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SLCO4A1 Governs PGE2-Mediated Natriuresis in the Kidney

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Abstract:	Background Renal sodium retention is a central driver of hypertension and fluid overload. Prostaglandin E2 (PGE2) has long been identified as a potent natriuretic and diuretic factor. However, the mechanisms governing intrarenal PGE2 signaling and tubular sodium transport remain incompletely understood. Methods Global and renal tubule-specific Slco4a1 knockout mouse, as well as renal tubule-specific Slco4a1 overexpressing mice, were generated to investigate the role of SLCO4A1 in renal sodium and water homeostasis. Computational docking, cellular studies, and in vivo functional analyses were performed to evaluate the role of SLCO4A1in intrarenal distribution of PGE_2 and its impact on tubular sodium transport. Results SLCO4A1 was predominantly localized to the basolateral membrane of multiple renal tubular epithelial cells. Global and renal tubule-specific Slco4a1 gene deletion increased urine output and sodium excretion and reduced sodium reabsorption across multiple nephron segments in mice. This was accompanied by downregulation of key sodium transporters and channels including SGLT2, NHE3, NKCC2, NCC and ENaC. In contrast, renal tubule-specific overexpression of Slco4a1 displayed an opposite effect. Mechanistically, Slco4a1 deficiency led to accumulation of PGE2 in the kidney interstitum, which suppressed the expression of sodium transporter and channels via the EP receptors. Specifically, EP1 mediated the PGE_2-induced suppression of NKCC2, α-ENaC, and β-ENaC. EP2 was responsible for the suppression of NCC, while EP3 was involved in suppressing SGLT2, NHE3 and γ-ENaC. Conclusions Collectively, these findings uncovered a previously unrecognized role of SLCO4A1 in regulating intrarenal PGE_2 distribution and identified SLCO4A1-PGE_2-EP receptor axis in fine-tuning renal tubular sodium transport.
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Reason for Restricted Access: as follow-up to "Data Availability *(select all that apply)**Additional information: - Original data generated for the study will be made available upon reasonable request to the corresponding author: This is not recommended for large datasets but is acceptable for low-throughput experimental data. If data are not deposited in a public access repository, or access will otherwise be subject to partial restriction, provide details in the textbox.- Data belong to a third party, and authors are not authorized to share the data: If data cannot be shared because they belong to a third party, specify the identity of the third party and reason for the restriction (e.g., proprietary data, administrative data governed by regulatory or legal frameworks).- Original data cannot be shared: This choice is allowable in select instances only, such as for research that applies to the CARE	The raw data generated in this study are not publicly available due to ongoing analyses and are available from the corresponding author upon reasonable request. Individual numerical data from our experiments will be made available to readers upon reasonable request.

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SLCO4A1 Governs PGE_2-Mediated Natriuresis in the Kidney

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Abstract

Background

Renal sodium retention is a central driver of hypertension and fluid overload. Prostaglandin E_2 (PGE_2) has long been identified as a potent natriuretic and diuretic factor. However, the mechanisms governing intrarenal PGE_2 signaling and tubular sodium transport remain incompletely understood.

Methods

Global and renal tubule-specific *Slco4a1* knockout mouse, as well as renal tubule-specific *Slco4a1* overexpressing mice, were generated to investigate the role of SLCO4A1 in renal sodium and water homeostasis. Computational docking, cellular studies, and in vivo functional analyses were performed to evaluate the role of SLCO4A1in intrarenal distribution of PGE_2 and its impact on tubular sodium transport.

Results

SLCO4A1 was predominantly localized to the basolateral membrane of multiple renal tubular epithelial cells. Global and renal tubule-specific *Slco4a1* gene deletion increased urine output and sodium excretion and reduced sodium reabsorption across multiple nephron segments in mice. This was accompanied by downregulation of key sodium transporters and channels including SGLT2, NHE3, NKCC2, NCC and ENaC. In contrast, renal tubule-specific overexpression of *Slco4a1* displayed an opposite effect. Mechanistically, *Slco4a1* deficiency led to accumulation of PGE_2 in the kidney interstitum, which suppressed the expression of sodium transporter and channels via the EP receptors. Specifically, EP_1 mediated the PGE_2 -induced suppression of NKCC2, α-ENaC, and β-ENaC. EP_2 was responsible for the suppression of NCC, while EP_3 was involved in suppressing SGLT2, NHE3 and γ-ENaC.

Conclusions

Collectively, these findings uncovered a previously unrecognized role of SLCO4A1 in regulating intrarenal PGE_2 distribution and identified SLCO4A1-PGE_2 -EP receptor axis in fine-tuning renal tubular sodium transport.

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Introduction

The kidney is a key organ in maintaining systemic water and salt homeostasis by precisely reabsorbing a large amount of water and sodium alone renal tubules [1, 2]. While this process is mainly regulated by the endocrine pathways such as the antidiuretic hormone (ADH)-vasopressin receptor axis and the renin-angiotensin-aldosterone system, accumulating evidence indicates that local paracrine signaling factors within kidney interstitium provides an additional layer of control over tubular sodium transport. Among these, prostaglandin E_2 (PGE_2) has emerged as a critical regulator of renal sodium and water handling [3, 4]. It has been repeatedly reported that PGE_2 acts on its receptors including EP_1, EP_2, EP_3 and EP_4 in a compartment-specific manner in the kidney. In microdissected tubules, basolateral, but not luminal, application of PGE_2 potently inhibits sodium and water reabsorption, highlighting the importance of interstitial PGE_2 as a spatially restricted signaling molecule in the kidney [5-7]. These findings suggest that precise regulation of interstitial PGE_2 availability, rather than receptor expression alone, is essential for fine-tuning tubular sodium transport. However, despite extensive characterization of downstream receptor signaling, the mechanisms governing extracellular PGE_2 levels within renal microenvironment remain poorly understood.

Renal interstitial PGE_2 concentration is tightly controlled by the efflux and influx of PGE_2 across the plasma membrane mediated by its membrane transporters in renal tubular epithelial cells and interstitial cells. Members of the solute carrier organic anion transporting polypeptide (SLCO/OATP) family have been shown to facilitate the transport of prostaglandins and other bioactive lipids [8]. To date, several membrane transporters including SLCO2A1 and SLCO4A1 have been found to be capable of transporting PGE_2 across cell membrane [9, 10]. Among them, SLCO4A1 (OATP4A1) is a 722-amino acid protein which is widely expressed throughout the body, with high expression in the kidney, stomach, brain and lung. SLCO4A1 exhibits a broad substrate spectrum and is responsible for

the transport of PGE_2, thyroid hormones, taurocholate, and estrogens [11-13]. It has significant functional specificity across different tissues. In brain, it is primarily expressed in microglia and implicated in brain development by regulating the transport of thyroid hormones [14, 15]. In placenta, it is highly expressed on the apical membrane of the trophoblasts to mediate the uptake of estrogens and bile acids from the maternal circulation into the fetus [16, 17]. In eye, SLCO4A1 is expressed in the corneal epithelium, ciliary body, iris, and retina, where it facilitates the intraocular cycling of thyroxine from the choroidal capillaries to the retinal pigment epithelium [18]. SLCO4A1 is also localized to the basolateral plasma membrane of the pars plana pigment epithelium, participating in prostaglandin transport [19]. However, the intrarenal localization of SLCO4A1 and its role in regulating PGE_2 homeostasis in the kidney, particularly within the tubular-interstitial compartment, has not been defined.

In the present study, we aimed to determine how PGE_2 signaling is spatially controlled within the kidney to fine-tune renal tubular sodium transport. We focused on SLCO4A1, an organic anion transporter with the capacity to transport PGE_2 , and tested whether its membrane transport processes shape intrarenal prostaglandin levels and sodium handling along renal tubules.

Methods

Experimental animals

All animal procedures were approved by the Ethical Committee of East China Normal University (Ethics No. m20231204) and conducted in accordance with international guidelines for the use of animals in research. Wild-type C57BL/6 mice (8–12 weeks old) were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China). Global *Slco4a1* knockout (KO) mice were generated on a C57BL/6 background using

CRISPR/Cas9. Renal tubule-specific *Slco4a1* knockout (cKO) mice were generated by crossing *Slco4a1* $^{flox/flox}$ mice with Ksp-Cre transgenic mice. Renal tubule-specific *Slco4a1*-overexpressing (OE) mice were generated by tail vein injection of AAV8 carrying full-length mouse *Slco4a1* cDNA under the kidney-specific KSP promoter (3×10^{11} vg/mouse). Experiments were performed using age-matched male mice unless otherwise specified for sex comparison. Additional details are provided in the Supplemental Materials and Methods.

Functional diuretic challenge tests

Diuretic sensitivity tests were performed to assess sodium transporter activity in different nephron segments as previously reported [20]. Separate cohorts of mice received intraperitoneal injections of empagliflozin (40 mg/kg), furosemide (40 mg/kg), or a fixed-dose combination of amiloride and hydrochlorothiazide (100 mg/kg) to evaluate sodium transport function in the proximal tubule, thick ascending limb of the loop of Henle, and distal convoluted tubule/collecting duct, respectively. Twenty-four-hour urine samples were collected before and after treatment, and changes in urinary sodium, chloride, or glucose excretion were determined as indicated. Additional details are provided in the Supplemental Materials and Methods.

Renal tubule suspension preparation and pharmacological treatment

Renal tubule suspensions were isolated from the cortex or medulla of male C57BL/6 mice by collagenase digestion as previously reported [21] and equilibrated in DMEM/F-12 medium. For PGE_2 stimulation, renal tubules were treated with PGE_2 (10 μM) for 6 hours. For EP

receptor inhibition, tubules were pretreated with subtype-selective EP receptor antagonists (10 nM) for 1 hour, followed by co-treatment with PGE_2 (10 μM) for 6 hours. For EP receptor activation, tubules were treated with subtype-selective EP receptor agonists (10 nM) for 6 hours. The EP receptor-selective agonists and antagonists are listed in Supplementary Table S2. Detailed procedures are provided in the Supplemental Materials and Methods.

