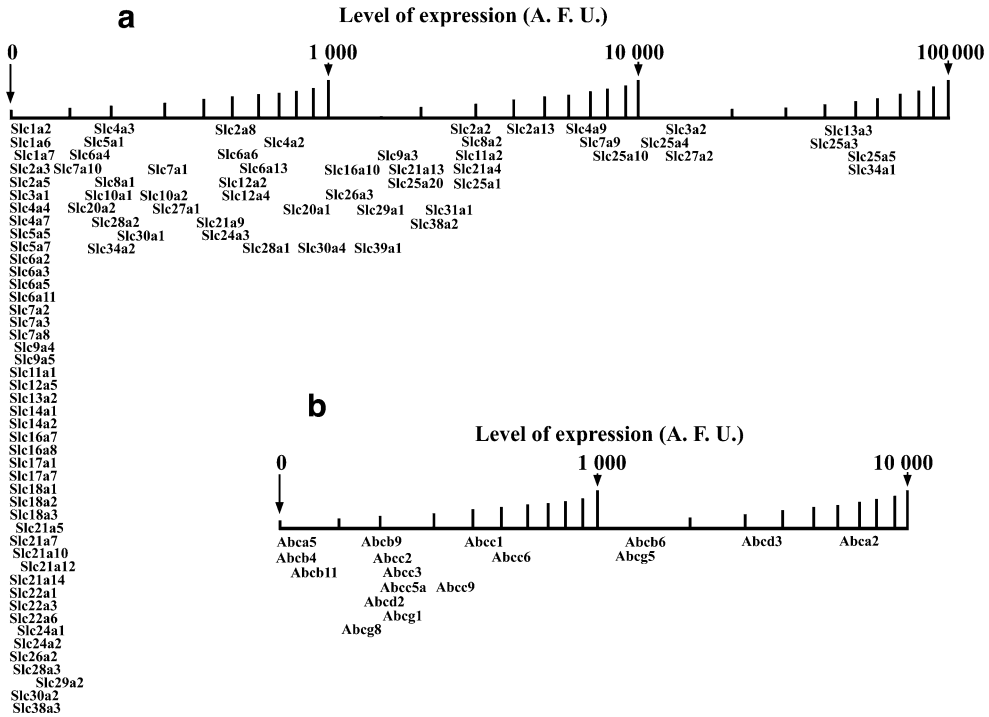

Fig. 2 Schematic presentation of the levels of mRNA expression, shown as arbitrary fluorescence units (A.F.U.), for various rat renal cortical transporters of Slc family (**a**) and Abc family (**b**) that did not exhibit gender differences in our microarray study. The level of mRNA expression for an individual transporter in M and F rats was averaged, and its symbol was positioned horizontally under the logarithmic scale according to its expression level. The center of the symbol indicates an average value of the mRNA expression. See text for other explanations

this difference may not be detected using RNA from the whole cortex, as also observed by Northern blotting [203]. (6) NKCC2 (Slc12a1) mRNA in this study exhibited an F-dominant expression, whereas in the previous study in renal medulla, the NKCC2 protein was expressed in an M-dominant pattern [29]. (7) It is interesting that Pept1 (Slc15a1), which is localized to the brush-border of proximal tubule S1 and S2 segments [224], exhibited an M-dominant expression, whereas Pept2 (Slc15a2), localized to the brush-border of proximal tubule S3 segment [224], exhibited a strong F-dominant expression. If similar gender differences in Pept1 and Pept2 mRNA are also present at the protein level, they may accordingly influence reabsorption of the filtered oligopeptides in the proximal tubule. The M-dominant expression of Pept1 protein could also explain the higher renal excretion of cyclacillin and its metabolites in F rats; higher Pept1-mediated reabsorption of these compounds in the M nephron may result in lower renal excretion, higher accumulation in the M proximal tubule cells, and higher nephrotoxicity in M [99, 132, 261, 262]. (7) Similarly, higher expression of Octn2 mRNA in M, a transporter of L-carnitine in the proximal tubule brush-border membrane [248], may explain the low renal excretion of carnitine in M rats due to its higher reabsorption in the proximal tubule [41]. (8) If accordingly translated into proteins, the higher expression of mRNA for Sat-1 (Slc26a1; localized at the basolateral membrane of proximal tubule cells [106]) in M and Glut1 (Slc2a1; localized to the cell basolateral membrane in proximal tubule S3 segments in F [258]) indicates a possible contribution of these carriers to a higher reabsorption of the respective substrates in M and F, respectively. Moreover, a higher expression of Glut1 in the basolateral membrane of proximal tubule S3 segment in F rats could perfectly match the elevated abundance of Sglt1 in brush-border membrane of the same tubule segment [203]. (9) The F-dominant gender differences (F>M) in the expression of mRNA for various carriers that transport protons, chloride, and bicarbonate and include AE1/Band 3 (Slc4a1; localized to the basolateral membrane of A-type intercalated cells [3]), NHE1 (Slc9a1; localized to the basolateral membrane along the nephron [19]), NHE2 (Slc9a2; localized to the apical membrane along the nephron [45]), and Pendrin (Slc26a4; localized largely to the apical membrane of B-type intercalated cells [200]) indicate that acid-base handling may be different in M and F nephron.

