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Renal organic anion transporter 1: clinical relevance and the underlying mechanisms in chronic kidney disease

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Abstract

Organic anion transporter 1 (OAT1), primarily found in the renal proximal tubule, is essential for the excretion of various uremic toxins that contribute to the onset and progression of chronic kidney disease (CKD). OAT1 also plays a vital role in the remote sensing and signaling network, facilitating the removal of metabolites through the kidneys. The function of OAT1 is impaired under conditions such as renal ischemia/reperfusion injury, oxidative stress, and fibrosis. Several transcription factors, post-translational modifications, and endocrine hormones control the activity and expression of OAT1. This review explores the unique contribution of OAT1 to the excretion of CKD-related UTs and the mechanisms involved.

Keywords OAT1, Chronic Kidney Disease, Uremic Toxins, Regulatory

Background

Chronic kidney disease (CKD) represents a significant worldwide health challenge with an increasing prevalence rate, characterized by a progressive decline in kidney function and elevated blood levels of uremic toxins (UTs) such as creatinine, urea, indoxyl sulfate (IS), and p-cresyl sulfate (PCS). These toxins, which accumulate primarily due to protein metabolism and gut microbiota activity, exacerbate cardiovascular risks and other complications in CKD patients [1–3]. Organic anion transporter 1 (OAT1), a key solute carrier located in the kidneys, plays a vital role in transporting numerous UTs and acts as a part of the remote sensing and signaling network that helps regulate metabolic balance through inter-organ communication [4]. When kidney structure and function are impaired, as expected, the capability of OAT1 is also affected. Renal ischemia–reperfusion injury (IRI) typically diminishes OAT1's function, thereby hindering the excretion of drugs and toxins [5]. In renal oxidative stress injury, OAT1 activity is compromised due to a decline in kidney function [6]. However, reducing oxidative metabolites and enhancing antioxidant gene expression can restore OAT1 activity [7]. In tubulointerstitial fibrosis, the decreased expression of OAT1-mRNA leads to reduced renal clearance [8]. In contrast, boosting OAT1 could mitigate fibrosis progression by promoting more effective transport of toxins and drugs [9, 10].

The regulation of OAT1 involves intricate mechanisms crucial for maintaining physiological function, including the influence of multiple transcription factors. The Hepatocyte nuclear factor (Hnf) family, such as Hnf1α and Hnf4α, bind to the OAT1 gene promoter to regulate its expression in response to physiological and external stimuli [11, 12]. Additionally, post translational

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modifications-glycosylation and ubiquitination affect protein stability and degradation, while phosphorylation and SUMOylation modulate OAT1's activity and localization, these modifications are critical for the proper functioning of OAT1 [13–16].

Endocrine hormones significantly impact the regulation of OAT1, which is essential for renal clearance and drug metabolism. 1a,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) reduces OAT1 expression, potentially decreasing drug clearance and altering efficacy and toxicity. In contrast, it also enhances cellular vitality and protects against renal damage [17, 18]. Sex hormones such as testosterone, estradiol, and progesterone create gender-specific differences in OAT1 levels, affecting drug metabolism rates and pharmacokinetics [19]. Insulin activates several signaling pathways that enhance OAT1 activity, which is critical for managing substances like urate in metabolic conditions like diabetes [20]. This review focuses on OAT1's function in transporting UTs associated with CKD, and further explores its clinical relevance in renal injury and the corresponding regulatory mechanisms.

Physiology of OAT1 in Kidney

The structure and expression of OAT1

OAT1, also called SLC22A6, is located on chromosome 11q13.1 and spans about 8.2 kb, consisting of 10 exons and 9 introns [21, 22]. It features twelve transmembrane domains (TMDs) that form a channel for substrate transport. Glycosylation sites are present on TMDs 1 and 2, while phosphorylation sites are located on TMDs 6 and 7. The N-terminal and C-terminal are positioned within the cytoplasm, contributing to protein localization and stability [23] (Fig. 1).

OAT1 is highly conserved across multiple species [24, 25] (Table 1), exhibiting significant homological similarities to its counterpart in mice through its evolutionary process [26]. Based on NCBI data, the OAT1 gene is predominantly expressed in the human kidney, but it is also widely distributed across other organs, showing varying expression levels among different organs. Detailed information is provided in Table 2. OAT1 expression is generally considered sex-dependent, with male animals often displaying more robust expression [24, 25, 27], influenced by genetically determined organ selection factors [28]. Specifically, studies have found that OAT1/3 expression is lower in female rats than in males, which limits mercury uptake and results in less renal damage in females compared to males [29]. However, this sex difference disappears in obese rats, indicating that obesity may modify the sex-specific expression of OAT1/3. This highlights how sex and body weight impact OAT1/3 expression, providing insights into gender disparities in renal disease and metabolism [27]. In contrast, there are no observed

Table 1 The species and gender-dependent characteristics of OAT1 expression

Transporter	Species	Gender-dependent	Reference
OAT1	Human	M = F	[24]
	Monkey	M > F*1.3	[24]
	Dog	M = F	[24]
	Rat/Mouse	M > F*1.3	[24]
	Rabbit	M = F	[25]

M Male, *F* Female, *LM* Lean males, * fold difference

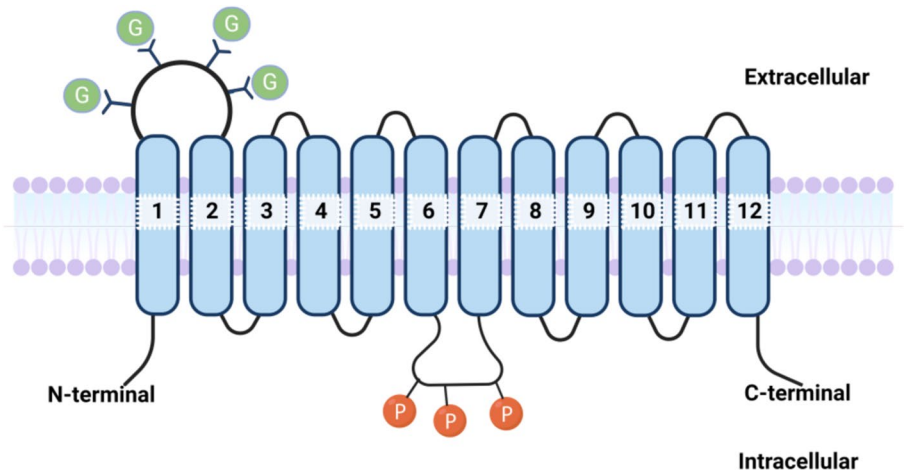

Fig. 1 This illustration describes the structure of OAT1. Twelve transmembrane domains (TMDs) span the plasma membrane. TMDs 1 and 2 are characterized by several glycosylation sites labeled 'G.' TMDs 6 and 7 contain potential phosphorylation sites labeled 'P.' N- and C-termini of the proteins are proposed to be located intracellularly. This illustration was created based on reference [23]