Prediction of the SLCO4A1-PGE_2 complex structure

The initial three-dimensional structure of SLCO4A1 was obtained from an AlphaFold3 prediction [22]. Using AutoDockTools (ADT) [23], the receptor protein was preprocessed: polar hydrogen atoms were added to maintain hydrogen-bonding capability, Gasteiger charges were calculated and assigned, and the final structure was saved in PDBQT format for subsequent docking calculations. The three-dimensional structure of prostaglandin E_2 (PGE_2) was downloaded from the PubChem [24]. Gasteiger charges were assigned to PGE_2 using ADT, and rotatable bonds were defined (retaining the rigid structure of functional groups such as the carboxyl and hydroxyl groups, while allowing free rotation of the aliphatic chain and the side chain of the five-membered ring). The ligand was then saved as a PDBQT file. Based on prior knowledge of the interaction mechanism between SLCO2A1 and PGE_2 and the predicted active pocket of SLCO4A1 [25], the docking region was defined as the central cavity of SLCO4A1. The docking search space was defined using the "Grid Box" function in AutoDockVina [26, 27], with a box size set to 40 Å × 40 Å × 40 Å to ensure coverage of the binding pocket and surrounding potential interaction regions. After docking, the optimal binding pose was selected based on two core criteria: 1) Binding energy, prioritizing the conformation with the lowest binding energy consistent with thermodynamic stability; and 2) Interaction pattern, analyzing ligand-receptor interactions using PyMOL [28] to select conformations where PGE_2 could form specific hydrogen bonds with ASN-121 and GLN-116, while its hydrophobic tail engaged in stable hydrophobic interactions with nonpolar amino acid residues of the receptor. The final optimal docking conformation for the

SLCO4A1-PGE_2 complex exhibited a predicted binding energy of -6.2 kcal/mol and was consistent with the previously predicted interaction sites, making it suitable for subsequent mechanistic analysis (Supplementary Table 3).

PGE_2 sensor AAV injection for monitoring PGE_2 dynamics in kidney interstitium

To monitor renal PGE_2 dynamics, an AAV carrying a genetically encoded PGE_2 sensor (PGE_2-1.0) with high specificity for PGE_2 when expressed both *in vitro* and *in vivo*, was injected into the kidney parenchyma of wild-type and renal tubule- specific *Slco4a1* gene knockout mice [29]. The mice were anesthetized by intraperitoneal injection of 2,2,2- tribromoethanol (Avertin, 240 mg/kg body weight, Sigma- Aldrich). Following anesthesia, a laparotomy was performed to expose the right kidney. Using a microinjection pump, 12 µL of viral solution (AAV2/9- EF1α- PGE_2- 1.0, titer 2.68×10^{12} vg/mL, packaged by BrainVTA) was slowly delivered at three sites: the upper, middle, and lower portions of the kidney. After each injection, the needle was kept in place for 1 minute before withdrawal. In vivo fluorescence imaging was conducted 2 weeks post- injection to visualize PGE_2- dependent fluorescence signals.

Statistical analysis

Statistical analysis was performed using GraphPad Prism v7 (GraphPad Software, San Diego, CA). Data analysis was performed in a blinded manner where applicable. Two-tailed *t* test was used for comparison between two groups. One-way ANOVA, followed by a Tukey multiple comparisons test, was used to analyze the differences between means. *P* value <0.05 was considered significant. Error bars show ±SEM.

Results

Basolateral localization of SLCO4A1 along renal tubules

Given its proposed role in prostaglandin transport, we first sought to define the intrarenal localization of SLCO4A1. Analysis of publicly available single-cell transcriptomic data revealed that the mRNA expression of *Slco4a1* was highly abundant in the nephron epithelium **(Figure 1A)**. To precisely define its subcellular localization in various renal tubule segments, we performed immunofluorescence staining on frozen sections of mouse kidney, co-staining SLCO4A1 with segment-specific markers for different tubular segments. The results showed that SLCO4A1 was widely expressed on the basolateral membrane across various renal tubule segments including the proximal tubule **(Figure 1B),** thick ascending limb **(Figure 1C)**, distal tubule **(Figure 1D)**, and collecting duct **(Figure 1E)**. This staining was absent in the kidneys from *Slco4a1* gene knockout (*Slco4a1*-KO) mouse, confirming antibody specificity **(Figure 1F)**. Collectively, these data indicate that SLCO4A1 protein is broadly expressed on the basolateral membrane of epithelial cells in almost all renal tubule segments.

Renal tubule-specific *Slco4a1* gene ablation induced natriuresis and diuresis

To determine the role of SLCO4A1 in tubular water and sodium handling, we generated renal tubule-specific *Slco4a1* knockout mice (cKO) and confirmed efficient deletion **(Figure 2A&B)**. Under baseline conditions, cKO mice exhibited increased urine sodium **(Figure 2C)** and chloride excretion **(Figure 2D)**, which was accompanied by a marked increase in urine volume, but unaltered expression of renal aquaporins **(Figure 2E, Supplemental Figure 1A)**. This phenotype was associated with a significant increase in water intake (polydipsia) **(Figure 2F)** without alterations in food intake and body weight **(Figure 2G&H)**. cKO mice also showed a decrease in urinary potassium excretion and an increase in urinary calcium and phosphate output **(Supplemental Figure 2A-C)**. However, no change in major blood electrolyte levels was observed between wild-type (WT) and cKO mice **(Supplemental Figure 2D-H)**. Consistent with this salt-losing phenotype, cKO mice exhibited significantly reduced systolic blood pressure **(Supplemental Figure 3A)**, accompanied by increased renal

aldosterone content **(Supplemental Figure 3B)** and upregulated prorenin and PRR expression **(Supplemental Figure 3C)**, suggesting compensatory activation of the intrarenal RAAS. Given the well-recognized sex differences in renal prostaglandin biology, we also examined the urine volume and urinary excretion of sodium and chloride in female mice. Consistent with male mice, female cKO mice exhibited increased urinary sodium and chloride excretion and urine volume, accompanied by increased water intake, whereas food intake and body weight were unchanged **(Supplemental Figure 4A-F)**. Together, these findings demonstrate that renal tubule-specific *Slco4a1* gene deficiency induces natriuresis and diuresis in mice.

To determine whether this phenotype is preserved at the whole-organism level, we generated global *Slco4a1* gene knockout (KO) mice **(Figure 3A-C)**, and measured urine sodium and chloride excretion. We found that urine sodium and chloride excretion was also significantly increased, accompanied by a marked increase in urine output and water intake **(Figure 3D-G)**, with little change in food intake and body weight **(Figure 3H-I).** Similar to cKO mice, global *Slco4a1* gene deficiency also significantly reduced urinary potassium excretion and markedly increased urinary calcium and phosphate excretion **(Supplemental Figure 5A-C)**. KO mice exhibited unaltered major blood electrolyte levels, except for a slight increase in serum calcium levels **(Supplemental Figure 5D-H)**. Although KO mice exhibited polyuria, little change in renal expression of aquaporins was evident **(Supplemental Figure 1B)**. Collectively, these results demonstrate that SLCO4A1, in particular renal tubular SLCO4A1, is essential in regulating sodium reabsorption in the kidney and SLCO4A1 modulates renal sodium handling possibly through the regulation of sodium ion transport.

Renal tubule-specific *Slco4a1* gene ablation inhibited the function and expression of key sodium transporters and channels alone renal tubules

To further define the role of SLCO4A1 in tubular sodium handling, we evaluated the functional activity of major sodium transporters using pharmacological approaches as previously reported [20]. The natriuretic and glucosuric response to the SGLT2 inhibitor empagliflozin was blunted in renal tubule-specific *Slco4a1* gene knockout (cKO) mice,

indicating a reduced SGLT2 activity **(Figure 4A&B)**. Similarly, the natriuretic and chloruretic response to the NKCC2 inhibitor furosemide was attenuated, implying a reduced NKCC2 activity **(Figure 4C&D)**. Consistently, the natriuretic response to a combination of ENaC and NCC inhibitor (amiloride+hydrochlorothiazide) was also diminished, in line with a reduced NCC and ENaC activity **(Figure 4E)**. Furthermore, western blot assays demonstrate that cKO mice exhibited a marked downregulation of SGLT2, NHE3 and NCC **(Figure 4F, Supplemental Figure 6A-C)**, as well as NKCC2 and all three ENaC subunits (α, β, γ) **(Figure 4G, Supplemental Figure 6D-G)** at the protein level, which was further confirmed by immunofluorescence analysis **(Supplemental Figure 7A-E)**. Collectively, these findings indicate that SLCO4A1 is required to maintain the activity and expression of key sodium transporters and channels along renal tubules.

Kidney-specific *Slco4a1* overexpression increasesd renal sodium reabsorption

To further investigate the role of SLCO4A1 in renal salt metabolism, we generated an AAV-mediated kidney-specific mouse *Slco4a1*-overexpressing mouse model (AAV-*Slco4a1*) **(Figure 5A-C)**. Kidney-specific *Slco4a1* overexpression reduced 24-hour urine sodium and chloride excretion **(Figure 5D&E)**, accompanied by decreased urine volume and water intake **(Figure 5F&G)**, without changes in food intake and body weight **(Figure 5H&I)**. In addition, the AAV- *Slco4a1* mice exhibited increased urinary potassium excretion and reduced phosphate excretion **(Supplemental Figure 8A&C)**, with a trend of increase in calcium excretion **(Supplemental Figure 8B)**. Circulating electrolyte levels remain largely unchanged **(Supplemental Figure 8D-H)**. Despite reduced urine output in the AAV-*Slco4a1* mice, renal expression of AQP1-4 remains unaltered **(Supplemental Figure 1C)**. Consistent with these physiological changes, major sodium transporters and channels were upregulated in the AAV-*Slco4a1* mice **(Figure 5J&K, S9A-G&S10A-E)**. Collectively, these findings demonstrate that SLCO4A1 promotes renal sodium reabsorption through upregulation of sodium transporters and channels along renal tubules.

SLCO4A1 promoted basolateral uptake of PGE_2 in renal tubular epithelial cells

SLCO4A1 has been reported as a critical transporter for PGE_2, however, its specific role in renal PGE_2 transport and spatial distribution remains undefined. To understand how SLCO4A1 specifically recognizes PGE_2, we utilized AlphaFold3 to predict the structure of SLCO4A1 and simulated its docked complex with PGE_2 (**Figure 6A**). The central cavity of the SLCO4A1-PGE_2 structure opened towards the extracellular space, adopting an outward-open conformation. The predicted complex structure revealed detailed interactions at the PGE_2 binding site within SLCO4A1 (**Figure 6A**). Specifically, the carboxyl group of PGE_2 formed hydrogen bonds with GLN-116 and ASN-121. The hydrophobic tail inserted into a small subpocket on the opposite side, engaging in hydrophobic interactions with ALA-369, ILE-399 and VAL-622. These hydrophobic interactions, cooperated with the hydrogen bond network, stabilized PGE_2 within the 19678 $Å^3$ central active pocket of SLCO4A1, resulting in a tight and specific binding mode **(Figure 6A)**, suggesting its strong PGE_2 transporting potential.

