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Sex differences in renal electrolyte transport

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Abstract

Purpose of review: Women experience unique life events, e.g., pregnancy and lactation, that challenge renal regulation of electrolyte homeostasis. Recent analyses of nephron organization in female versus male rodent kidneys, revealed distinct sexual dimorphisms in electrolyte transporter expression, abundance, and activity. This review aims to provide an overview of electrolyte transporters organization and operation in female compared to the commonly studied male kidney, and the (patho)physiologic consequences of the differences.

Recent findings: When electrolyte transporters are assessed in kidney protein homogenates from both sexes, proximal transporters, overall, exhibit female to male ratios less than one, and post macula densa transporters, overall, exhibit ratios greater than one, which is indicative of a "downstream shift" in fractional reabsorption of electrolytes in females. This arrangement improves the excretion of a sodium load, challenges potassium homeostasis, and is consistent with the lower blood pressure and greater pressure natriuresis observed in pre-menopausal females.

Summary: We summarize recently reported new knowledge about sex differences in renal transporters: 1) abundance and expression along nephron, 2) implications for regulation by Na^+, K^+ and angiotensin II, and 3) mathematical models of female nephron function.

Keywords

renal electrolyte transporters; sex differences; proximal tubule; distal nephron; computational models

Introduction

Evolutionary forces have shape organisms to optimize reproduction, resulting in notable sex differences in most tissues, including the kidney. Sexual dimorphism in the structure and function of the kidney reflects the different life cycle changes faced by the two sexes: females undergo pregnancies and lactation that increase fluid and electrolyte input, balanced by output to growing offspring, and then menopause; in contrast, males develop

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to adulthood, mate and age with static renal function. The female kidney adapts to maintain homeostasis through these normal life cycle challenges. During the past six years a substantial body of new information has revealed sex specific differences in renal transporter expression [1–4], relative abundance [5–8], activity and regulation [5, 6, 9–16]. Herein we discuss these reports, their implications, gaps, and future opportunities.

Experimental data collection on Female vs Male renal transporters

How does sex impact epithelial transport along the nephron? To answer that question requires: 1) consideration of factors that determine the pool size and activity of transporters, then 2) understanding of the functional implications of these sex differences. Transporters are defined herein to include: co-transporters, channels, pumps and claudins. Transporter abundance in the membrane is a function of respective rates of synthesis and degradation as well as trafficking to and from the membrane. Transporter activity is determined by the abundance of active transporters in the cell membrane and may be influenced by morphometrics (kidney size and proximal tubular segments are smaller in females) hemodynamics, covalent modifications (phosphorylation, cleavage, protein-protein associations), as well as activators or inhibitors delivered in the tubule fluid. An important consideration for experimental designs is estrus cycling. In our rat studies, estrus cycling, assessed by vaginal smears, does not significantly impact renal transporter abundance or covalent modification [5]. Cowley and colleagues assessed variability of 142 phenotypes in 50 inbred strains and found no evidence for greater variability in females vs. males [17]. Thus, the notion of restricting studies to males to avoid complications of estrus cycling is not supported by data.

Veiras et al [5] explored the sex differences in transporters along the nephron in untreated female and male rats and mice. Fig. 1 summarizes the relative abundance of a sub-set of transporters in female rats normalized to abundance in male rats (defined as 1). The ratios were determined in homogenates by semi-quantitative immunoblotting [18]. Cortex homogenates represent proximal tubules, cortical thick ascending limbs, distal convoluted tubules, connecting tubules and cortical collecting ducts; medullary homogenates represent some proximal tubules, medullary thick ascending limbs and medullary collecting ducts. Fig 1. Legend details definitions of transporter abbreviations.

Proximal tubule.

Female rats receive less filtrate, yet exhibit 1/3 lower proximal tubule bicarbonate reabsorption, 2-fold higher endogenous lithium clearance (marker of volume flow from the proximal nephron), and excrete a saline bolus twice as fast as males; along the proximal nephron, females reabsorb ½ of the filtered load vs. 2/3 of the filtered load reabsorbed in males [5]. The Na/H exchanger, NHE3, a major Na transporter in the proximal tubule, is not correspondingly less abundant in female than male rats. However, two observations support lower NHE3 activity in female rats: 1) NHE3 localizes to the base of the proximal tubule brush border microvilli in both rats and mice (Fig 2) [5, 11] where transport activity is lower [19, 20], and 2) NHE3 phosphorylation (NHE3pS552), a marker for redistribution to the base of the microvilli [19], is greater in female rats. NaPi2, claudin-2 and AQP1 are also

less abundant in female vs. males (Fig 1). Taken together these measurements predict the lower fractional reabsorption along the proximal tubule (Fig 3) and more rapid excretion of a saline bolus in females vs. males. In contrast, the sodium glucose co-transporters SGLT1 and 2 are 20–30% higher in female vs male proximal tubule [8, 21], likely a compensation to completely reabsorb filtered glucose in a shorter tubule [22]. In comparison, NHE3 abundance in mice is 50% lower in female vs. male [5].

