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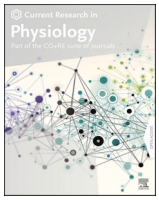

Urotensin II system in chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) is a progressive and long-term condition marked by a gradual decline in kidney function. CKD is prevalent among those with conditions such as diabetes mellitus, hypertension, and glomerulonephritis. Affecting over 10% of the global population, CKD stands as a significant cause of morbidity and mortality. Despite substantial advances in understanding CKD pathophysiology and management, there is still a need to explore novel mechanisms and potential therapeutic targets. Urotensin II (UII), a potent vasoactive peptide, has garnered attention for its possible role in the development and progression of CKD. The UII system consists of endogenous ligands UII and UII-related peptide (URP) and their receptor, UT. URP pathophysiology is understudied, but alterations in tissue expression levels of UII and UT and blood or urinary UII concentrations have been linked to cardiovascular and kidney dysfunctions, including systemic hypertension, chronic heart failure, glomerulonephritis, and diabetes. UII gene polymorphisms are associated with increased risk of diabetes. Pharmacological inhibition or genetic ablation of UT mitigated kidney and cardiovascular disease in rodents, making the UII system a potential target for slowing CKD progression. However, a deeper understanding of the UII system's cellular mechanisms in renal and extrarenal organs is essential for comprehending its role in CKD pathophysiology. This review explores the evolving connections between the UII system and CKD, addressing potential mechanisms, therapeutic implications, controversies, and unexplored concepts.

1. Introduction

The urotensin II (UII) system consists of two peptide ligands, UII and its paralog UII-related peptide (URP), and their receptor, UT (Vaudry et al., 2015). UII, a peptide initially isolated from teleost fish urophysis in the 1960s, has been found in mice, rats, sheep, pigs, monkeys, and humans (Bern and Lederis, 1969; Charles et al., 2005; Douglas et al., 2004; Itoh et al., 1987; Pearson et al., 1980; Vaudry et al., 2015). While the N-terminus of UII exhibits structural variability, its C-terminus remains highly conserved across different mammalian species and orchestrates its bioactive functions (Conlon et al., 1990; Coulouarn et al., 1998; Douglas et al., 2004; Itoh et al., 1987; Ross et al., 2010). Whereas UII is found in most peripheral tissues, the kidney has been proposed to be a major source of UII in mammals (Charles et al., 2005; Elshourbagy et al., 2002; Matsushita et al., 2001; Nothacker et al., 1999; Song et al., 2006). URP, on the other hand, was discovered in rat brains in 2003 (Sugo et al., 2003). Subsequent work demonstrated URP expression in different tissues, including the heart, colon, kidneys, livers, placenta, ovary, and testes (Vaudry et al., 2015). URP is conserved across all vertebrates and shares the same cyclic hexapeptide core sequence (CFWKYC) with UII (Sugo et al., 2003; Vaudry et al., 2015). However, UII and URP exhibit different N-terminal amino acid sequences (Vaudry et al., 2015). UII and URP activate the near-ubiquitously expressed orphan receptor GPR14, now renamed UT (Douglas et al., 2004; Vaudry et al., 2015).

Renal expression of UII includes tubules and glomeruli (Ashton, 2006; Balat and Büyükçelik, 2012). UT in the kidneys is localized to the renal medulla and cortex, with the renal medulla having a considerable

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abundance (Abdel-Razik et al., 2008; Song et al., 2006). Also, the kidney expresses UT in the tubular epithelium, mesangial cells, and blood vessels (Adebiyi, 2014; Ashton, 2006; Balat and Büyükçelik, 2012). UII and URP are potent vasoconstrictors but also exhibit vasodilatory effects, depending on vascular beds and species (Forty and Ashton, 2012; Itoh et al., 1987; Itoh et al., 1988; Prosser et al., 2006; Stirrat et al., 2001; Vaudry et al., 2015). Circulating or urine UII and URP concentrations, as well as tissue UII, URP, and UT, are associated with several cardiovascular and kidney dysfunctions, making the UII system a potential therapeutic target for cardiovascular and kidney disease (Vaudry et al., 2015).