To further define the role of SLCO4A1 in PGE_2 transport, we manipulated SLCO4A1 expression in mIMCD3 cells by either gene overexpression or knockdown. PGE_2 measurement of intracellular and culture media showed that adenovirus-mediated human *SLCO4A1* overexpression significantly increased intracellular PGE_2 levels, but markedly decreased PGE_2 contents in culture media **(Figure 6B&C)**. In contrast, knockdown of *Slco4a1* showed an opposite effect **(Figure 6D&E)**. These results suggested that SLCO4A1 mediated PGE_2 uptake rather than efflux and may play an important role in intrarenal PGE_2 distribution and metabolism. In support of this speculation, we measured PGE_2 contents in the kidney and urine. AAV-*Slco4a1* mice exhibited a significant decrease in renal PGE_2 contents **(Figure 6F)**, but markedly increased 24-hour urinary PGE_2 excretion **(Figure 6G)**. Conversely, cKO mice showed opposite changes **(Figure 6H&I)**. Similarly, female renal tubule-specific *Slco4a1* gene knockout mice exhibited increased renal PGE_2 levels, accompanied by decreased urinary PGE_2 excretion **(Supplemental Figure 11 A&B)**. To further determine intrarenal distribution and level of PGE_2, we used an AAV-based PGE_2 sensor to visualize its spatiotemporal dynamics *in vivo*. Renal tubule-specific *Slco4a1* gene

deletion increased the PGE_2 levels in kidney interstitium, suggesting basolateral expression of SLCO4A1 is responsible for the uptake of PGE_2 in renal tubules **(Figure 6J)**. Importantly, *Slco4a1* gene deletion did not substantially alter the renal expression of PGE_2 -metabolizing enzymes or EP receptors at either the mRNA or protein level **(Supplemental Figure 12 A&B)**. Collectively, these findings define SLCO4A1 as a key transporter that mediates PGE_2 uptake in renal tubular epithelial cells and determines renal interstitial PGE_2 levels.

SLCO4A1 attenuated intrarenal PGE_2 infusion-induced natriuresis and diuresis

Acute renal medullary PGE_2 infusion is known to induce natriuresis and diuresis [4]. To investigate whether SLCO4A1 directly modulates these processes via PGE_2 transport, we conducted PGE_2 acute infusion studies. As expected, intrarenal PGE_2 robustly increased urine output and sodium excretion in wild-type (WT) mice. However, the natriuretic and diuretic effect of PGE_2 was significantly blunted in the AAV-*Slco4a1* mice **(Supplemental Figure 13A&B)**. In contrast, although urine and sodium excretion rates are greater in cKO mice than that in WT mice, no difference was observed between two genotypes after PGE_2 infusion **(Supplemental Figure 13C&D)**. Taken together, these findings indicated that SLCO4A1 attenuated intrarenal PGE_2 infusion-induced natriuresis and diuresis, likely through its PGE_2 transport activity.

PGE_2 suppressed sodium transporters and channels in an EP receptor-dependent manner

PGE_2 exerts it biological actions via four G protein-coupled receptors (EP_1-EP_4). To further confirm the role of SLCO4A1-mediated PGE_2 transport in the regulation of renal sodium reabsorption, we treated renal tubule suspensions of wild-type mice with PGE_2 with or without various EP receptor agonists and antagonists and measured the protein expression levels of several major sodium transporters and channels. The results showed that PGE_2 suppressed the expression of multiple sodium transporters and channels in an EP receptor subtype-dependent manner **(Figure 7A-N)**. Specifically, PGE_2 downregulated SGLT2 **(Figure 7A&H),** NHE3 **(Figure 7B&I)** and γ-ENaC **(Figure 7G&N)** protein expression

mainly via EP_3, inhibited NKCC2 **(Figure 7C&J**, α-ENaC **(Figure 7E&L)**, and β-ENaC **(Figure 7F&M)** expression via EP_1, and lowered NCC **(Figure 7D&K)** expression via EP_2. These findings demonstrated that PGE_2 broadly suppressed tubular sodium transport through distinct EP receptor-mediated signaling pathways. Together with the regulation of interstitial PGE_2 by SLCO4A1, this mechanism provideds a molecular basis for SLCO4A1-mediated control of renal sodium reabsorption along renal tubules.

Discussion

The present study uncovered an essential role of SLCO4A1 in the regulation of renal water and salt homeostasis. SLCO4A1 was found to be localized to the basolateral membrane of epithelial cells along multiple renal tubules. By utilizing global *Slco4a1* gene knockout, renal tubule-specific *Slco4a1* gene deletion or overexpression mice, we found that SLCO4A1 plays a critical role in the regulation of renal sodium reabsorption by modulating the expression and function of several major sodium transporters and channels including SGLT2, NHE3, NKCC2, NCC and ENaC in multiple renal tubular segments. We further revealed that SLCO4A1 mediated the basolateral uptake of PGE_2 in renal tubular epithelial cells to fine-tune the levels of interstitial PGE_2, which suppressed the expression of major sodium transporters and channels by acting on the EP_1, EP_2 and EP_3 receptors in various renal tubules. These findings established SLCO4A1 as a critical regulator of PGE_2-driven natriuresis and highlighted SLCO4A1 inhibition as a potential therapeutic strategy for sodium retention-associated diseases, including hypertension and heart failure.

PGE_2 is a predominant prostaglandin synthesized in the kidney and has been well known as a natriuretic and diuretic lipid mediator [30, 31]. It is produced from arachidonic acid via three sequential enzymatic processes involving a few enzymes including two cyclooxygenases (COX1 and COX2) and three PGE synthases (mPGES1, mPGES2 and cPGES) [32]. Once synthesized, PGE_2 is released into kidney interstitium and acts on its four G protein-coupled receptors (GPCR) including EP_1, EP_2, EP_3 and EP_4 to regulate the expression, subcellular translocation and function of multiple sodium transporters and channels along various

segments of renal tubules, ultimately leading to natriuresis, diuresis, and a reduction in blood pressure [33-36]. To avoid overactivation on its receptors, timely termination of PGE_2 signaling is critical to prevent potential damages. Excessive PGE_2 has to be removed from kidney interstitium presumably by the uptake of renal tubular epithelial cells, where it is intracellularly inactivated by 15-ketoprostaglandin dehydrogenase (encoded by *HPGD*) [37]. However, the transporter responsible for the uptake of PGE_2 in renal tubular epithelial cells remains largely unknown. It has been increasingly recognized that solute carrier organic anion transporter family member 2A1 (OATP2A1, encoded by the *SLCO2A1* gene) acts as a prostaglandin transporter (PGT) mediating the influx transport of PGE_2 [38, 39]. Nevertheless, since SLCO2A1 was reported to be localized on the apical membrane of renal tubular epithelial cells, where it facilitates PGE_2 transport in the apical-to-basolateral direction [40], it is unlikely that SLCO2A1 is responsible for basolateral uptake and metabolic clearance of PGE_2 along renal tubules.

The present study identified, for the first time, SLCO4A1 as a key transporter mediating basolateral uptake of PGE_2 along various renal tubules. We found that SLCO4A1 is localized at the basolateral membrane of renal tubular epithelial cells in the proximal tubule, thick ascending limb, distal tubule and collecting duct. Using the cryo-EM structure of SLCO2A1 as a model [41], AlphaFold3 structural prediction revealed a high-affinity PGE_2 binding site in SLCO4A1, supporting SLCO4A1 as an inward transporter of PGE_2 [12, 42] This speculation is further supported by the findings that overexpression of *SLCO4A1* significantly increased, while knockdown of *Slco4a1* markedly reduced, intracellular levels of PGE_2 in cultured mIMCD3 cells. As expected, renal tubule-specific knockout of *Slco4a1* resulted in PGE_2 accumulation, whereas renal tubule-overexpression of *Slco4a1* led to reduced PGE_2 contents in kidney tissues. To further determine the spatiotemporal distribution of PGE_2, the AAV particles carrying a genetically encoded PGE_2 sensor (PGE_2-1.0) with high specificity for PGE_2 were injected into the kidney parenchyma of wild-type and renal tubule- specific *Slco4a1* gene knockout mice, allowing to visualize PGE_2- dependent fluorescence signals in kidney interstitium with high spatiotemporal resolution. The results clearly showed a marked increase in PGE_2 contents in renal extracellular spaces in renal tubule-specific *Slco4a1* gene

knockout mice. The increased PGE_2 contents in renal interstitial space appear not to be a result of altered expression of PGE_2-metabolizing enzymes, since little change was observed in their expression in the kidneys of renal tubule-specific *Slco4a1* gene knockout mice. Together, these findings demonstrated that SLCO4A1 precisely controlled renal interstitial PGE_2 levels by fine-tunning the uptake of PGE_2 across basolateral membrane of epithelial cells in multiple renal tubule segments.

It has been well known that intrarenal infusion of PGE_2 causes natriuresis and diuresis [4, 43]. Therefore, altered renal interstitial PGE_2 level is expected to change urine sodium and water excretion. In fact, mice with renal tubule-specific *Slco4a1* gene deletion exhibited a significant increase, while mice with renal tubule-selective *Slco4a1* overexpression displayed a marked decrease, in urine sodium excretion and urine volume. Although renal water reabsorption primarily depends on proximal tubule aquaporin 1 (AQP1) and collecting duct AQP2-AQP4, little change in their expression was evident upon *Slco4a1* gene manipulations in renal tubules, suggesting changes in urine output is likely a result of altered urine sodium excretion. As expected, natriuretic effect of renal tubule-specific *Slco4a1* gene deletion or anti-natriuretic action of renal tubule *Slco4a1* overexpression was associated with a marked decrease or increase in protein expression and biological function of several major sodium transports and channels including SGLT2, NHE3, NKCC2, NCC and ENaC, respectively. Collectively, these findings indicated that renal tubule SLCO4A1 plays a critical role in modulating the expression and function of several major sodium transporters and channels by fine-tuning the basolateral uptake of PGE_2 along renal tubules.

PGE_2 is the major prostanoid synthesized in the kidney where it potently regulates the salt and water transport [44]. However, the cellular and molecular basis of PGE_2-induced natriuresis is only partially understood. As previously reported [4, 45-48], renal medullary infusion of PGE_2 significantly increased urine sodium excretion and urine output, accompanied by a marked reduction in protein expression of several major sodium transporters and ENaC, suggesting that PGE_2-induced natriuresis and diuresis result from suppressed sodium reabsorption along renal tubules. However, *Slco4a1* gene deletion or

overexpression in renal tubules had little effect on the expression of four PGE_2 receptors in the kidneys, implying that altered sodium reabsorption is not due to the change in the expression of the EP receptors. To further determine the EP receptor subtype responsible for PGE_2-mediated suppression of sodium reabsorption in each segment of renal tubules, we pretreated renal tubule suspension with various EP subtype-selective agonists and agonists, followed by PGE_2 treatment. The results showed that multiple EP receptors are involved in PGE_2-mediated inhibition of sodium reabsorption. In the proximal tubules, PGE_2 suppressed SGLT2 and NHE3 protein expression mainly via the EP_3 receptor. In the thick ascending limbs PGE_2 selectively activated the EP_1 receptor to reduce NKCC2 protein expression, while in the distal renal tubules PGE_2-mediated suppression of NCC protein expression was mainly through the activation of the EP_2 receptor. In terms of ENaC, PGE_2 downregulated ENaCα and ENaCβ protein expression via the EP_1 receptor, but reduced ENaCγ through the EP_3 receptor in renal collecting ducts. Together, these findings suggested that SLCO4A1-depedent PGE_2 transport affected renal tubular sodium reabsorption via multiple EP receptors located on the basolateral membrane of epithelial cells across various renal tubules. Since each EP receptor has its unique G protein-coupled signaling pathway(s) [49-53], it would be important to elucidate the underlying mechanism by which PGE_2 suppresses sodium absorption via its receptors in each segment of renal tubules in the future. In the present study, we did not use EP receptor subtype-deficient mice or selective receptor antagonists to confirm the specific receptor subtypes involved in PGE_2-elicited natriuresis. Future studies employing genetic or pharmacological EP receptor blockade will be important to further define the receptor-mediated pathways underlying the natriuretic effect of SLCO4A1 deficiency.