Na^+ transporters along medullary thick ascending loop of Henle.

The thick ascending limb receives greater fluid and electrolyte delivery from the proximal tubule in females due to their lower proximal fractional reabsorption. A compensatory "downstream shift" in Na^+ and volume reabsorption must occur post-proximal tubule to maintain homeostasis (Fig 3). The apical NKCC2 and the basolateral Na,K-ATPase are collectively 20 – 40% greater in female vs. male rats (Fig 1). In comparison, female mice do not exhibit higher medullary sodium transporters, indicating species specific differences along the proximal and medullary tubules [5].

Na^+ transporters along distal nephron and collecting duct.

The female-to-male transporter ratio is elevated post-macula densa in females consistent with compensation for the higher delivery from upstream (Fig 3). NCC and NCCp (a marker for apical distribution) [23], which meters Na^+ downstream to ENaC, is 2-fold higher in females than males (Fig 1). Additionally, ENaC, as well as claudin −7 and −8 abundance, which facilitate and amplify net ENaC reabsorption [24, 25], are greater in females vs males and drive higher K^+ secretion via K channels in the collecting duct. Consequently, female rats present with lower baseline plasma [K^+][5, 26] compared to males. It is possible that the elevated NCCp in females indicates a response to defend plasma [K^+] during ENaC activation in females [27], a response that can prevent hyperkalemia in states of high dietary K^+ intake during pregnancy and lactation [28]. Overall, the pattern of transporters along the distal nephron is similar in mice and rats; however, plasma [K^+] is comparable between sexes in mice [5].

mRNA, hormones and genes.

Ransick *et al* categorized single cell RNA in adult male and female mouse kidneys and discovered that proximal tubule cells clustered according to sex [1]. Their analysis of the many sex differences along the proximal tubule is provided in the very useful Kidney Cell Explorer web resource (https://cello.shinyapps.io/kidneycellexplorer/). Recently, Chen *et al* [4] conducted a transcriptomic and proteomic analysis of microdissected proximal tubule S1, S2, S3 segments and found that sex differences are primarily evident in the S2-S3 segments of the proximal tubule, in agreement with previous reports [2, 3], they also reported correlation between proteome and transcriptome in sex biased proteins; information is provided at https://esbl.nhlbi.nih.gov/MRECA/PT/. Messenger RNA analyses like these can provide novel information regarding cell specific expression, developmental trends, regulatory impact and disease related changes [2, 29]. Importantly, transporter mRNA levels are not effective predictors of transporter abundance or activity because of the prominent differences in rates of protein synthesis and degradation, post-translational modifications,

and subcellular trafficking of transporters. A combination of mRNA and protein analyses [4] can theoretically provide novel information about relative turnover rates [30].

Investigators have provided evidence for gonadal hormone regulation of sexual dimorphism in the structure and function of the kidneys: testosterone regulates ammonia metabolism and excretion [6, 31–34], as well as SGLT2 and organic anion transporter (OAT) expression [8, 35]. Androgen receptor mRNA and protein are expressed exclusively along the proximal tubule [1, 33], while transcripts of estrogen receptor α and β are detected in both proximal and distal tubules [1]. Opportunities exist to determine whether sex differences are due to hormonal versus sex chromosome differences (or both) by utilizing a Four Core Genotype approach that produces Male XX and Female XY as well as conventional Male XY and Female XX strains that are amenable to baseline and (patho)physiological studies [36].

Implications of sexual dimorphisms for renal (patho)physiology

How do distinct female vs. male transporter profiles impact the physiologic responses to electrolyte and hormonal challenges?

Female transporter pattern allows a more rapid natriuretic response to a high-salt diet.