Table 2 The organ distribution and gene expression levels of OAT1 in human

Transporter	Human organs	OAT1 Gene Expression (RPKM)
OAT1	Kidney	148.997 ± 68.309
	Brain	0.974 ± 0.538
	Colon	0.222 ± 0.223
	Fat	0.041 ± 0.044
	Gall bladder	0.021 ± 0.016

This table's content is sourced from the National Center for Biotechnology Information (NCBI). RPKM: Reads Per Kilobase of the transcript, per Million mapped reads. The numbers in the table represent the expression levels of the OAT1 gene in various human organs

sex differences in renal OAT1 expression in rabbits, highlighting species-specific biological variations crucial for assessing drug metabolism and toxicity [25]. While human studies lack evidence of gender differences in OAT1, these differences in other species underscore the importance of considering physiological characteristics in drug therapy.

The function of OAT1

OAT1 is situated on the basolateral aspect of proximal tubule cells and employs a counter-transport system using α-ketoglutarate (α-KG), regulated by sodium dicarboxylate cotransporter 3 (NaDC3). This system facilitates the identification and excretion of metabolites and toxins in the nephron, with intracellular chloride enhancing anion uptake through allosteric regulation [30]. Other studies have found that OAT1 is initiated by the primary Na(+)-K(+)-ATPase, which establishes a sodium gradient. This gradient activates the secondary NaDC3, enabling the terminal OAT1 to function effectively [31] (Fig. 2).

OAT1 is capable of transporting a diverse array of substances, such as drugs [32–35], endogenous metabolites [33, 36–38], and environmental toxins [39] (Table 3). Another member of the OAT family, OAT3, shares some substrates with OAT1 [40]. Vallon et al. [40] discovered that the efficacy of furosemide is reduced when OAT1 function is compromised or inhibited, and diclofenac's renal toxicity is increased by blocking hOAT1/3, highlighting OAT1's critical role in drug metabolism and renal toxicity in humans [41]. Recent studies have found that drugs blocking OAT1/3 can interfere with the clearance of UTs in individuals who have received kidney transplants, suggesting potential interactions between drugs and UTs [42]. Additionally, when OAT1/3 is inhibited, there are increased drug-drug interactions and decreased renal clearance [43]. Impairment or blockade of OAT1 can reduce drug effectiveness and increase toxicity, especially in kidney disease patients. Thus, preserving OAT1

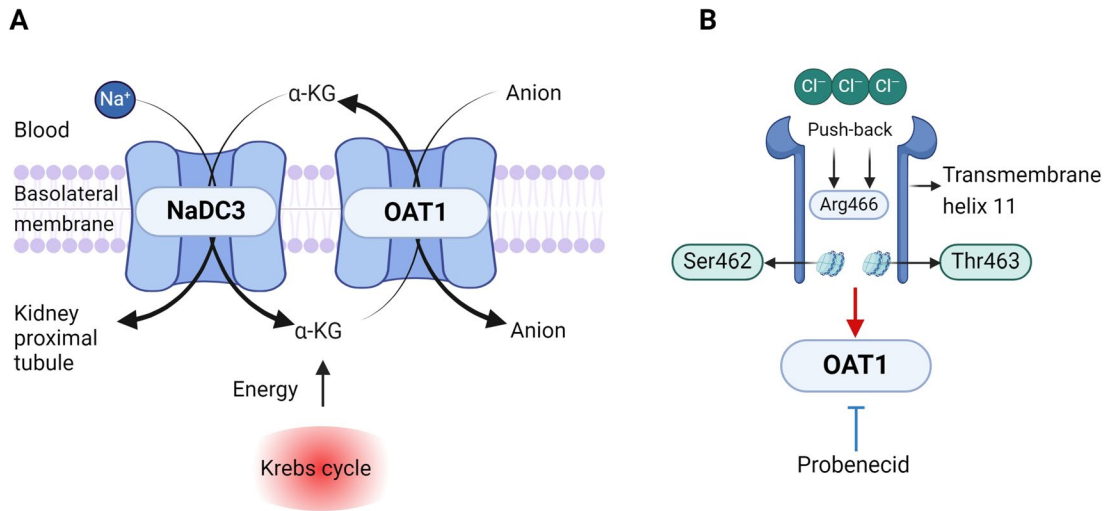

Fig. 2 Panel A: This illustration describes the mechanism of OAT1 transport. The Krebs cycle generates α-KG and provides energy. NaDC3 operates through a secondary active transport mechanism, utilizing the sodium gradient established by the Na(+)-K(+)-ATPase pump as an energy source to facilitate the uptake of α-KG into the cell. OAT1 uses the outwardly directed α-KG gradient, maintained by the NaDC3 and the Krebs cycle, to drive the uptake of organic anions from the blood across the basolateral membrane of the kidney proximal tubules. Panel B: This illustration describes the mechanism of OAT1 transport. When probenecid inhibits the function of OAT1, intracellular Cl – pushes Arg466 back into TM11, leading to tight engagements with Ser462 and Thr463, thereby achieving allosterically controlling and enhancing OAT1 function. NaDC3: Sodium-dependent dicarboxylate transporter 3, α-KG: alpha-Ketoglutarate, Arg466: Arginine residue at position 466, Ser462: Serine residue at position 462, Thr463: Threonine residue at position 463. This illustration was created based on references [30, 31]

Table 3 Examples of substrates transported by OAT1

Transporter	Drug substrates	Endogenous metabolites	Environmental toxins
OAT1	Cilastatin [32]	Creatinine [38]	Mercury [39]
	Adefovir [33]	Urea [37]	Arsenic [39]
	Ciprofloxacin [33]	Indoxyl sulfate [33]	
	Benzylpenicillin [34]	Uric acid [33]	
	Cefdinir or cefadroxil [35]	p-Cresol sulfate [36]	

The number following each drug name represents the reference number

function is vital for preventing drug-induced kidney damage and ensuring effective toxin removal.