The present study has several limitations. First, while we demonstrated that SLCO4A1 broadly affected the expression and function of several major sodium transporters and channels by fine-tuning PGE_2 levels in kidney interstitium, the genetically manipulated mouse lines employed do not allowed us to pinpoint the tubule segment-specific contribution of SLCO4A1. The generation of conditional knockout models specifically targeting proximal tubule, thick ascending limb, distal tubule and collecting duct would be required to dissect the

precise roles of SLCO4A1 in these locations. Second, as a multi-specific solute carrier, SLCO4A1 transports substrates beyond PGE_2, including taurocholate, thyroid hormones, and estrogen. Whether and how these alternative substrates contribute to the observed phenotypes in water-salt metabolism remains an open question for future investigation. Third, although our findings established a mechanistic role of SLCO4A1 in regulating renal sodium handling in experimental models, validation in human populations remained limited. Future studies integrating human kidney transcriptomic data, genetic association analyses, and clinical cohorts are required to further substantiate the translational relevance of SLCO4A1 in sodium retention-related diseases.

In conclusion, the present study reported a critical role of SLCO4A1 in maintaining intrarenal PGE_2 homeostasis and fine-tuning sodium reabsorption along renal tubules. SLCO4A1 is a potent inward PGE_2 transporter and was selectively localized on the basolateral membrane of renal tubular epithelial cells in various renal tubule segments, where it facilitated the uptake of PGE_2 to help remove PGE_2 from the kidney interstitium and timely terminated PGE_2 signaling via the EP receptors (Visual Abstract). Pharmacological blockade of SLCO4A is expected to raise extracellular levels of PGE_2 in the kidney to suppress the expression and function of multiple major sodium transporters and ENaC, leading to natriuresis and diuresis. Our findings not only revealed a previously unrecognized mechanism involved in spatiotemporal regulation of PGE_2 in the kidney but also identified SLCO4A1 as an attractive molecular target to develop novel natriuretic and diuretic drugs to treat diseases with sodium and fluid retention.

Acknowledgments

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Supplemental Material

Supplemental Figure 7. Immunofluorescence analysis of major sodium transporters and channels in the kidneys of *Slco4a1*^{cKO} mice.

Supplemental Figure 8. The effects of kidney-specific *Slco4a1* gene overexpression on urine and blood electrolyte levels.

Supplemental Figure 9. Kidney-specific *Slco4a1* gene overexpression increased the expression of major sodium transporters and channels alone renal tubule.

Supplemental Figure 10. Immunofluorescence analysis of renal major sodium transporters and channels in the kidney-specific *Slco4a1* overexpression mice.

Supplemental Figure 11. Increased renal and reduced urinary PGE_2 levels in female renal tubule-specific *Slco4a1* knockout mice.

Supplemental Figure 12. Renal expression of PGE_2-metabolizing enzymes and EP receptors in renal tubule-specific *Slco4a1* gene knockout mice.

Supplemental Figure 13. Diuretic and natriuretic response to intramedullary infusion of PGE_2 in mice with kidney-specific *Slco4a1* overexpression or renal tubule-specific *Slco4a1* gene deficiency.

References

1. Pallone, T.L., et al., *Requirement of aquaporin-1 for NaCl-driven water transport across descending vasa recta.* J Clin Invest, 2000. **105**(2): p. 215-22.
2. King, L.S., et al., *Defective urinary concentrating ability due to a complete deficiency of aquaporin-1.* N Engl J Med, 2001. **345**(3): p. 175-9.
3. Hockel, G.M. and A.W. Cowley, *Prostaglandin E2-induced hypertension in conscious dogs.* American Journal of Physiology-Heart and Circulatory Physiology, 1979. **237**(4): p. H449-H454.
4. Chen, J., et al., *Increased dietary NaCl induces renal medullary PGE2 production and natriuresis via the EP2 receptor.* Am J Physiol Renal Physiol, 2008. **295**(3): p. F818-25.
5. Culpepper, R.M. and T.E. Andreoli, *PGE2, forskolin, and cholera toxin interactions in modulating NaCl transport in mouse mTALH.* Am J Physiol, 1984. **247**(5 Pt 2): p. F784-92.
6. Stokes, J.B., *Effect of prostaglandin E2 on chloride transport across the rabbit thick ascending limb of Henle. Selective inhibitions of the medullary portion.* J Clin Invest, 1979. **64**(2): p. 495-502.
7. Culpepper, R.M. and T.E. Andreoli, *Interactions among prostaglandin E2, antidiuretic hormone, and cyclic adenosine monophosphate in modulating Cl- absorption in single mouse medullary thick ascending limbs of Henle.* J Clin Invest, 1983. **71**(6): p. 1588-601.
8. Meier-Abt, F., Y. Mokrab, and K. Mizuguchi, *Organic anion transporting polypeptides of the OATP/SLCO superfamily: identification of new members in nonmammalian species, comparative modeling and a potential transport mode.* Journal of Membrane Biology, 2006. **208**(3): p. 213-227.
9. Joshi, C., et al., *Structural basis for prostaglandin and drug transport via SLCO2A1.* Nature Communications, 2026. **17**(1): p. 2285.
10. Pang, Q., et al., *Targeting Metabolomics in Primary Hypertrophic Osteoarthropathy: Uncovering Novel Insights into Disease Pathogenesis.* J Clin Endocrinol Metab, 2025. **110**(8): p. e2591-e2604.
11. Fujiwara, K., et al., *Identification of thyroid hormone transporters in humans: different molecules are involved in a tissue-specific manner.* Endocrinology, 2001. **142**(5): p. 2005-12.
12. Tamai, I., et al., *Molecular identification and characterization of novel members of the human organic anion transporter (OATP) family.* Biochem Biophys Res Commun, 2000. **273**(1): p. 251-60.
13. Hagenbuch and Bruno, *The SLCO (former SLC21) superfamily of transporters.* Molecular Aspects of Medicine, 2013. **34**(2–3): p. 396-412.
14. Braun, D., et al., *Developmental and cell type-specific expression of thyroid hormone transporters in the mouse brain and in primary brain cells.* Glia, 2011. **59**(3): p. 463-71.
15. Chan, S.Y., et al., *The expression of thyroid hormone transporters in the human fetal cerebral cortex during early development and in N-Tera-2 neurodifferentiation.* J Physiol, 2011. **589**(Pt 11): p. 2827-45.
16. Loubière, L.S., et al., *Expression of thyroid hormone transporters in the human placenta and changes associated with intrauterine growth restriction.* Placenta, 2010. **31**(4): p. 295-304.
17. Nishikawa, M., et al., *Placental transfer of conjugated bisphenol A and subsequent reactivation in the rat fetus.* Environ Health Perspect, 2010. **118**(9): p. 1196-203.
18. Ito, A., et al., *Distribution of rat organic anion transporting polypeptide-E (oatp-E) in the rat eye.* Invest Ophthalmol Vis, 2003. **44**(11): p. 4877-4884.
19. Gao, B., et al., *Localization of organic anion transporting polypeptides in the rat and human ciliary body epithelium.* Exp Eye Res, 2005. **80**(1): p. 61-72.
20. Jesus, E.F., et al., *SGLT2 Inhibitors Blunt Kidney Magnesium Wasting in Acute Cisplatin-Induced Hypomagnesemia with Effects on the Thick Ascending Limb and Distal Convoluted Tubule.* J Am Soc Nephrol, 2025. **36**(9): p. 1689-1701.
21. Poulsen, S.B., et al., *Activation of the kidney sodium chloride cotransporter by the β2-adrenergic receptor agonist salbutamol increases blood pressure.* Kidney Int, 2021. **100**(2): p. 321-335.
22. Abramson, J., et al., *Accurate structure prediction of biomolecular interactions with AlphaFold*