Rodents respond to a high-salt diet (4% NaCl) with natriuresis by translocating NHE3 to the base of the microvilli, decreasing NCC abundance, phosphorylation and surface expression, and reducing ENaC activating cleavage among other adjustments [12, 37]. Females exhibit a more rapid and robust natriuretic response, in part, due to their lower baseline NHE3 activity and lower fractional sodium reabsorption along the proximal nephron. In response to equivalent challenges with a bolus of injected saline (which expands the effective circulating volume and increases both GFR and the filtered load of sodium), a lower fraction of the filtered bolus will be reabsorbed along the proximal tubule in females vs. males; thus, a higher fraction will be excreted at earlier time points in females than males. Balance will be achieved in both males and females following a bolus injection of saline, but more rapidly in females.. This is consistent with the observations by Torres-Pinzon et al [11] in female and male C15BL/6J mice on 15 days of high-salt vs. normal-salt diet. In males, NHE3 trafficked to the base of the microvilli associated with higher NHE3p, whereas in females, NHE3 remained at the base of the microvilli at ½ the abundance in males on same high-salt diet. This observation logically extends to chronic dietary salt intake: Gohar *et al* [12] reported that female rats on high-salt diet achieved salt balance within one day while male rats required more than 5 days, correlating with higher endothelin −1 excretion in females. Further evidence for the “female advantage” in the response to high-salt diet was provided by Veiras et al. [10] who reported that 4 wk high-salt diet raised blood pressure in diabetic (db/db) male but not in female mice, and that ENaC subunit abundance and cleavage were reduced with high-salt diet in controls as well as db/db females but not in db/db males, correlating with higher inflammation in males.

AngII hypertension transporter profile in males resembles the female profile at baseline.

In male rodents, 3 days of Angiotensin II (AngII) infusion provokes sodium transporter activation along both the proximal (NHE3) and distal nephron (NKCC2, NKCC2p, NCC,

NCCp, and cleaved ENaC subunits) [38] which leads to sodium retention and hypertension. With prolonged infusion times, the elevated blood pressure provokes a pressure natriuresis response, in order to restore and maintain effective circulating volume, typified by reductions in abundance of proximal and medullary thick ascending limb NHE3 and medullary NKCC2 [9, 39, 40]. Interestingly, this transporter profile exhibited in males with prolonged AngII infusion resembles the baseline female transporter profile (lower proximal and medullary TAL sodium transporters and higher distal transporters) consistent with higher fractional excretion of sodium during persistent AngII stimulated ENaC activation [40]. Female mice respond to prolonged AngII infusion by amplifying their "beneficial" baseline pattern: by decreasing the already lower pool sizes of NHE3 and medullary NKCC2 in response to the AngII driven increases in the pool sizes of NCC and ENaC [9].

Responses to K dietary and K load.

Xu *et al* [15] compared the regulation of NCC in adaptation to a low-K diet for 7 days in male and female mice. With a normal K diet hydrochlorothiazide (HCTZ)-induced changes in Na excretion were larger in females than males, consistent with their greater NCC abundance. However, with a low-K diet, HCTZ-induced natriuresis increased in males but not in females, blunting the sex differences in NCC function observed with normal salt diet, and at odds with the observation that NCC phosphorylation increases during low K diet in both sexes (albeit lower fold change in female than in males) [15]. In another recent study, Saha *et al* [41] reported that a K^+ load rapidly stimulated ENaC processing, plasma membrane localization and raised activity in wildtype mice but not in the signaling kinase mTOR complex-2 knockout mice. Notably, female knockout mice exhibited a milder phenotype than male knockouts.

Mathematical modelling of female nephron based on data collection

What are the functional implications of the sex differences in renal transporters in normal physiology, pathophysiology, and pharmacological therapy? Given the complexity of the kidney, computational models based on biophysical principles can facilitate the analysis of the impact of the sexual dimorphism. Comprised of a series of epithelial transport cell models, computational nephron models can simulate kidney functions in male and female rats (Fig. 3A). Model parameters can be specified to account for the sex and species differences in apical and basolateral transporter abundance, based on the transporter profile (Fig. 1) and physiological data [5, 42], such as less NHE3 activity when it is at the base of the microvilli (Fig 0) [19, 20], as well as in single-nephron GFR, and in tubular dimensions [43]. Model simulations predict fluid and solute delivery to individual tubular segment, separately for male and female, (e.g., segmental delivery of Na^+, K^+, and fluid; Fig. 3B–D)), water and solute fluxes through individual transporters or channels, as well as urine flow and solute excretion rates (e.g., last bar labelled "urine" in Fig. 3B–D)[42]. A model parameter set can also be chosen to simulate kidney function in a man or women, in normal physiology, pathophysiology, or pharmacological therapy.