Protein-bound solutes are mainly conveyed to the renal tubule by OAT1, which is situated on the basolateral side of cells in the proximal renal tubules [44]. As renal disease progresses and nephron volume decreases, the plasma levels of toxins rise, highlighting the crucial role of OAT1/3. These transporters are essential for detecting and removing UTs, especially small organic anions originating from the gut microbiome, significantly contributing to CKD [45]. Consequently, any reduction in the transport capacity of OAT1 can affect the renal elimination of UTs, disrupting the standard process of renal excretion and potentially leading to increased toxicity.

Basic information about UTs associated with CKD

The origin and accumulation of UTs

The European Uremic Toxin Work Group introduced a novel classification system for uremic solutes based on molecular weights and identified key markers of UTs [44], which has gained widespread acceptance and use [45]. UTs are derived from both endogenous sources and the gut, with the kidneys playing a critical role in their removal. Endogenous UTs, such as creatinine and urea, are products of metabolism [46, 47]. Conversely, gut-derived UTs stem from dietary inputs and the metabolic activity of gut microbiota, with the dietary composition influencing the balance and metabolic activity of the gut microbiome, thus facilitating the production of UTs. IS is a significant protein-bound uremic toxin, originating as a small organic molecule—an organic anion in the gut [36, 48]. High-protein diets can alter gut bacteria, increase fecal pH, and elevate metabolite levels linked to inflammation and kidney dysfunction [49]. As a result, diet plays a crucial role in modulating gut-derived UTs, particularly those produced through bacterial fermentation [36]. The excessive production of UTs by gut flora during protein fermentation can accelerate the progression of CKD [50, 51]. The accumulation of UTs induces degradation of epithelial tight junctions protein and increases intestinal permeability, which in turn leads to enhanced systemic absorption of toxins [52, 53].

The relationship between OAT1 and CKD

The role of OAT1 in UTs transport in CKD

CKD is marked by a reduction in functional nephrons, and the risk of uremic syndrome and its associated complications significantly contributes to the increasing incidence rates in CKD patients [3]. CKD is also characterized by significant pathological change, e.g., glomerular filtration rate, progressive glomerulosclerosis, tubular atrophy, interstitial fibrosis, and increased plasma UTs [54]. An essential function of OAT1 is the active transportation of these UTs from the bloodstream into the renal proximal tubule cells, thus aiding their removal through urine. As the nephrons deteriorate, the expression of OAT1 decreases, directly affecting the kidney's capacity to eliminate UTs [55] (Fig. 3). Chronic renal failure may impair the renal tubules' ability to process drugs and the substrates of these transport proteins, the expression levels of OAT1/3, for both protein and mRNA, were significantly reduced, leading to a decreased capacity to excrete UTs [56]. The accumulation of these toxins damages various body systems, contributing to the multisystem complications seen in CKD. IS, absorbed by proximal tubular cells via OAT1/3, promotes ROS production, impairing the cellular antioxidative system and accelerating CKD progression by elevating renal levels of profibrotic cytokines such as transforming growth factor beta 1 [57]. OAT1 is critical in identifying metabolites and toxins within the renal unit and ultimately excreting them through urine [30]. A systems biology study revealed that OAT1/3 continues to transport UTs in the kidney despite declining glomerular filtration rates, maintaining residual tubular function and balancing small molecules in CKD, thereby preserving systemic homeostasis [58].

Research indicates that OAT1 is crucial for the renal clearance of drugs, especially in treating Hepatitis B Virus. Prolonged use of nucleoside medications may elevate the risk of CKD due to impaired OAT1 function [59]. Specific CKD treatments might interact with OAT1, potentially affecting the clearance of drugs mediated by OAT1, which could further impair remaining renal functions and the management of Protein-Bound UTs [60]. Additionally, the presence of albumin significantly affects

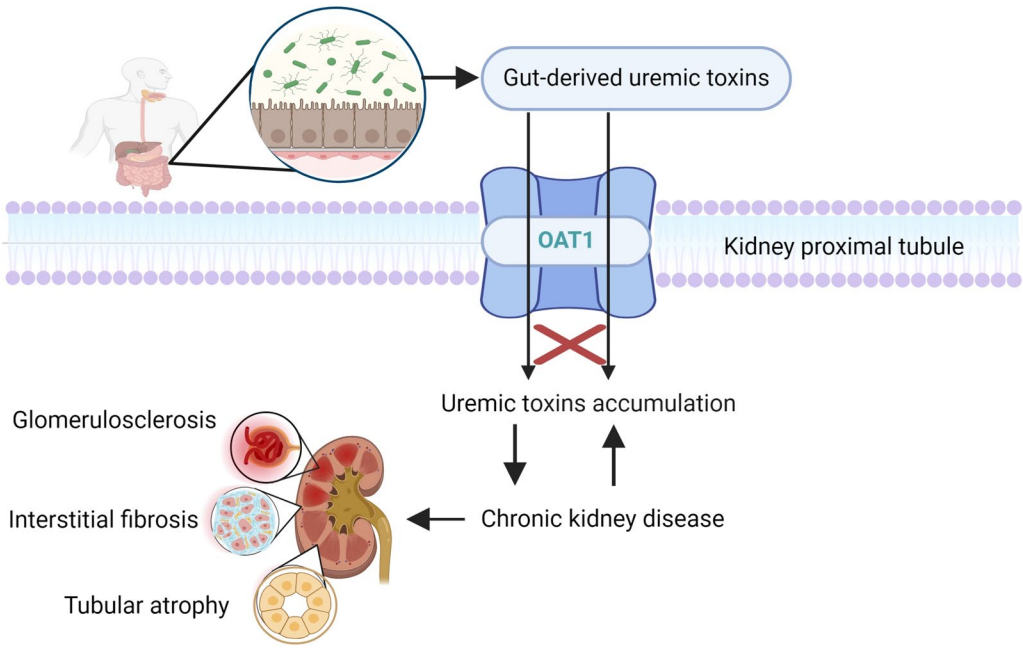

Fig. 3 This diagram illustrates the pathophysiological mechanisms by which gut-derived UTs contribute to CKD progression. OAT1 is located primarily in the proximal tubular epithelial cells of the kidney. Inhibition or dysfunction of OAT1 leads to toxin accumulation, exacerbating CKD progression. This results in glomerulosclerosis, interstitial fibrosis, and tubular atrophy—fundamental pathological changes driving CKD advancement

the renal clearance of IS, particularly in the case of CKD-modified albumin, where the clearance efficiency of IS is substantially reduced [61]. Subsequently, researchers discovered that increasing OAT1 transporters and speeding up the dissociation rate of IS in uremic conditions effectively enhances its elimination. Additionally, changes in plasma albumin's structure can modify its binding with IS, impacting the release rate of IS and its capture efficiency by OAT1 transporters. Essentially, the quicker IS dissociates, the more freely it circulates, facilitating its removal by OAT1 [62]. Furthermore, experiments using rat OAT1/3 inhibitors and OAT1/3 double gene knockout models revealed that Kynurenic Acid, being 99% bound to albumin, is not filtered in the glomerulus, leading to increased plasma concentrations [63].