3. Nature, 2024.
23. Morris, G.M., et al., *AutoDock4 and AutoDockTools4: Automated Docking with Selective Receptor Flexibility.* Journal of Computational Chemistry, 2009. **30**(16): p. 2785-2791.
24. Kim, S., et al., *PubChem 2025 update.* Nucleic Acids Research, 2024. **53**(D1): p. D1516-D1525.
25. Xia, Z., et al., *Structure and transport mechanism of the human prostaglandin transporter SLCO2A1.* Nat Commun, 2025. **16**(1): p. 8124.
26. Eberhardt, J., et al., *AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings.* Journal of Chemical Information and Modeling, 2021. **61**(8): p. 3891-3898.
27. Trott, O. and A.J. Olson, *AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization, and Multithreading.* Journal of Computational Chemistry, 2010. **31**(2): p. 455-461.
28. Schrödinger, L. and W. DeLano, *PyMOL.* 2020: p. http://www.pymol.org/pymol.
29. Wang, L., et al., *A genetically encoded fluorescent sensor for monitoring spatiotemporal prostaglandin E2 dynamics in vivo.* Neuron, 2026.
30. Villa, E., et al., *Comparative effect of PGE2 and PGI2 on renal function.* Hypertension, 1997. **30**(3 Pt 2): p. 664-6.
31. Jabs, K., M.L. Zeidel, and P. Silva, *Prostaglandin E2 inhibits Na+-K+-ATPase activity in the inner medullary collecting duct.* American Journal of Physiology-Renal Physiology, 1989. **257**(3): p. F424-F430.
32. Wang, J., et al., *Physiological and pathophysiological implications of PGE(2) and the PGE(2) synthases in the kidney.* Prostaglandins Other Lipid Mediat, 2018. **134**: p. 1-6.
33. Hall, J.E., et al., *Regulation of arterial pressure: role of pressure natriuresis and diuresis.* Fed Proc, 1986. **45**(13): p. 2897-903.
34. Guyton, A.C., *Blood pressure control--special role of the kidneys and body fluids.* Science, 1991. **252**(5014): p. 1813-6.
35. Roman, R.J. and E. Lianos, *Influence of prostaglandins on papillary blood flow and pressure-natriuretic response.* Hypertension, 1990. **15**(1): p. 29-35.
36. Carmines, P.K., et al., *Prostaglandins in the sodium excretory response to altered renal arterial pressure in dogs.* American Journal of Physiology-Renal Physiology, 1985. **248**(1): p. F8-F14.
37. Sun, C.C., et al., *Recent advances in studies of 15-PGDH as a key enzyme for the degradation of prostaglandins.* Int Immunopharmacol, 2021. **101**(Pt B): p. 108176.
38. Nakanishi, T. and I. Tamai, *Roles of Organic Anion Transporting Polypeptide 2A1 (OATP2A1/SLCO2A1) in Regulating the Pathophysiological Actions of Prostaglandins.* Aaps j, 2017. **20**(1): p. 13.
39. Nakanishi, T., Y. Nakamura, and J. Umeno, *Recent advances in studies of SLCO2A1 as a key regulator of the delivery of prostaglandins to their sites of action.* Pharmacol Ther, 2021. **223**: p. 107803.
40. Endo, S., et al., *Expression of PGT in MDCK cell monolayers: polarized apical localization and induction of active PG transport.* Am J Physiol Renal Physiol, 2002. **282**(4): p. F618-22.
41. Zhu, Z., et al., *Molecular basis of prostaglandin E(2) reuptake by organic anion transporter PGT.* Nat Commun, 2025. **17**(1): p. 315.
42. Kobayashi, Y., et al., *[Molecular cloning and functional characterization of a novel gene encoding human prostaglandin carrier, hPrC].* Yakugaku Zasshi, 2011. **131**(10): p. 1493-501.
43. Haas, J.A., et al., *Mechanism of natriuresis during intrarenal infusion of prostaglandins.* Am J Physiol, 1984. **247**(3 Pt 2): p. F475-9.
44. Breyer, M.D., et al., *Regulation of renal function by prostaglandin E receptors.* Kidney International, 1998. **54**: p. S88-S94.
45. Kaji, D.M., et al., *Prostaglandin E2 inhibits Na-K-2Cl cotransport in medullary thick ascending limb cells.* Am J Physiol, 1996. **271**(1 Pt 1): p. C354-61.
46. Esteva-Font, C., et al., *Acute and Chronic Effects of Prostaglandin E2 on NKCC2, NCC and ENaC in Ex Vivo Renal Tubules.* The FASEB Journal, 2020. **34**(S1): p. 1-1.
47. Nasrallah, R., et al., *PGE2 EP1 receptor inhibits vasopressin-dependent water reabsorption and sodium transport in mouse collecting duct.* Laboratory Investigation, 2018. **98**(3): p. 360-370.
48. Guan, Y., et al., *Prostaglandin E2 inhibits renal collecting duct Na+ absorption by activating the EP1 receptor.* The Journal of Clinical Investigation, 1998. **102**(1): p. 194-201.

49. Sugimoto, Y. and S. Narumiya, *Prostaglandin E Receptors*.* Journal of Biological Chemistry, 2007. **282**(16): p. 11613-11617.
50. Regan, J.W., *EP2 and EP4 prostanoid receptor signaling.* Life Sciences, 2003. **74**(2): p. 143-153.
51. Hatae, N., Y. Sugimoto, and A. Ichikawa, *Prostaglandin Receptors: Advances in the Study of EP3 Receptor Signaling.* The Journal of Biochemistry, 2002. **131**(6): p. 781-784.
52. Furuyashiki, T. and S. Narumiya, *Stress responses: the contribution of prostaglandin E2 and its receptors.* Nature Reviews Endocrinology, 2011. **7**(3): p. 163-175.
53. Matsuoka, T. and S. Narumiya, *Prostaglandin receptor signaling in disease.* ScientificWorldJournal, 2007. **7**: p. 1329-47.

Figure Legends

Figure 1. Basolateral localization of SLCO4A1 along mouse renal tubules.

(**A**) The expression of SLCO4A1 in various kidney cell populations based on a mouse single-cell RNA-seq database (https://cello.shinyapps.io/kidneycellexplorer/). (**B-E**) Immunofluorescence staining of mouse kidney sections demonstrated co-localization of SLCO4A1 (red) with renal tubule segment-specific markers (green) including LTL for proximal tubule (B), NKCC2 for thick ascending limb (C), NCC for distal tubule (D), and AQP2 for collecting duct (E). (**F**) Negative control using a kidney section from a global *Slco4a1* gene knockout (KO) mouse. Nuclei are stained with DAPI (blue). Scale bars, 25μm.

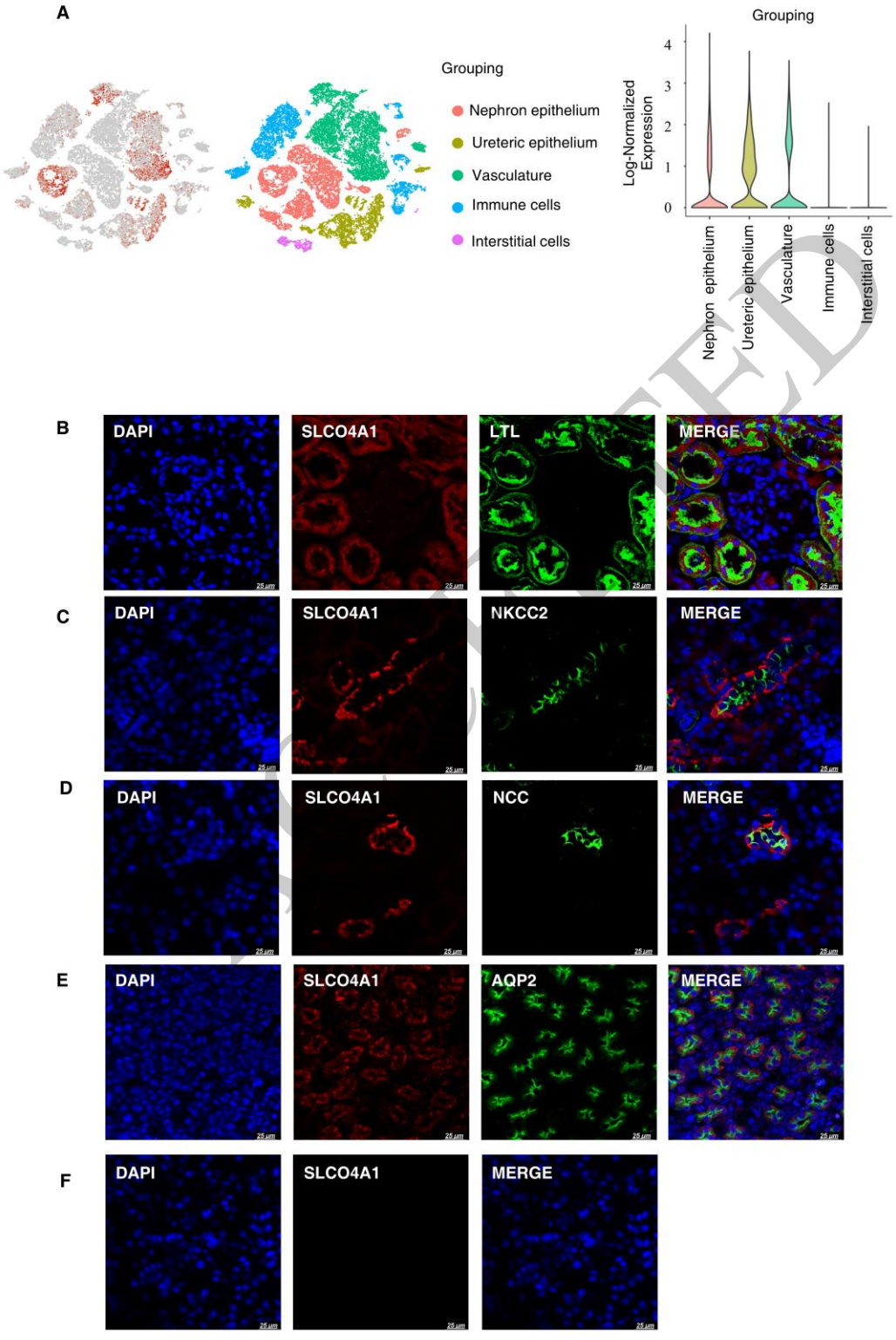


Figure 2. Renal tubule-specific *Slco4a1* gene deletion promoted natriuresis and diuresis in mice.

(**A**) Schematic of the strategy for generating a renal tubule-specific *Slco4a1* gene knockout mouse line (*Slco4a1*^{cKO}). (**B**) PCR-based genotyping for the floxed allele (242 bp) and Ksp-Cre transgene (413 bp). (**C-D**). 24-h urinary excretion of Na^+ (C) and Cl^- (D) in *Slco4a1*$^{f/f}$ and *Slco4a1*^{cKO} mice (n = 10). (**E-H**). Measurement of 24-h urine output (E), daily water intake (F), daily food intake (G) and body weight (H) using metabolic cages in the *Slco4a1*$^{f/f}$ and *Slco4a1*^{cKO} mice (n = 10). Data were presented as mean ± SEM. Statistical comparisons were performed using an unpaired two-tailed Student's *t* test.