Compared to humans, many of the morphological and molecular properties of rodent kidneys have been experimentally measured. As such, computational models of the kidney

have traditionally been based on rodents. Such models have recently been applied to simulate kidney function to answer a series of physiologically and clinically relevant questions, including risk factors for acute kidney injury [44], the role of the renin-angiotensin system in hypertension [45, 46], and the following:

How does the kidney adapt to the challenges posed by pregnancy to its ability to maintain electrolyte and fluid homeostasis?

Particularly intriguing is that the demands of the developing fetus and placenta change throughout pregnancy. The kidney adapts, involving marked elevation in GFR, renal hypertrophy, and transporter regulation. To understand the functional implications of these complex changes, Stadt and Layton incorporated known renal adaptations of pregnancy [28, 47] into a computational model of nephron transport in a pregnant rat kidney [43, 48]. Model simulations predict that the increased NHE3 and ENaC activities, together with morphological adaptations, drive the drastically enhanced Na^+ reabsorption observed during pregnancy. During late pregnancy, K^+ retention and thus enhanced renal K^+ reabsorption is required despite many kaliuretic factors. Model simulations showed that the increased activity of H,K-ATPase and decreased K^+ secretion along the distal segments help retain K^+.

How does the circadian control of renal transport genes affect overall kidney function, and how does that process differ between male and female mice?

The circadian regulation of renal transporters appears to be sexually dimorphic [49]. Layton and collaborators [50–52] simulated the effects of sex and the circadian clock on renal hemodynamics and transporter activity. Model simulations of the BMAL1 (clock gene) knockout mice predicted a significant reduction in distal Na^+reabsorption in both sexes, but more so in males than in females; a sex-specific effect that may lead to blood pressure reduction in BMAL1-null males [51]. Further, the model predicts that the natriuretic and diuretic effects of thiazide diuretics exhibited sex and time-of-day differences, whereas the effects of K^+-sparing diuretics exhibited a significant time-of-day difference in females only [50].

What about humans?

Given the major differences in anatomy and hemodynamics between the rat and human kidneys, findings obtained using a rodent kidney model may not translate to humans. The sparsity of data has hindered the development of computational models of the human kidney. While human GFR and gross kidney size have been measured, transport activity pattern is mostly uncharacterized. Little is known about sex differences that almost surely exist. Nonetheless, computational models have been developed by extrapolating our knowledge, including sex differences, from rodents to humans [53–56]. While extrapolation may be justified by the similar challenges that female rats and women face in circulating volume adaptation during pregnancy and lactation, the substantial uncertainty must be acknowledged. Using biopsy materials, (e.g., NIDDK Kidney Precision Medicine Project. https://www.niddk.nih.gov/research-funding/research-programs/kidney-precision-medicine-project-kpmp), morphometrics of nephrons of men versus women, and in male versus female rodents could be better quantified with super-resolved 3D imaging of kidneys [57] or renal optical clearing techniques [58]. Relative abundance of

renal electrolyte transporters could be evaluated with antibody and/or proteomic approaches of biopsy material.

Conclusions and Implications

While research and discoveries in sex differences in renal transport is still in the early stages, its relevance to renal disease epidemiology, manifestations, and outcomes is of high relevance and impact. Disparities exist between sexes in kidney disease incidence and progression [59–64]; further research is needed to understand whether those differences are due to electrolyte transporter differences, sex hormones, hemodynamics, or sex dependent incidence of contributing diseases such as diabetes and hypertension (more prevalent in men and women post-menopause) or autoimmune diseases (more prevalent in females) [63, 65–68]. The sympathetic nervous system, renin-angiotensin-aldosterone system and immune system, all impact disease progression and hypertension, all exhibit differential activation in females vs. males, and all impact renal transporter activity [69–72]. Na^+, glucose and water transporters expressed along the renal tubule are effective therapeutic targets for hypertension as well as cardiovascular, metabolic and renal diseases. This calls for further research into mechanistic explanations for the sexual dimorphisms to optimize impact in both sexes. Finally, further investigation of additional renal transporter sex differences will likely provide insight into sex dependent disease mechanisms and new therapies.