The impact of uremic toxins on CKD

The kidney maintains blood homeostasis by managing toxin uptake, retention, and elimination. Reduced kidney clearance leads to UTs accumulation, speeding up the progression of CKD to end-stage renal disease and heightening the necessity for dialysis or transplantation [50]. Additionally, CKD is associated with an altered gut microbiome, where bacterial-derived UTs contribute to cardiovascular disease and systemic inflammation. Compounding these issues, endocrine disruptions linked to CKD further elevate all-cause mortality in these patients [64]. The systemic spread of UTs severely impacts multiple organ systems in CKD patients, leading to complications such as cardiovascular disease, neurological disorders, and gastrointestinal problems, which significantly affect their quality of life [44, 65, 66] (Fig. 4). Probiotics and dietary changes positively influence the modulation of gut-derived toxins by reducing the production of UTs in CKD patients [50, 67]. A study demonstrated that OAT1 significantly impacts gut microbiome-derived metabolites in a CKD model, highlighting its central role in drug-metabolite interactions, gut microbe-dependent metabolism, and host-microbiome communication [68].

OAT1 as a central node in the remote sensing and signaling network in CKD

The OAT1 mediating in substrate transport is crucial for inter-organ communication and maintaining host homeostasis, as described in Nigam S's remote sensing and signaling hypotheses [69]. Jansen et al. found that IS activates the ligand-dependent transcription factor Aryl Hydrocarbon Receptor (AhR), significantly increasing OAT1 expression. Besides activating AhR, IS also binds to the extracellular domain of the Epidermal Growth Factor Receptor(EGFR), further enhancing OAT1 expression. Moreover, IS-induced

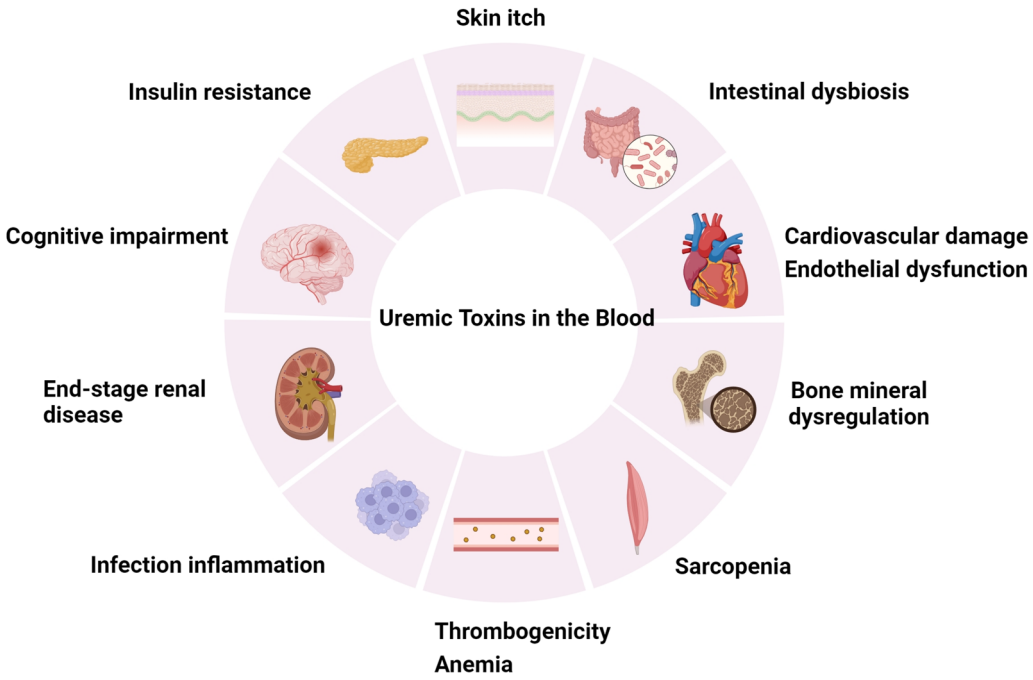

Fig. 4 Each section of the diagram outlines distinct disorders, detailing the impacts of blood UTs on various organ systems in CKD patients. This illustration was created based on references [44, 65, 66]

OAT1 transport activity is inhibited by AhR or EGFR-selective antagonists, which effectively block the transporter-mediated intracellular accumulation of IS, confirming its role in sensing and signaling [4]. Moreover, in OAT1 knockout rats, the increased presence of ring structures and sulfate groups in metabolites like IS, PCS, and deoxycholate suggests a pathway involving gut microbes, liver phase II metabolism, and renal OAT1 transport, highlighting its crucial role in regulating gut-derived metabolites significant in CKD pathology [68]. After subtotal nephrectomy and probenecid treatment, levels of colon-derived uremic solutes increased, similar to findings in OAT1/3-KO rats, indicating a connection between colonic microbial metabolites and the blood-urine barrier through OAT1/3 [55]. Ermakov et al. [70] revealed that OAT1 facilitates inter-organ communication by regulating the composition and metabolic capabilities of the gut microbiome, particularly in CKD. However, this inter-organ connection was also evident in a rat model of cardiac ischemia with AKI, where ischemia significantly reduced both renal blood flow and OAT1 function, leading to the accumulation of metabolic waste [71]. Based on these findings, potential therapeutic strategies can be explored, including pharmacological interventions to preserve OAT1 function and mitigate metabolic waste accumulation.