Despite the similarity in UII and URP C-terminus, the peptides show differential expressions and pathophysiology in several tissues. For example, unlike UII, URP mRNA is highly expressed in the abducens nucleus, the dorsal motor nucleus of the vagus, and the gigantocellular nucleus of the mouse brainstem (Dubessy et al., 2008). The mouse medial vestibular nucleus expresses only UII (Dubessy et al., 2008). Whereas URP is predominantly expressed in mouse seminal vesicles, hearts, thymus, and colon, UII expression levels are higher in the vagina, uterus, and testis (Dubessy et al., 2008). Rat UII caused larger vasodilation in rat coronary arteries than rat URP (Prosser et al., 2006). Unlike UII, URP did not stimulate astrocyte proliferation (Jarry et al., 2010). Plasma levels of UII and URP are increased in patients with acute heart failure, but the change in URP levels was higher than that of UII (Jani et al., 2013). Unlike UII, URP mRNA expression levels are higher in the kidneys of 5- and 11–12-week-old spontaneously hypertensive rats (SHR) compared with age-matched Wistar Kyoto (WKY) rats (Hirose et al., 2009). However, URP is the least studied among the UII components, and its involvement in chronic kidney disease (CKD) is poorly understood.

CKD is a progressive disease marked by a deterioration of kidney function, culminating in end-stage kidney disease (ESKD) and the need for renal replacement therapy (dialysis or transplantation) (Romagnani et al., 2017). CKD is characterized by structural and functional abnormalities of the kidneys, including a decline in glomerular filtration rate (GFR), nephron loss, and the glomerular filtration barrier breakdown (Romagnani et al., 2017). Over 10% of the global population is affected by CKD, causing over 1.2 million deaths worldwide in 2017 ("Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017," 2020). In 2020, the World Health Organization categorized CKD as the 10th primary cause of mortality, and it is projected to become the 5th foremost cause of death by 2040 (Foreman et al., 2018). The global impact of CKD on mortality and morbidity is enormous due to its involvement in elevating the risk associated with cardiovascular diseases (Foley et al., 1998; Romagnani et al., 2017). The most common causes of CKD are diabetes mellitus and hypertension ("Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study, 2015," 2016; Webster et al., 2017). Other causes of CKD include glomerulonephritis, obesity, aging, genetic abnormalities, and environmental nephrotoxins (Romagnani et al., 2017).

Vasoactive peptides, including angiotensin II (Ang II), prostaglandins, and endothelin, have been implicated in CKD progression (Klahr, 1999; Klahr and Morrissey, 1998; Kohan and Barton, 2014; Nasrallah et al., 2014). Hence, pharmacological modulators of these peptide systems offer therapeutic benefits in CKD. Several publications have provided excellent reviews on the function and regulation of UII in the kidney (Ashton, 2006; Balat and Büyükçelik, 2012; Douglas et al., 2004; Gilbert et al., 2004; Langham and Kelly, 2013; Takahashi et al., 2009; Tölle and van der Giet, 2008; Zhu et al., 2006; Zoccali and Mallamaci, 2008). Understanding of the involvement of the UII system in CKD is steadily emerging. Here, we discuss the UII system in CKD, shedding light on potential mechanisms, therapeutic implications, controversies, and unexplored concepts in its pathophysiology.