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Key Points

- Recent studies in rodents have yielded exciting findings highlighting the sexually dimorphic patterns of transporter expression and salt handling, with major implications in renal function.
- A first step in assessing how the structure and function of the kidney is regulated by sex hormones and chromosomes involves the determination and analysis of the abundance and activity of transporters.
- The distinct female vs. male transporter profiles impact the physiologic responses to electrolyte and hormonal challenges.
- The physiologic consequences of the sex differences in kidney structure were revealed in computational modeling studies.
- The field of sex differences in renal transporters is still growing, with major knowledge gaps that remain to be filled concerning the lifecycle of the female kidney, including development, pregnancy, lactation, menopause, and aging.

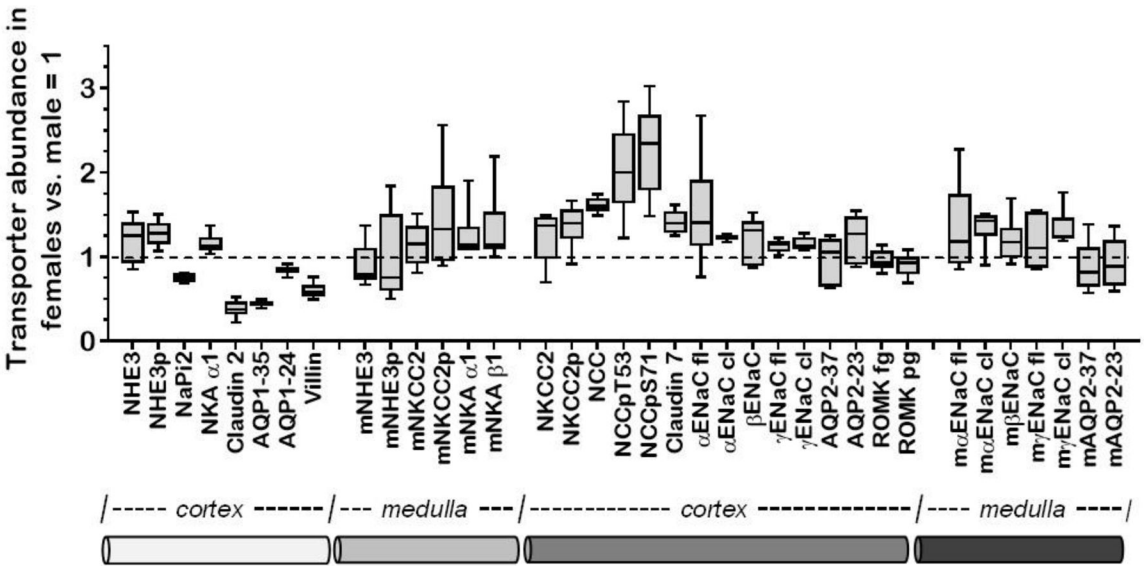

Fig 1. Profile of Sprague Dawley rat renal transporters along the female nephron plotted relative to mean male abundance defined as 1

Box whisker plots: the ends of the box are the upper and lower quartiles such that the box spans the interquartile range, the median is marked by the vertical line inside the box, the whiskers outside the box extend to the highest and lowest observations.

Abbreviations: **NHE3**: Na^+/H^+ exchanger isoform 3, **-pS552** is a NHE3 phosphorylation site associated with less activity. **NaPi2**: Na^+-phosphate cotransporter 2. **NKA α1**: Na,K-ATPase alpha 1 catalytic subunit. **AQP**: aquaporin water channel subunit. **NKCC2:** apical Na+-K^+ $2Cl^-$co-transporter, **-pThr 96 Thr 101** is phosphorylation associated with activation. **NCC:** Na^+-Cl^- co-transporter, **-pS71, -pT53** are NCC phosphorylation sites associated with activation. **ENaC:** epithelial Na^+ channel, **-fl, and –cl:** full length and cleaved forms of ENaC subunits, respectively. **ROMK**: renal outer medulla potassium channel.

Previously published: Hu R, McDonough AA, Layton AT. Functional implications of the sex differences in transporter abundance along the rat nephron: modeling and analysis. Am J Physiol Renal Physiol. 2019;317(6):F1462-F74.