OAT1 in the context of various renal injury

The impact of IRI on OAT1

In clinical practice, the long-term sequelae of AKI are gaining attention, with recognized associations with adverse outcomes, including higher mortality and the development of CKD [72]. IRI is a well-established critical contributor to AKI; in this context, the renal accumulation of IS triggers oxidative stress that downregulates OAT1, ultimately leading to renal damage [73]. OAT1 is activated by the primary Na(+)-K(+)-ATPase pump [31], however, during IRI, the diminished activity of Na(+)-K(+)-ATPase further compromises the function of OAT1/3, thereby hindering the excretion of drugs and toxins [74].

In AKI, IRI leads to decreased OAT1/3 expression through the action of prostaglandin E2 in rat tubules, but this can be mitigated by low-dose indomethacin, which helps restore OAT1/3 and thus rescues kidney function [5]. Cyclooxygenase 1 derivatives reduce hOAT1/3 expression via E prostanoid receptor type 4 in renal IRI, affecting renal organic anion transport [75]. In rat models with cardiac ischemia-induced AKI, a rapid decrease in OAT1 during ischemic events worsens PAH transport. Insulin stimulation further complicates the trafficking of OAT1/3, potentially exacerbating AKI by down-regulating protein kinase C zeta (PKC zeta)/protein kinase B (Akt) pathways and

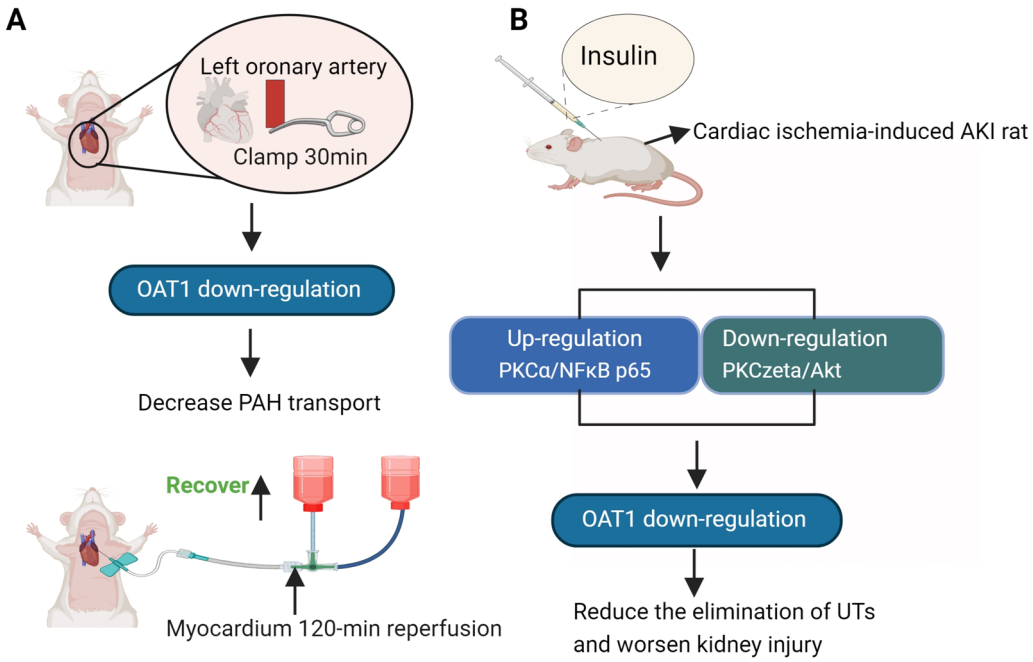

Fig. 5 Panel A: In a mouse model study, cardiac ischemia was induced by clamping the left coronary artery for 30 min, followed by a reperfusion period of 120 min. This procedure resulted in the down-regulation of OAT1 and decreased PAH transport. These changes are reversible after reperfusion. Panel B: The detrimental effect of insulin on the activity of OAT1 during cardiac ischemia-induced AKI rat. The upregulation of PKCα/NFκB p65 and the downregulation of PKC zeta/Akt weaken OAT1/3 function, reduce the elimination of UTs, and worsen kidney injury. PAH: para-aminohippurate, PKC zeta: Protein Kinase C zeta, Akt: Protein Kinase B. This illustration was created based on reference [71]

upregulating PKCα and nuclear transcription factor kappa B (NFκB) p65 [71] (Fig. 5).

In a recent study, it was found that in ischemia/reperfusion (I/R) induced mouse models, the enhancer of zeste homolog 2 (EZH2) fuels the transition from AKI to CKD by promoting epithelial-mesenchymal transition (EMT), resulting in OAT1 loss. However, inhibiting EZH2 either through conditional deletion or pharmacological inhibition with 3-DZNeP has been shown to improve renal function and reduce pathological changes effectively [76]. During AKI, decreased expression of OAT1 impairs medication metabolism and waste removal, potentially worsening or prolonging AKI. Thus, targeting the regulation of OAT1 presents a promising therapeutic approach for AKI, and a thorough understanding of the involved pathways could be beneficial.

The impact of oxidative stress on OAT1

Oxidative stress is a critical pathological factor in renal injury, arising from an imbalance between ROS and antioxidant mechanisms. Research demonstrates that oxidative stress exacerbates AKI by damaging renal cells and decreasing OAT1 transport function, thereby impairing toxin clearance [6]. In contrast, overexpression of OAT1/3 shifts cellular energy production towards oxidative metabolism instead of glycolysis, driven by increased utilization and synthesis of α-ketoglutarate [77].

Mitochondrial dysfunction impairs the energy transport chain, leading to decreased ATP production and increased energy leakage, the compromised mitochondria activate apoptotic pathways and reduce energy availability, severely impairing kidney function by hindering detoxification and waste processing in renal cells [78]. In a study on mitochondrial dysfunction induced by bromoacetic acid, suppressing of mitochondrial biogenesis genes and oxidative phosphorylation complex I genes significantly impaired cellular energy processes. Additionally, altered expression of nuclear factor erythroid 2-related factor 2(Nrf2) antioxidant response genes (Nrf2, Keap1, HO-1, NQO1, GCLM, GCLC) led to dysfunction in renal transporters like multidrug resistance-associated proteins(MRP)2/4, Bcrp, OAT1/2, and OAT3, exacerbating renal function decline [79]. Chen et al. [7] found that apetala seed oil could mitigate renal oxidative damage by enhancing the activation and translation of antioxidant genes Nrf2 and related antioxidative enzymes, aiding in the recovery of OAT1 expression. However, direct evidence proving the relationship between OAT1 and antioxidant genes needs to be confirmed. A metabolomic analysis indicates that the Aryl hydrocarbon receptor and

EGFR mediate ischemia-induced OAT1 expression, concurrently producing ROS regulating OAT1 activity, thus stabilizing plasma metabolite levels [4].