The levels of expression for the members of Slc family that did not exhibit gender differences are summarized in Fig. 2 (a). The individual members of the Slc family were positioned horizontally under the logarithmic scale according to their level of mRNA expression (average of the M and F levels) shown by arbitrary fluorescence units (A.F.U.). Nearly half (46 out of 95) of the transporters exhibited quite low expression (<100 A.F.U.), the expression of most other transporters (42 members) was between 100 and 10,000 A.F.U., whereas a very few transporters (seven members) exhibited an expression of >10,000 A.F.U. The highest expression (40,000–60,000 A.F.U.) was recorded for the Pi transporter (Slc25a3) and the ADP/ATP exchanger (Slc25a5) in mitochondria, for the basolateral Na^+-dicarboxylate cotransporter NaDC3 (Slc13a3) in the proximal tubules and for the Na^+-Pi cotransporter NaPi-3 (Slc34a1) in the proximal tubule brush-border membrane.

In Table 8 we included a few more microarray data for the Abc family members and other transporters and channels that exhibited gender differences at the mRNA level. Multidrug resistance proteins belong to the Abc/ABC superfamily of pumps that use energy of ATP to extrude a variety of endogenous and exogenous anionic (Mrp/MRP subfamily) and cationic compounds (Mdr/MDR subfamily). Various members of this family were localized to the apical or contraluminal cell membranes in distinct segments of the mammalian nephron (reviewed in [89, 126, 128, 132, 198, 217, 218, 267]). Although the roles of some of these transporters in the rat, mouse, and human kidneys have been well described, our microarray data showed a very low mRNA expression with M-dominant gender differences only for Mdr-1/P-glycoprotein and Mdr1a/TAP (both from the Abcb subfamily). A number of other Abc family members exhibited no gender differences, and their expression is listed in Fig. 2 (b). Mrp4 (Abcc4) and Bcrp (Abcg2), with previously described M-dominant expression in the rat kidney [46, 252], were not represented in this study. However, among 17 presented gender-independent members was also Mrp3 (Abcc3), a transporter that in mice exhibited F-dominant expression [145].

As further shown in Table 8, an M-dominant gender expression of mRNA was also recorded for B2 isoform of the 56 kDa subunit of V-ATPase (dependent on the nephron segment and cell type, localized to the apical or basolateral membrane [181]) and chloride channels Clc4, Clc5, and Clc7 (localized to cell membrane and intracellular vesicles in various nephron segments; mutations associated with formation of kidney stones and osteopetrosis in humans [73, 93, 140, 213]), whereas an F-dominant expression of mRNA was recorded for the Ca^{2+}-sequestring ATPase (calcium pump, localized in endoplasmic reticulum and Golgi membranes; mutations associated with impaired regulation of cytoplasmic Ca^{2+} [91]), cubilin (localized to the proximal tubule brush-border membrane; contributes as a receptor in endocytosis-mediated reabsorption of filtered cationic proteins, vitamins, lipids, and hormones [155]), chloride channel Clc-K2 (localized to the basolateral membrane of distal tubule segments; role in transepithelial chloride transport [114]), and claudins 1, 11, and 16 (tight junction integral membrane proteins that control the