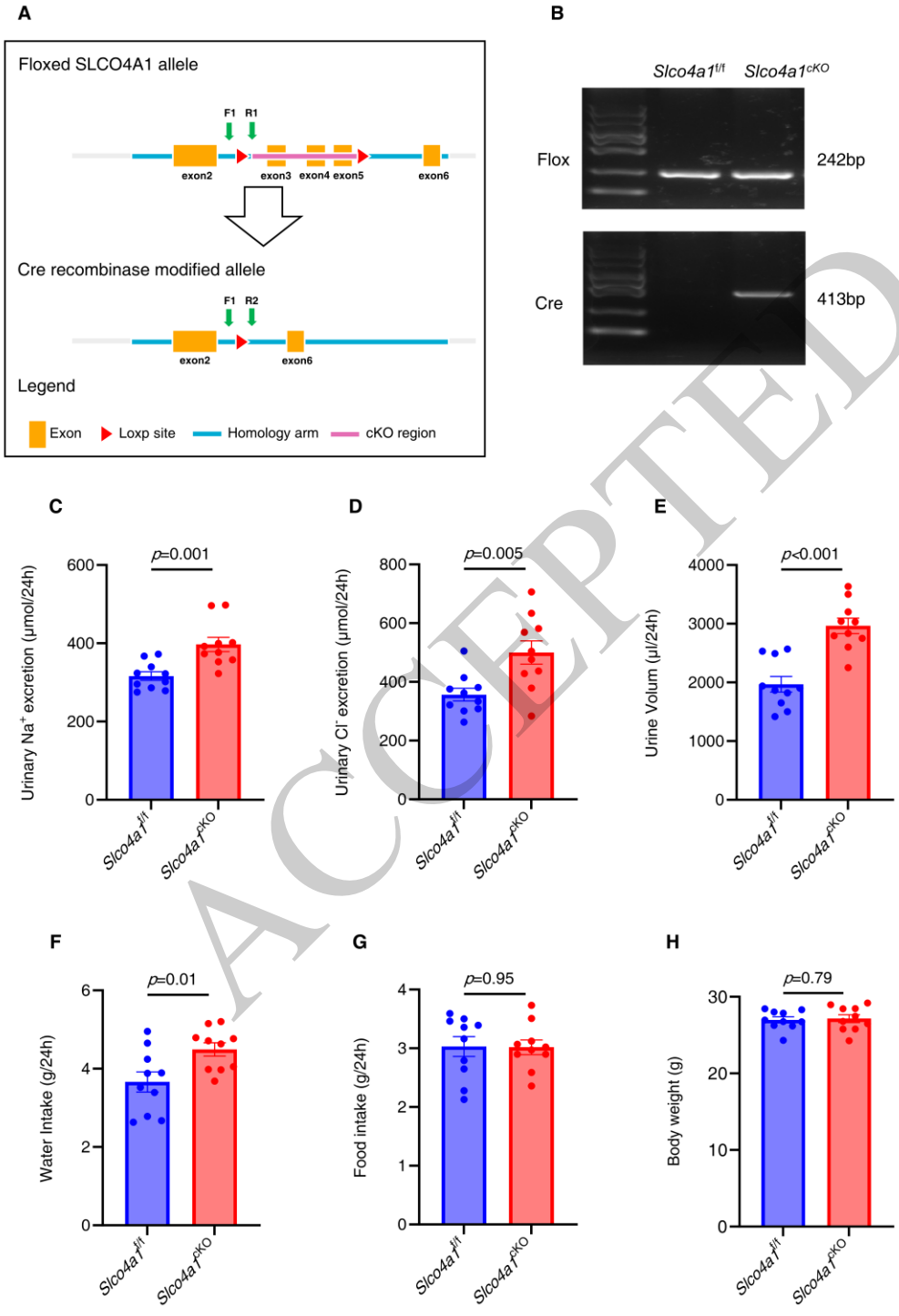


Figure 3. Global *Slco4a1* gene knockout caused natriuresis and diuresis in mice.

(**A**) Schematic of the CRISPR/Cas9 strategy used for targeting the exon 4-6 of mouse *Slco4a1* gene. (**B**) PCR-based genotyping for wild-type (WT, 850 bp) and knockout (KO, 474 bp) alleles. (**C**) Western blot assay confirmed the absence of SLCO4A1 protein in the tissues of the KO mice including heart, kidney and lung. (**D&E**). 24-h urinary excretion of Na^+ (D) and Cl^- (E) in WT and KO mice (n = 10). (**F-I**). Measurement of 24-h urine output (F), daily water intake (G), daily food intake (H) and body weight (I) by using metabolic cages in WT and KO mice (n = 10). Data were presented as mean ± SEM. Statistical comparisons were performed using an unpaired two-tailed Student's *t* test.

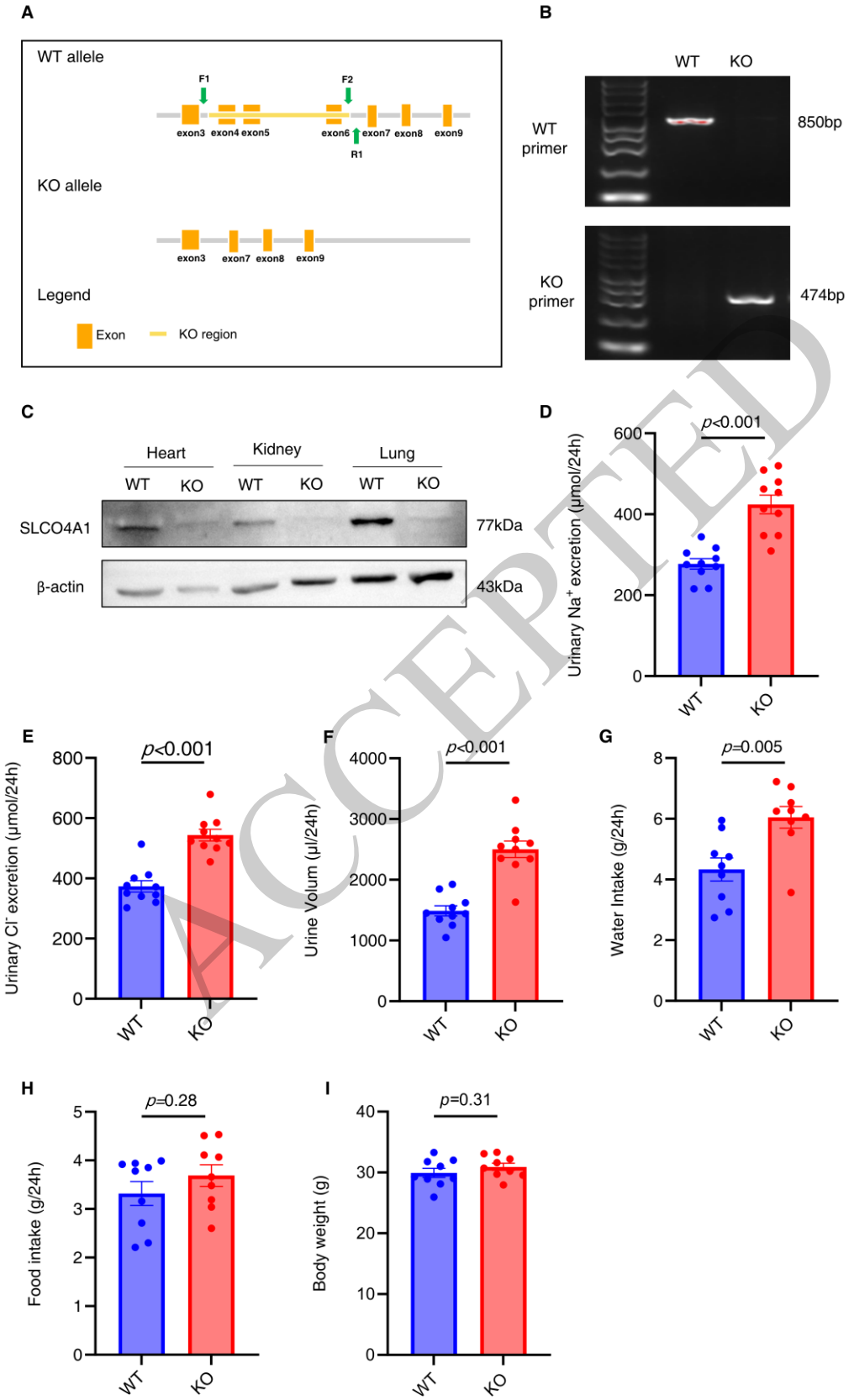


Figure 4. Renal tubule-specific *Slco4a1* gene ablation inhibited the function and expression of several major sodium transporters and channels along renal tubules.

(**A&B**) Natriuretic (A) and glucosuric (B) response to the SGLT2 inhibitor empagliflozin showed attenuated urine Na^+ and glucose excretion in renal tubule-specific *Slco4a1* gene knockout (*Slco4a1*^{cKO}) mice (n = 6). (**C&D**) Natriuretic (C) and chloruretic (D) response to the NKCC2 inhibitor furosemide showed reduced urine Na^+ and Cl^- excretion in the *Slco4a1*^{cKO} mice (n = 6). (**E**) Natriuretic response to the NCC and ENaC inhibitor (amiloride+hydrochlorothiazide) showed reduced Na^+ excretion in the *Slco4a1*^{cKO} mice (n = 6). (**F&G**) Representative western blots of SGLT2, NHE3, NCC, NKCC2 and α-, β-, γ-ENaC subunits in kidney cortex (F) and medullas (G) of the *Slco4a1*$^{f/f}$ and *Slco4a1*^{cKO} mice. Data were presented as mean ± SEM. Statistical comparisons were performed using an unpaired two-tailed Student's *t* test.

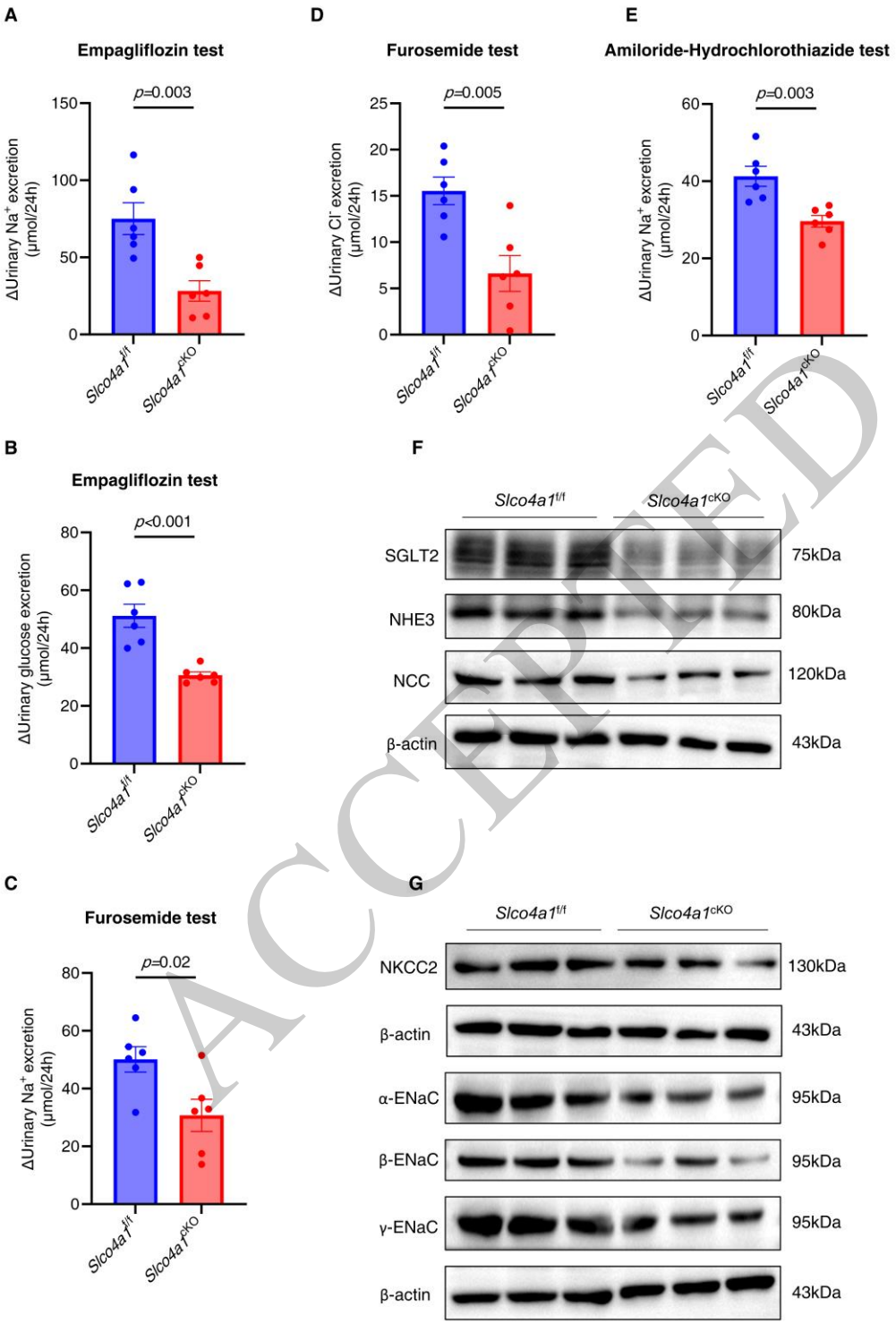


Figure 5. Kidney-specific *Slco4a1* gene overexpression resulted in decreased urine sodium and water excretion and increased expression of major sodium transporters and channels along renal tubules.