The impact of renal fibrosis on OAT1

In the progression of CKD to tubulointerstitial fibrosis, lower OAT1-mRNA levels were observed [8]. EZH2, an enzyme key in chromatin modification and gene regulation, contributes to the loss of OAT1 protein, thereby facilitating EMT in renal tubules [76]. In contrast, asperulosidic acid has been shown to increase both mRNA and protein levels of OAT1/3 via Hnf1α in mice with unilateral ureteral obstruction, enhancing the clearance of IS and reducing renal interstitial fibrosis [9]. Similarly, inhibitors targeting OAT1, ASK1, ERK1/2, and p38MAPK in cardiorenal syndrome effectively prevent fibrosis induced by UTs. These toxins aggravate cardiac hypertrophy and increase collagen synthesis in cardiac myocytes, fibroblasts, proximal tubular, and renal mesangial cells, while also activating pro-hypertrophic (α-skeletal muscle actin and β-MHC) and pro-fibrotic genes (TGF-β1 and ctgf) [80]. Additionally, inhibition of OAT1/3 led to adefovir accumulation in the renal interstitium, triggering interstitial fibrosis with mast cells playing a crucial role. However, treatment with sodium cromoglycate and valsartan alleviated this accumulation by upregulating OAT1/3 and MRP4 expression, potentially reversing the fibrosis caused by adefovir [10]. Interestingly, studies have shown that obese male rats display higher levels of glomerulosclerosis and tubulointerstitial fibrosis compared to female rats, whereas lean females exhibit higher expression of OAT1/3 [27].

Additional clinical research is necessary to confirm whether these results are applicable to humans. Although the link between OAT1 and renal fibrosis is still emerging, comprehending the broader biological and pathological mechanisms remains crucial. Ultimately, preventing the onset of fibrosis is paramount.

Regulatory mechanisms of OAT1

Hepatocyte nuclear factor family regulation of OAT1 transcription

Research findings highlight that hepatocyte nuclear factor family proteins, specifically Hnf1α, Hnf1β, and Hnf4α, play pivotal roles as upstream regulators in modulating the expression and operational dynamics of OAT1, influencing its role in transporting organic anions. In HNF1α-null mice, the expression of various organic anion transporters (OATs) and organic anion transporting polypeptides (OATPs) in the liver and kidney is significantly reduced, with OAT1 expression in the kidney being markedly lower compared to wild-type mice [81]. The activity of both human and mouse OAT1 promoters is enhanced by Hnf1α alone or combined with Hnf1β, an effect that is not seen with Hnf1β alone. Furthermore, mutations in the Hnf1-motif markedly decreased transactivation [11]. DNA methylation, a key epigenetic modification, adds methyl groups to cytosine bases in DNA, typically leading to transcriptional repression. In the case of OAT1, methylation at the promoter region impedes the binding of essential transcription factors, thereby reducing gene expression and affecting transporter activity. Jin et al. [82] observed that the methylation levels of cytosine-phosphate-guanine dinucleotides around the OAT1/3 transcription start sites are lower in the kidney cortex than in the liver, explaining the tissue-specific expression of OAT1 in the kidney. Moreover, Hnf1 mediates this tissue-specific activation, which is also influenced by gene silencing due to DNA methylation [82, 83].

B-cell lymphoma 6 activates and interacts with the Hnf1α response elements to enhance OAT1 promoter activity and stimulate OAT1 gene transcription indirectly, increasing the cellular expression of OAT1 [84, 85]. A recent study demonstrated that hyperoside, a flavonoid, enhances mRNA levels of OAT1 regulators Hnf1α and pregnane X receptor, potentially protecting against cisplatin-induced AKI. It effectively reduced serum creatinine, BUN, and IS levels while increasing urinary excretion of IS [86]. These findings underscore the crucial role of Hnf1 in regulating OAT1 expression in the kidney, highlighting the need for further studies to discover more factors that interact with Hnf1 to influence this expression.

Hnf4α, a key transcription factor in the Hnf family, plays a crucial role in the basal transcription of OAT1. It co-localizes with genes enriched in the proximal tubule and explicitly governs drug transporters regulation. The simultaneous expression of Hnf4α with OAT1/3 genes supports the development and maturation of renal tubules. Additionally, Hnf4α directly engages with the proximal promoters of OAT1/3, influencing the handling capacity of drugs and toxins in the nascent proximal tubule [12]. Deletion analysis of the OAT1 promoter revealed that the regions spanning −1191 to −700 base pairs and −140 to −79 bp are crucial for Hnf4α-driven transactivation [87]. Nonetheless, Hnf4α's interaction with IR-8, an inverted repeat separated by eight nucleotides, can adversely affect OAT1 promoter activity [87]. Furthermore, GATA binding protein 4 and forkhead box protein A2/3 appear to modify the regulatory effects of Hnf1α/4α, causing cells to adopt more hepatocyte-like features rather than proximal tubule characteristics, though the underlying mechanisms remain to be elucidated [88].

Indeed, Hnf plays a pivotal role in renal tubule development and the basal transcription of OAT1 through

direct activation, tissue-specific adjustments, and interactions with other transcriptional regulators. Hnf6, part of the human hepatic progenitor cells group, is associated with the expression of various genes. Yet, its impact on the expression of renal transport proteins remains unexplored [89].

Post-translational modification of OAT1

The effects of glycosylation on OAT1

Glycosylation alters membrane proteins by appending sugar moieties: N-linked glycosylation attaches to the NH_2 group of asparagine, while O-linked glycosylation connects to the OH group of serine or threonine [90]. OAT1 is a heterogeneous protein requiring extensive N-glycosylation for accurate plasma membrane localization and effective transport functionality [91, 92]. Tanaka et al. [14] identified glycosylation sites on mOAT1 at aspartic acid residues 56, 86, 91, and 107, and hOAT1 at residues 39, 56, 92, and 97. Removing all glycosylation from OAT1 significantly reduced its expression levels. Glycosylation is crucial for adequately situating and stabilizing OAT1, facilitating its standard functionality.