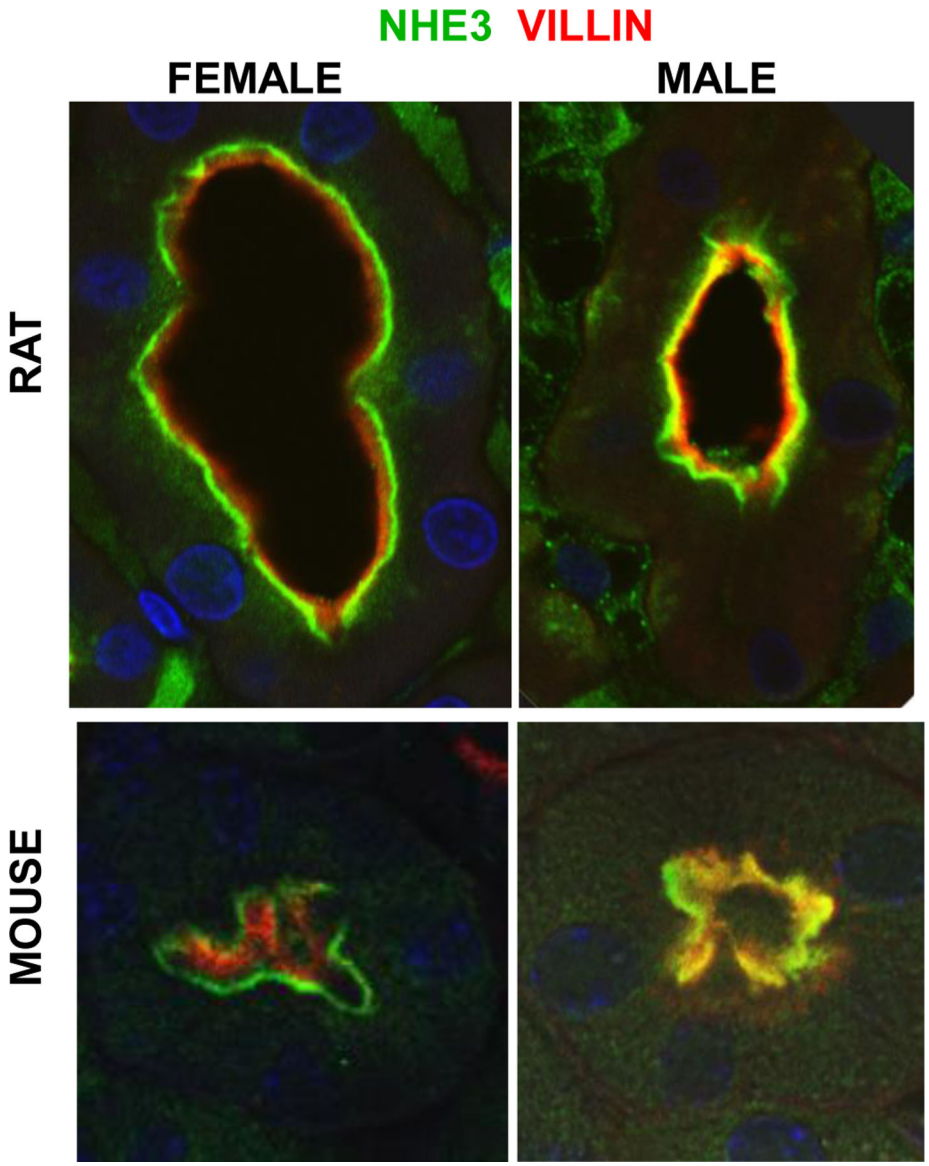

Fig.2. NHE3 preferentially distributes to the base of the microvilli in female rats and mice.
Indirect immunofluorescence microscopy of NHE3 distribution and abundance in kidney samples from untreated male and female Sprague Dawley rats and C57Bl/6J mice. NHE3 detected with polyclonal anti-NHE3 (labelled green) and microvilli identified using monoclonal anti-villin (labelled red). In males, the microvilli, primarily yellow, indicate colocalization of NHE3 with villin in the body of the villi, whereas in the females relatively more NHE3 (green) is focused at the base of the microvilli, revealing more red- stained microvilli.