(**A**) Quantitative PCR analysis showed the *Slco4a1* mRNA expression levels in the kidneys of mice injected with control AAV (AAV-CON) and AAV- *Slco4a1* (AAV- *Slco4a1*). (**B**) Immunoblot assay demonstrated a significant increase in SLCO4A1 protein levels in the AAV- *Slco4a1* mice. (**C**) Quantification of SLCO4A1 protein levels in (B). (**D&E**). Daily urinary excretion of Na^+ (D) and Cl^- (E) in control (AAV-CON) and kidney-specific *Slco4a1* gene overexpression (AAV-*Slco4a1*) mice (n = 6). (**F-I**). Measurement of 24-h urine output (F), daily water intake (G), daily food intake (H) and body weight (I) in AAV-CON and AAV- *Slco4a1* mice (n = 6). (**J&K**) Representative western blots of SGLT2, NHE3, NCC, NKCC2 and α-, β-, γ-ENaC subunits in kidney cortex (J) and medullas (K) of AAV-CON and AAV- *Slco4a1* mice. Data were presented as mean ± SEM. Statistical comparisons were performed using an unpaired two-tailed Student's *t* test.

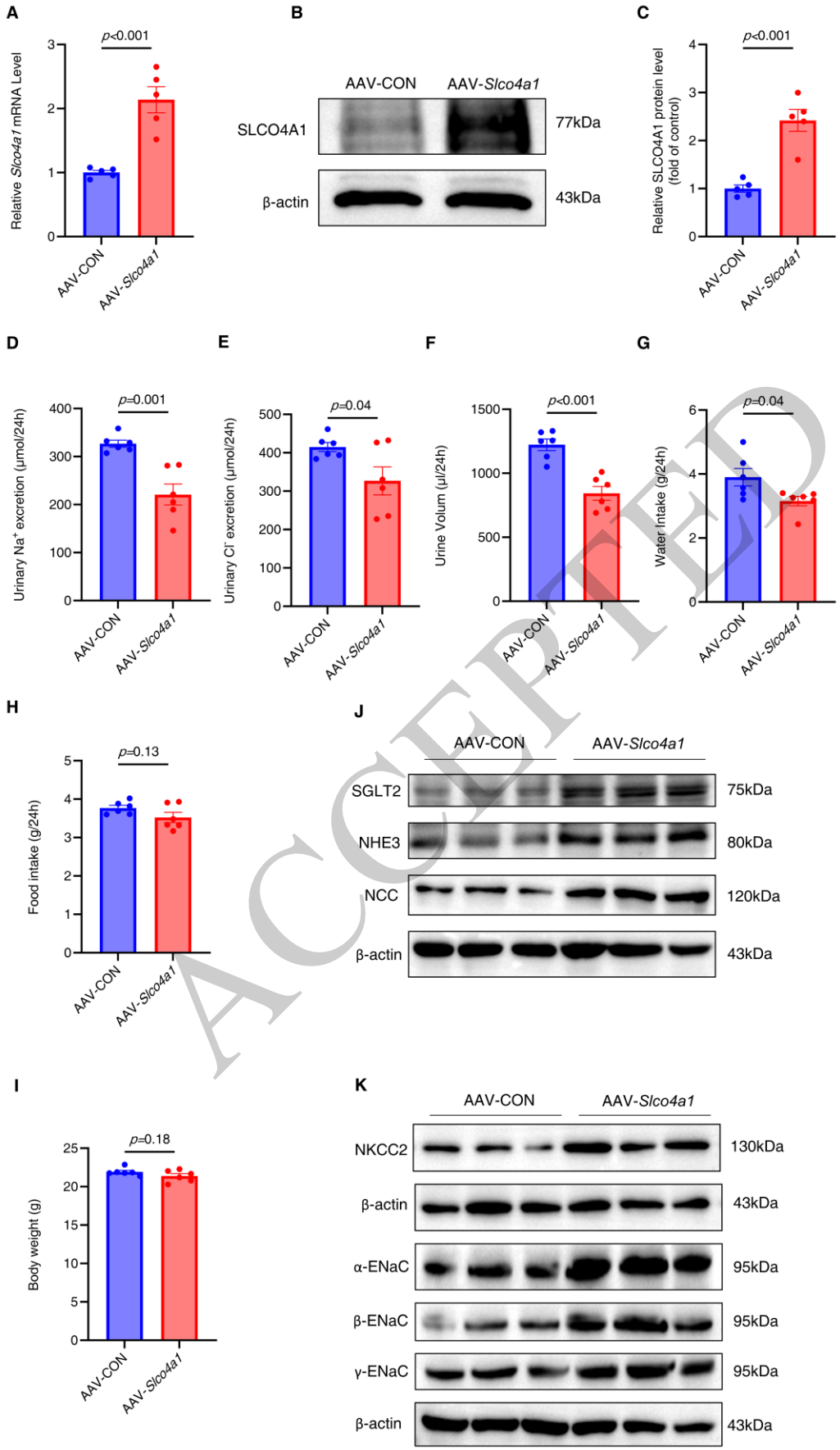


Figure 6. SLCO4A1 promoted basolateral uptake of PGE_2 in renal tubular epithelial cells.

(**A**) AlphaFold3 prediction revealed high-affinity PGE_2 binding site in the SLCO4A1 protein structure. (**B&C**) Human SLCO4A1 overexpression (ad-*SLCO4A1*) in mIMCD3 cells resulted in increased intracellular PGE_2 levels (B) and reduced supernatant PGE_2 concentrations (C) (n = 4). (**D&E**) Mouse *Slco4a1* gene knockdown (si- *Slco4a1*) significantly decreased intracellular PGE_2 levels (D) and increased supernatant PGE_2 concentrations (E) (n = 4). (**F&G**) The AAV-*Slco4a1* mice exhibited decreased kidney tissue PGE_2 content (F) and increased 24-h urinary PGE_2 excretion (G) (n = 6). (**H&I**) The *Slco4a1*^{cKO} mice exhibited increased kidney tissue PGE_2 content (H) and decreased 24-h urinary PGE_2 excretion (I) (n = 6). (**J**) A representative *in vivo* fluorescence imaging of the interstitial PGE_2 distribution and content in the *Slco4a1*$^{f/f}$ (left) and *Slco4a1*^{cKO} (right) mice after injection of the PGE_2-1.0 AAV sensor for 2 weeks. Data were presented as mean ± SEM. Statistical comparisons were performed using an unpaired two-tailed Student's t test.