The effects of ubiquitination on OAT1

Ubiquitination of OAT1 involves attaching ubiquitin molecules to the protein, which can impact OAT1's degradation or functionality, often involving processes mediated by PKC and neural precursor cell expressed developmentally down-regulated protein 4 (Nedd4) [13]. PKC, a serine/threonine kinase, reduces OAT1 surface expression by phosphorylating serine/threonine residues and accelerating internalization through PKC-mediated ubiquitination. Specific lysine residues, namely 48, 297, 303, and 315, have been identified as critical for PKC-driven ubiquitin attachment to OAT1 [93, 94]. The research demonstrated that overexpression of neuronal precursor cell expressed developmentally down-regulated protein 4–1(Nedd4-1), an E3 ubiquitin ligase, significantly affects the ubiquitination, surface expression, and transport activity of hOAT1, while the ubiquitin ligase-inactive mutant, Nedd4-1/C867S, exhibited no influence. A reduction in endogenous Nedd4-1 also resulted in decreased ubiquitination of hOAT1. Immunoprecipitation and immunofluorescence experiments established a direct interaction between OAT1 and Nedd4-1. Significantly, mutations in the WW2 and WW3 domains of Nedd4-1 hindered its ability to bind and ubiquitinate hOAT1, consequently diminishing its regulatory impact on the transport functionality of hOAT1 [95]. Similarly, PKC activation phosphorylates Nedd4-2, producing effects on OAT1 comparable to those of Nedd4-1. On the contrary, the quadruple mutant of Nedd4-2 (T197, S221, S354, S420) partially hindered the effects of PKC-induced phosphorylation on OAT1 transport activity [96].

Deubiquitination is a dynamic process where a class of ubiquitin-specific peptidases catalyzes deubiquitination and counteracts protein ubiquitination by detaching ubiquitin molecules from target proteins. Ubiquitin specific peptidase 8 (USP8) is a deubiquitinating enzyme that regulates endocytosis and proteolysis, impacting transporters' surface presentation and activity. Specifically, biotinylation experiments demonstrated that USP8-induced increase in hOAT1 expression and transport activity occurred through decelerating the hOAT1 internalization and degradation rates. Suppressing the natural expression of USP8 using USP8-specific siRNA leads to heightened ubiquitination of OAT1, undoing these improvements [97]. Table 4 summarizes the information regarding the ubiquitination of OAT1.

Recently, a small ubiquitin-like modifier SUMO has been identified as another essential modification that can be covalently conjugated to target proteins and exerts regulatory effects on protein expression and trafficking [98]. The study demonstrated that insulin treatment

Table 4 The impact of ubiquitination and deubiquitination on OAT1

Chemical Modification	Regulatory Site	Effects	Model	References
Ubiquitination	Nedd4-1	↓Cell surface expression ↓Transport function	COS-7/HEK293Tcells	[95]
	Lysine-48/297/303/315	↓Cell surface expression ↓Transport function	COS-7 cells	[93, 94]
	Nedd4-2	↓Cell surface expression ↓Transport function	COS-7 cells	[96]
Deubiquitination	USP8	↑Surface expression ↑Endocytosis rate ↑Degradation and internalization	HeLa cells	[97]

USP8 Ubiquitin-specific peptidase 8, *Nedd4-1* Neuronal precursor cell expressed developmentally down-regulated protein 4–1, *Nedd4-2* Neuronal precursor cell expressed developmentally down-regulated protein 4–2, *PKC* Protein Kinase C, Up arrows mean increase, down arrows mean decrease

significantly increases the maximal transport velocity of OAT1-mediated uptake in cells expressing OAT1 via the PKB signaling pathway, likely due to increased OAT1 expression on the cell surface or faster substrate turnover. The results also showed that insulin significantly enhanced OAT1 SUMOylation by ~ 50% and endogenously expressed OAT1 by ~ 25%, confirming the insulin-modulated increase of OAT1 SUMOylation in rat kidneys [15]. In contrast, deubiquitination stabilizes OAT1 on the plasma membrane, promoting efficient toxin and drug excretion. Disruptions in these processes can impair kidney detoxification, potentially causing toxin buildup and increased nephrotoxicity risk. They may also alter the pharmacokinetics of drugs metabolized by OAT1, affecting their effectiveness and safety. However, further research is needed in this area.

The effects of phosphorylation on OAT1

Phosphorylation involves the enzyme-catalyzed addition of a phosphate group to a protein substrate. Dephosphorylation can reverse this process, thereby allowing dynamic regulation of protein function in response to cellular signals. The study found that okadaic acid reduced PAH transport by enhancing the phosphorylation levels of mOAT, whereas PKC activation decreased the maximum transport velocity of PAH through non-phosphorylation pathways. These findings provide the first demonstration that the regulation of organic anion transport by mOAT is tightly controlled by both direct and indirect phosphorylation and dephosphorylation mechanisms and suggest that other kinases may also be involved in this process, offering new insights into the molecular mechanisms of organic anion transport and potential therapeutic targets for related diseases [16]. However, subsequent studies on the phosphorylation of OAT1 are notably limited.

Limited research has been done on OAT1's post-translational modifications, such as acetylation and palmitoylation. The sparse studies on its phosphorylation and SUMOylation particularly underline a significant knowledge gap in understanding how these modifications affect OAT1's functionality and stability.

Endocrine hormone regulation

Regulation OAT1 by sex hormones

Previous studies have highlighted gender differences in OAT1 expression; however, the regulation by sex hormones offers further insight into these differences. Ljubojevic et al. [19] demonstrated that castration can significantly reduce OAT1 levels in the renal cortex of adult male rats. The levels can be fully restored, further reduced, or partially recovered with the administration of testosterone, estradiol, or progesterone. In adult female rats, ovariectomy slightly increased OAT1 expression, while estradiol administration significantly decreased it [19]. Further studies have indicated that mOAT1 protein is predominantly expressed in males and is regulated by testosterone, especially post-castration [99]. Although androgen receptors may not directly mediate sex differences in OAT1 expression, B-cell lymphoma 6 protein does [84]. Additionally, recent research has demonstrated that the estrogen receptor can regulate OAT1 expression by binding to its promoter region, indirectly influencing OAT1 transcription [100]. These findings suggest that sex hormones play a significant role in OAT1 expression, profoundly affecting drug metabolism across different genders.