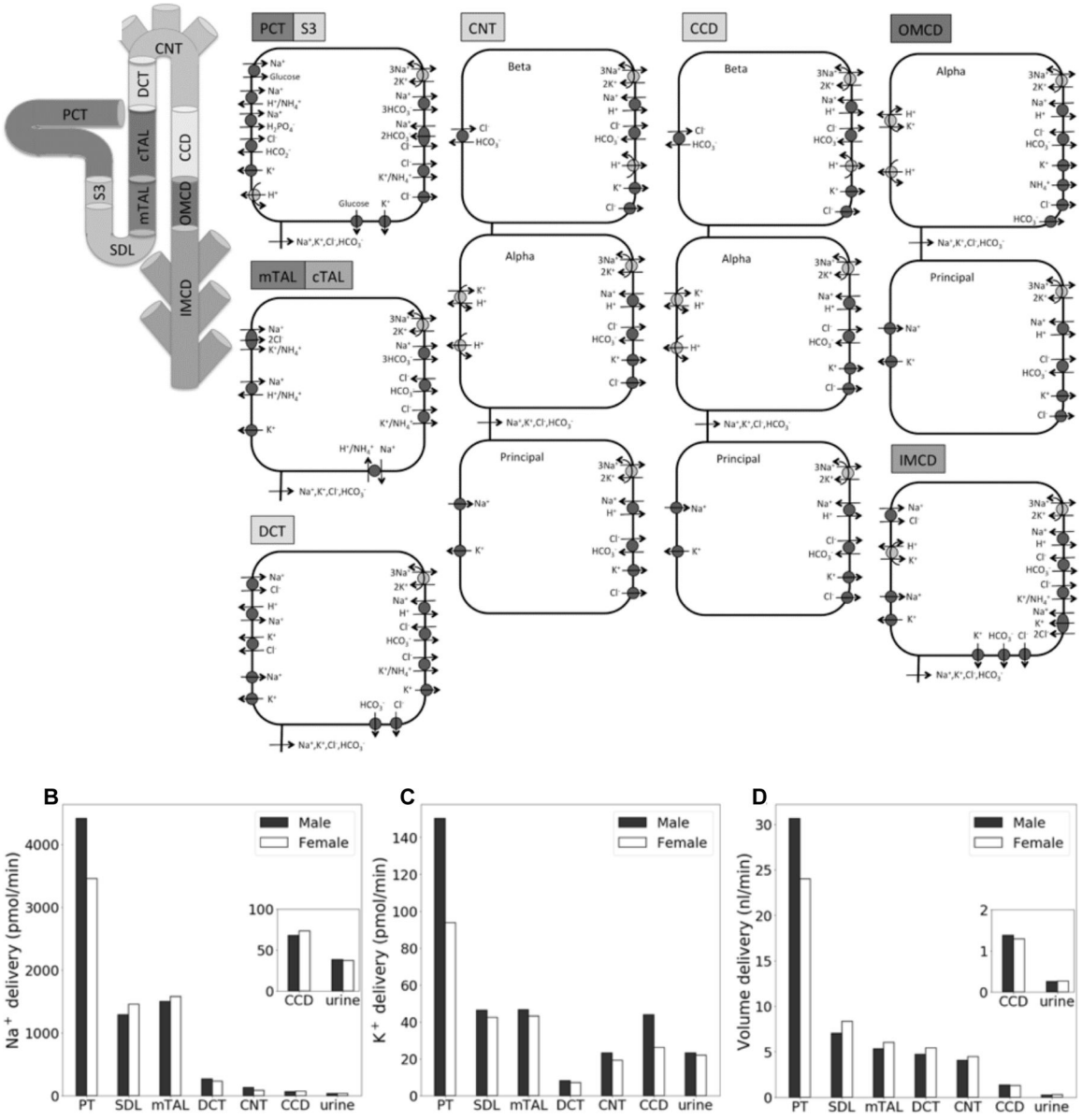

Figure 3. Computational modeling of female versus male nephrons.

Fig 3A. Schematic diagram of the superficial nephron. The model accounts for the transport of water and 15 solutes. The diagram displays only the main Na^+, K^+, and Cl^- transporters.

Abbreviations. PCT, proximal convoluted tubule; mTAL, medullary thick ascending limb; cTAL, cortical thick ascending limb; DCT, distal convoluted tubule; CNT, connecting tubule; CCD, cortical collecting duct; OMCD, outer medullary collecting duct; IMCD, inner medullary collecting duct.

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Fig 3. B,C,D. Delivery of Na^+ (B), K^+ (C), and fluid (D) to the beginning of individual nephron segments in male and female rats. Insets: reproductions of distal segment values. PT, proximal tubule; SDL, short descending limb.

Previously Published: Hu R, McDonough AA, Layton AT. Functional implications of the sex differences in transporter abundance along the rat nephron: modeling and analysis. Am J Physiol Renal Physiol. 2019;317(6):F1462-F74.