Table 8 The microarray data: Abc family members, other transporters and channels in the rat renal cortex that exhibited significant gender differences

Marker symbol	Protein (description)/alias	Predominant substrate(s)/function	Mean±S.E.M. (A.F.U.)		M / F
			M	F	
Abcb/Pgy1	Mdr-1 (Multidrug resistance protein 1)/P-glycoprotein	Various endogenous and egzogenous compounds	95±6	70±9	1.4
Abcb1a	Mdr-1a/TAP (Multidrug resistance protein 1a)	Various endogenous and egzogenous compounds	99±7	67±5	1.5
Atp2c1	Ca^{2+}-sequestring ATPase	Ca^{2+}	336±33	464±36	0.7
Atp6b2	V-ATPase B2 subunit (brain isoform)	Vacuolar H^+ pump, 56 kDa subunit	12,327±194	10,177±523	1.2
Cubn	Cubilin	Various cationic proteins and other substances	5,734±118	9,152±436	0.6
Clcn4	Clc4/chloride channel 4	Cl^-, H^+	248±13	167±6	1.5
Clcn5	Clc5/chloride channel 5	Cl^-, H^+	147±9	122±5	1.2
Clcn7	Clc7/chloride channel 7	Cl^-	355±18	296±12	1.2
Clcnk1l	Clc-K2	Cl^-	15,503±664	23,427±1,287	0.7
Cldn1	Claudin 1	Cl^- and other anions that cross tight junction	241±16	476±26	0.5
Cldn11	Claudin 11	Cl^- and other anions that cross tight junction	333±73	1,734±127	0.2
Cldn16	Claudin 16	Mg^{2+}, Ca^{2+} that cross tight junction	831±62	1,097±70	0.8

Shown are the statistically significant ($P<0.05$) microarray data (arbitrary fluorescence units; A.F.U.) for the expression of protein-specific mRNA from six male (M) and six female (F) rats. The details on the microarray analysis are described in the legend of Table 7.

permeability of monovalent anions or divalent cations in proximal or distal tubule segments [108, 112, 195]). As outlined above, all microarray data should be considered as putative, unless the protein expression is known.

Conclusion

Sex hormones affect the structure of renal tubules and various aspects of renal functions in experimental animals and humans. Most of today's knowledge is based on studies in rodents showing that gender-dependent phenomena in kidneys take place at the level of mRNA and/or protein expression of various transporters in the apical and basolateral membranes of the cells in specific nephron parts. Due to contradictory data on the presence, abundance, and intracellular localization of sex hormone receptors in renal tubules, it is presently impossible to correlate gender-dependent expression of these receptors with renal functions and expression of various transporters. Studies relevant to transporter expression in mice with testicular feminization (Tfm mice), which lack functional androgen receptors, and in ERKO mice, knockouts for estrogen receptors, have not been reported. Poorly studied is also expression at the mRNA and protein level of various renal transporters in the female hormonal cycle (oestrus in rodents), pregnancy, and ageing, e.g., in various conditions during life in animals and humans, which are associated with significant changes in blood levels of M and F sex hormones. Furthermore, studies in experimental animals indicate an important role of sex hormones in the development of some renal diseases and in influencing pharmacotherapy, drug–drug interactions, and drug-induced nephrotoxicity, largely by affecting the expression of transporters of organic anions and cations that contribute to reabsorption, secretion, and toxic accumulation of these compounds. In humans, many drugs and other substances that are transported by the kidneys cause more adverse and nephrotoxic effects in F, but detailed studies on gender-dependent renal expression of relevant transporters in humans have not been performed. Finally, our microarray data indicate that, besides OATs and OCTs, a number of transporters and regulatory and functional proteins in the rat nephron exhibit gender differences at the mRNA level; these observations should be further tested for protein expression and relevant functions in both rodents and humans.

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