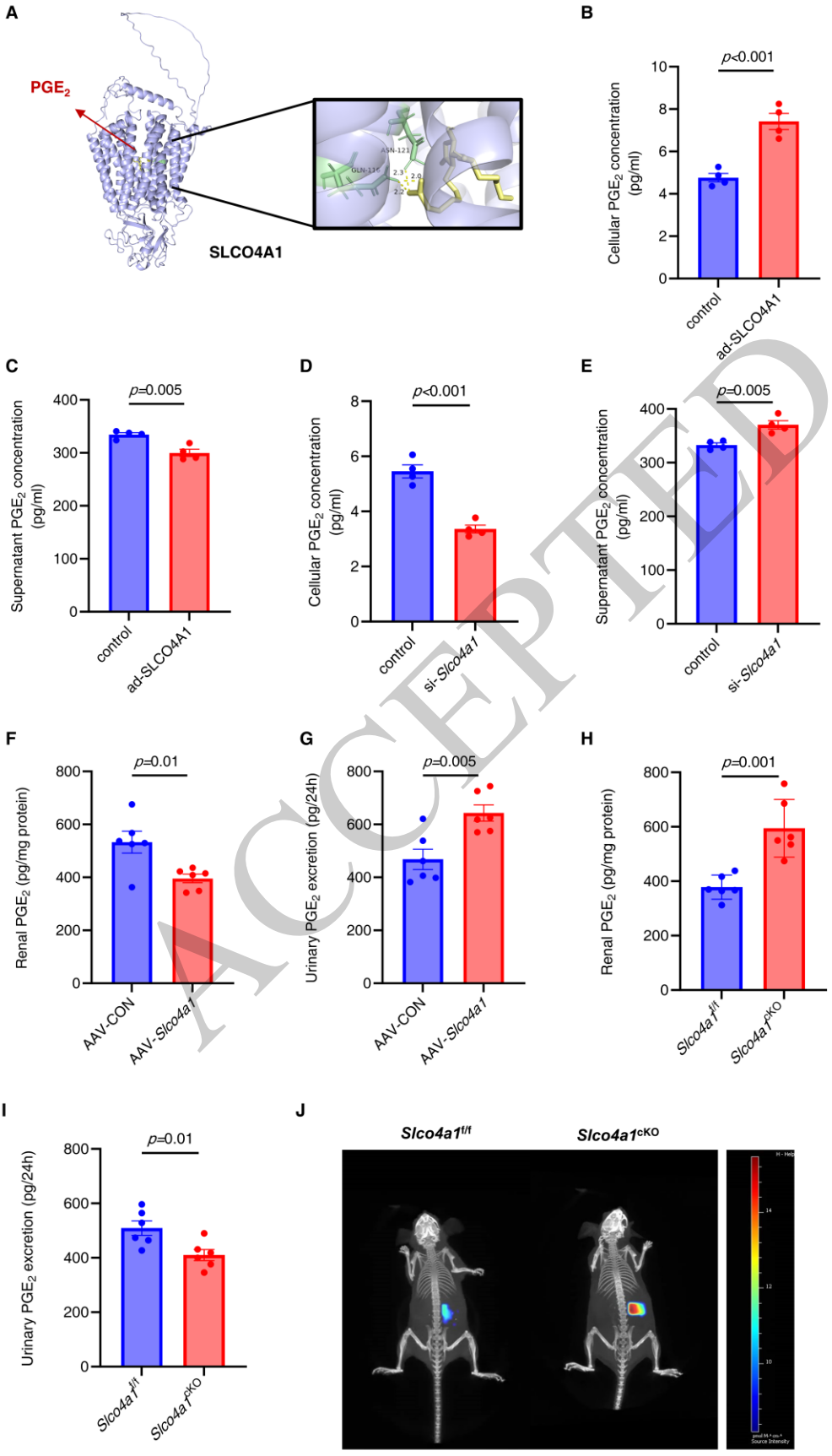
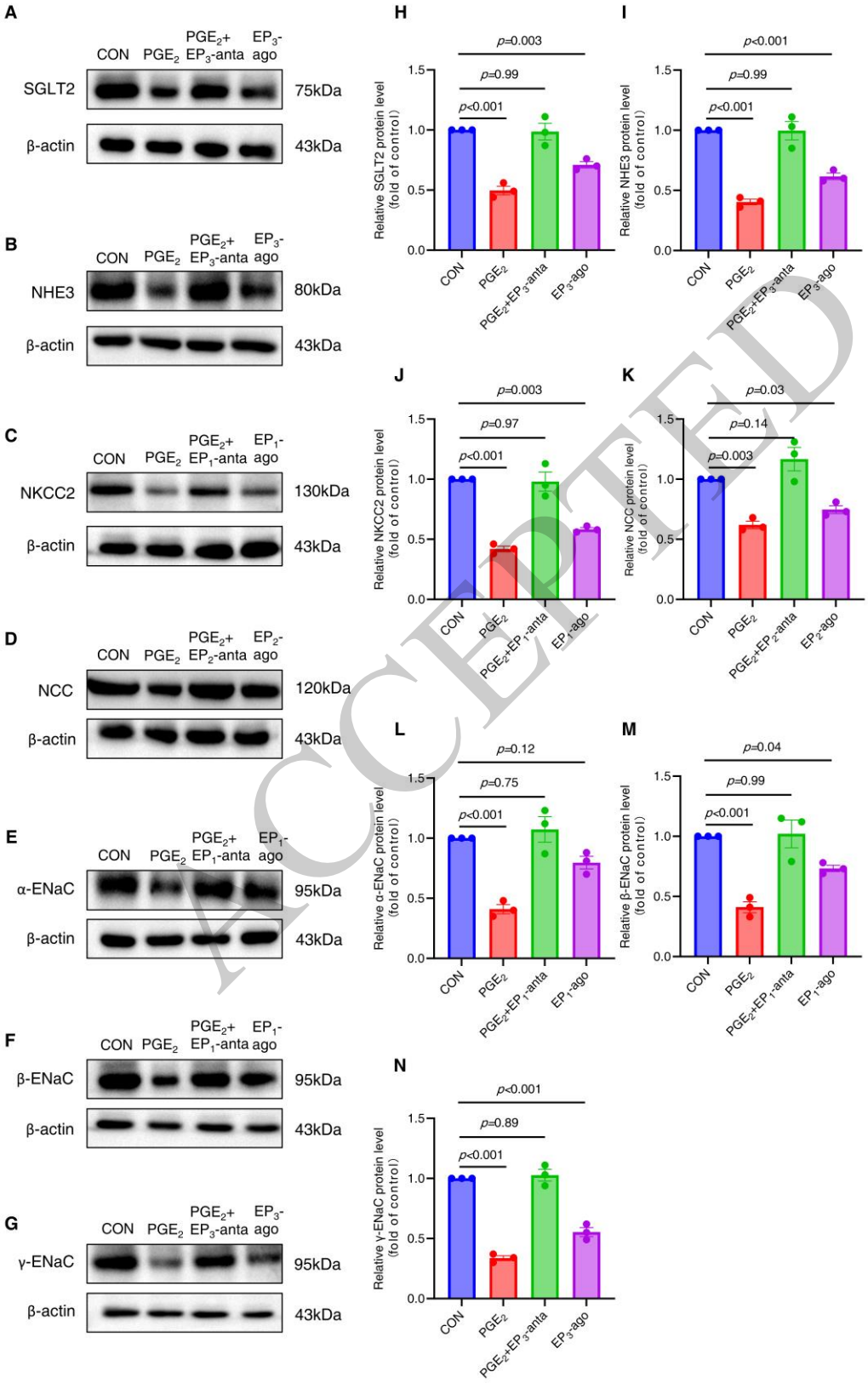


Figure 7. PGE_2 treatment suppresseed the expression of major sodium transports and channels in kidney tissue suspensions.

Kidney tissue suspensions were pretreated for 1 hour with vehicle (CON) and the EP receptor subtype-selective antagonists (anta, 10 nM), followed by co-treatment with or without PGE_2 (10 μM) or agonists alone (ago, 10 nM) for 6 hours. (**A-G**) western blot analysis showed that PGE_2 suppressed the protein expression of SGLT2 (A), NHE3 (B), NKCC2 (C), NCC (D), and α-ENaC (E), β-ENaC (F) and γ-ENaC (G) subunits. (**H-N**) Semi-quantification of protein expression of major sodium transporters and channels in A-G (n = 3). Statistical comparisons were performed using one-way ANOVA followed by Tukey's multiple-comparison test.



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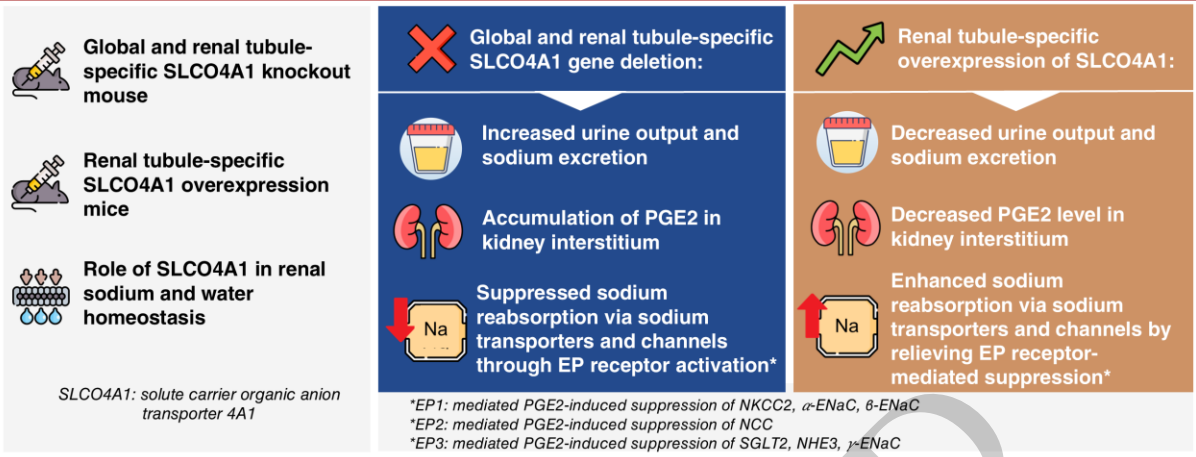

Conclusions: These findings identify the SLCO4A1-PGE_2-EP receptor axis as a key regulator of renal sodium transport.

Yanlin Guo, Beibei Ma, Chunxiu Du, et al. ***SLCO4A1 Governs PGE2-Mediated Natriuresis in the Kidney***. JASN DOI: 10.1681/ASN.0000001258.
Visual Abstract by Ana Flávia Moura, MD, PhD, FASN

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L. Chen has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Lihong Chen
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C. Du reports the following:
Employer: Perelman School of Medicine, University of Pennsylvania

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Chunxiu Du
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Y. Guan has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Youfei Guan
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X. Guixiang has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Xie Guixiang
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Y. Guo has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Yanlin Guo
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Y. Huang has nothing to disclose.

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Name: Yingzhi Huang
Manuscript ID: JASN-2026-000682R1
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Z. Jiang has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Zaifang Jiang
Manuscript ID: JASN-2026-000682R1
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B. Li has nothing to disclose.

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Name: Bin Li
Manuscript ID: JASN-2026-000682R1
Manuscript Title: SLCO4A1 governs PGE2-mediated natriuresis in the kidney
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R. Li has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Ruifen Li
Manuscript ID: JASN-2026-000682R1
Manuscript Title: SLCO4A1 governs PGE2-mediated natriuresis in the kidney
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Y. Li has nothing to disclose.

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Name: Yulong Li
Manuscript ID: JASN-2026-000682R1
Manuscript Title: SLCO4A1 governs PGE2-mediated natriuresis in the kidney
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T. Luo has nothing to disclose.

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Name: Taotao Luo
Manuscript ID: JASN-2026-000682R1
Manuscript Title: SLCO4A1 governs PGE2-mediated natriuresis in the kidney
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B. Ma has nothing to disclose.

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Name: Beibei Ma
Manuscript ID: JASN-2026-000682R1
Manuscript Title: SLCO4A1 governs PGE2-mediated natriuresis in the kidney
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J. Sun has nothing to disclose.

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Name: Jie Sun
Manuscript ID: JASN-2026-000682R1
Manuscript Title: SLCO4A1 governs PGE2-mediated natriuresis in the kidney
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X. Sun has nothing to disclose.

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Name: Xiaowan Sun
Manuscript ID: JASN-2026-000682R1
Manuscript Title: SLCO4A1 governs PGE2-mediated natriuresis in the kidney
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L. Wang has nothing to disclose.

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Name: Lei Wang
Manuscript ID: JASN-2026-000682R1
Manuscript Title: SLCO4A1 governs PGE2-mediated natriuresis in the kidney
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H. Xu reports the following:
Employer: East China Normal University

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Name: Hu Xu
Manuscript ID: JASN-2026-000682R3
Manuscript Title: SLCO4A1 Governs PGE2-Mediated Natriuresis in the Kidney
Date of Completion: August 28, 2026
Disclosure Updated Date: August 28, 2026

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C. Ye has nothing to disclose.

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Name: Caichao Ye
Manuscript ID: JASN-2026-000682R1
Manuscript Title: SLCO4A1 governs PGE2-mediated natriuresis in the kidney
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F. Ye has nothing to disclose.

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Name: Fang Ye
Manuscript ID: JASN-2026-000682R3
Manuscript Title: SLCO4A1 Governs PGE2-Mediated Natriuresis in the Kidney
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Y. Lin has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Yulong Lin
Manuscript ID: JASN-2026-000682R1
Manuscript Title: SLCO4A1 governs PGE2-mediated natriuresis in the kidney
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X. Zhang has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Xiaoyan Zhang
Manuscript ID: JASN-2026-000682R1
Manuscript Title: SLCO4A1 governs PGE2-mediated natriuresis in the kidney
Date of Completion: August 4, 2026
Disclosure Updated Date: August 4, 2026

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F. Zheng reports the following:
Patents or Royalties: Renal medicine and technology inc; and Other Interests or Relationships: renal medicine and technology inc.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Feng Zheng
Manuscript ID: JASN-2026-000682R2
Manuscript Title: SLCO4A1 Governs PGE2-Mediated Natriuresis in the Kidney
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JASN Journal of the American Society of Nephrology
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H. Zhou has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

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