Regulation of OAT1 by insulin

Insulin, a hormone the pancreas produces, influences OAT1 function through several signaling pathways. Previous research has revealed that insulin, acting as an upstream activator of PKC zeta, can enhance the function of OAT1/3 [20]. Direct activation of OAT1 by insulin signaling occurs via the PI3 kinase/Akt, MEK/ERK, and p38 MAPK pathways in xenopus oocytes [101]. In type 2 diabetic rats, the function of insulin-stimulated OAT1/3 was reduced, associated with increased PKC zeta and decreased PKCα levels. However, this reduction was reversed with cladophora glomerata extract, suggesting further studies investigating its components and mechanisms, potentially leading to new therapeutic strategies [102]. Insulin-like growth factor-1(IGF-1) through endogenous IGF-1 receptor-stimulated urate transport mediated by OAT1/3 [103]. These findings underscore the importance of insulin's impact on OAT1 in metabolic diseases and highlight the need for more research into its clinical relevance and therapeutic potential.

Regulation of OAT1 by 1a, 25-dihydroxyvitamin D_3

$1,25(OH)_2D_3$, the active form of vitamin D and natural ligand for the vitamin D receptor. The study finds that $1,25(OH)_2D_3$ treatment causes a dose-dependent decrease in OAT1/3 mRNA levels in the kidneys, affecting renal clearance and altering plasma concentrations of various drugs and metabolites [104]. This reduction in OAT1/3 expression impairs renal clearance mechanisms, increasing plasma concentrations of drugs such as cefdinir and cefadroxil, and the compound cyclo-trans-4-L-hydroxyprolyl-L-serine (JBP485) [35, 105]. Consequently, these alterations can potentially influence the efficacy and toxicity of these drugs. However, the specific molecular mechanisms driving this regulatory effect remain unclear. Interestingly, while $1,25(OH)_2D_3$ decreases OAT1/3 expression, it also offers protective benefits. For instance, in a conditionally immortalized proximal tubule

Table 5 Impact of $1,25(OH)_2D_3$ on OAT1

Regulatory Molecule	Effects	Associated Outcomes	Model	References
$1,25(OH)_2D_3$	↓OAT1 expression	↑AUC of cefdinir/cefadroxil	Rat kidney	[38]
	↓OAT1 expression	↑AUC of JBP485	Rat kidney	[105]
	↓OAT1expression	↑Blood pressure	Rat kidney	[106]
		Renal vascular calcification		
		Changes in kidney tissue structure		
	Beneficial to ciPTEC-0AT1 cells	Maintain the renal epithelial barrier	CiPTEC-OAT1 cells	[18]

$1,25(OH)_2D_3$ 1alpha, 25-dihydroxyvitamin D_3, *AUC* Area Under the Curve, *JBP485* cyclo-trans-4-L-hydroxyprolyl-L-serine, *CiPTEC-OAT1* Conditionally Immortalized Proximal Tubule Epithelial Cells—Organic Anion Transporter 1, Up arrows mean increase, down arrows mean decrease

epithelial cells line overexpressing OAT1, $1,25(OH)_2D_3$ improved cell vitality and epithelial barrier function through reduced increase in IL-6 levels and ROS production even in the presence of UTs [18]. These findings indicate that while $1,25(OH)_2D_3$ may reduce OAT1 expression and metabolite clearance, it also enhances cellular resilience and barrier integrity, demonstrating its dual role in managing renal diseases. In rats, Vitamin D_3-induced renal vascular calcification decreases OAT1 protein expression, leading to elevated blood pressure and kidney structural changes such as tubular alterations and smaller glomeruli. Clinically, this indicates that patients with vascular calcium overload, common in aging, smoking, or diabetes, might see reduced efficacy of drugs that are transported by OAT1. Thus, dosage adjustments may be required to sustain therapeutic drug levels and improve treatment effectiveness in these individuals [106]. Future research should further investigate $1,25(OH)_2D_3$'s effects on OAT1, uncover the molecular mechanisms involved in its pathophysiological processes, and assess its therapeutic potential for renal disease management. The impacts of $1,25(OH)_2D_3$ on OAT1 are detailed in Table 5.

Conclusion

In conclusion, OAT1 plays a crucial role in the excretion of UTs related to CKD and emerges as a vital target for drug development. Over the last two decades, extensive research has highlighted the significant function of OAT1 in the renal elimination of UTs and drugs, along with various regulatory mechanisms. However, most of these studies have primarily used animal models and in vitro methods, which may only partially replicate human conditions. Potential differences in transporter expression and activity between species might affect the translatability of the findings to humans, thereby limiting their clinical relevance. Research on OAT1 often focuses narrowly on individual factors, overlooking the network's broader interplay. To deepen our understanding of OAT1's function, adopting an integrated approach that encompasses genetic, environmental, and metabolic influences is essential. Few studies have investigated the single nucleotide polymorphisms of OAT1 in patients with CKD [107]. Thus, clinical research on OAT1 polymorphism is urgently required. Additionally, while 4-pyridoxic acid (PDA) has been identified as a sensitive plasma biomarker for OAT1 activity and could be critical for drug adjustments in kidney dysfunction, the clinical application of PDA as a biomarker is yet to be evaluated [108]. All of these need to be addressed in future studies.

Abbreviations

CKD	Chronic Kidney Disease
UTs	Uremic Toxins
OAT1	Organic Anion Transporter 1
IS	Indoxyl Sulfate
AKI	Acute Kidney Injury
PCS	P-Cresyl Sulfate
IRI	Ischemia-Reperfusion Injury
Hnf	Hepatocyte Nuclear Factor
$1,25(OH)_2D_3$	1-25-Dihydroxy Vitamin D3
TMDs	Transmembrane Domains
α-KG	Alpha-Ketoglutarate
NaDC3	Sodium Dicarboxylate Cotransporter 3
AhR	Aryl Hydrocarbon Receptor
EGFR	Epidermal Growth Factor Receptor
EMT	Epithelial-Mesenchymal Transition
PKC	Protein Kinase C
Akt	Protein Kinase B
ATP	Adenosine Triphosphate
ROS	Reactive Oxygen Species
MRP	Multidrug Resistance-associated Protein
USP8	Ubiquitin Specific Peptidase 8
PAH	Para-Aminohippurate.
CiPTEC	Conditionally Immortalized Proximal Tubule Epithelial Cells
AUC	Area Under the Curve

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Declarations

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