2. Urotensin II system in diabetic kidney disease

Kidney disease is a major complication of diabetes with severe implications of progressing to ESKD. Therapeutic or effective pharmacological strategies are urgently needed to reverse or slow the advancement toward ESKD in patients with established diabetic kidney disease (DKD) (Caramori and Mauer, 2003; Fioretto et al., 2008; Giunti et al., 2006). Increased kidney tissue expression levels of UII and UT in humans and rodents have been linked to DKD, diabetic retinopathy, and carotid atherosclerosis (Langham et al., 2004; Suguro et al., 2008; Tian et al., 2008b). In patients with diabetic nephropathy, kidney biopsies showed up to 45-fold upregulation of UII mRNA and a 2000-fold increase in UT mRNA expression (Langham et al., 2004). Circulating and urinary concentrations of UII are elevated in patients with diabetes and metabolic syndrome and are associated with retinopathy, atherosclerosis, and nephropathy (Gruson et al., 2010; Suguro et al., 2008; Totsune et al., 2003, 2004). The serum levels of UII were increased in obese children and adolescents with metabolic syndrome and hypertension (Simunovic et al., 2022). Tian and colleagues showed that UII mRNA and protein expression were upregulated in the glomeruli and distal and collecting tubes epithelial cells of diabetic rats (Tian et al., 2008b). Furthermore, the authors reported that kidney dysfunction and fibrosis characterized by increased renal extracellular matrix (fibronectin and collagen IV) accumulation were associated with increased UII and UT mRNA and protein expression levels in diabetic rats (Tian et al., 2008b).

The pathological hallmarks of diabetic nephropathy include glomerular changes, such as increased mesangial cell proliferation and extracellular matrix (ECM) expansion that results in obstruction of the glomerular capillaries and progressive impairment of ultrafiltration (Mason and Wahab, 2003; Steffes et al., 1989). We have reported functional expression of UT in cultured glomerular mesangial cells (GMCs) (Adebiyi, 2014). We have also demonstrated that UII-induced calcium signaling via transient receptor potential cation channel, subfamily C, member 4 stimulates CaMKII/CREB-dependent GMC proliferation and ECM protein production (Soni and Adebiyi, 2017). Under a high glucose milieu, GMCs synthesized UII, which contributes to proliferation and ECM accumulation, suggesting that increased UII production in GMCs and UII-induced Ca^{2+}-dependent proliferation and ECM accumulation are involved in the pathophysiological mechanisms of mesangial dysregulation in DKD (Soni and Adebiyi, 2017). Recent publications supported the findings in cultured GMCs. UT knockout in mice attenuated streptozotocin-induced kidney endoplasmic reticulum stress, epithelial-mesenchymal transition (EMT), fibrosis, extracellular matrix production, glomerular lesion, and mesangial expansion (Pang et al., 2016; Peixoto-Neves et al., 2022). Findings from Clozel and colleagues indicated UT inhibition increased kidney perfusion and ameliorated proteinuria and kidney damage in diabetic rats (Clozel et al., 2006). UII has also been documented to dose-dependently stimulate peripheral vasoconstriction in diabetic patients, suggesting that increased UII levels may promote diabetic vascular complications (Zomer et al., 2008).

Although alterations in UII and UT are well established, it is unclear whether renal URP levels are altered in a hyperglycemic milieu or associated with DKD. Here, we present our unpublished data demonstrating that changes in the UII system in DKD are not limited to UII and UT but include the less-studied URP. All experimental animal protocols were reviewed and approved by the Animal Care and Use Committee of the University of Tennessee Health Science Center. Mice were injected intraperitoneally with 35 mg/kg STZ dissolved in sodium citrate buffer (0.01 M; pH 4.5) for 5 consecutive days to induce diabetes. The following week, blood glucose was determined by test strip methods (Bayer Contour test strips, Bayer HealthCare LLC, Pittsburgh, PA, USA) from tail-tip whole blood. Animals with blood glucose >250 mg/dL were considered diabetic and used 4 weeks following STZ injection. The results show that exposure of mice to STZ caused a 3-fold increase in blood glucose concentration compared to their age-matched littermate

controls (Fig. 1A). STZ treatment also resulted in a 3-fold increase in the urine albumin-creatinine (ACR) ratio (Fig. 1B). STZ treatment upregulated UII and URP mRNA expression levels in the kidneys of the mice (Fig. 1C and D). Immunostaining indicated that UII and URP are mostly expressed in renal tubules (Fig. 2B and D). Moreover, a marked increase in renal UII and URP immunostaining was observed in STZ-treated mice (Fig. 2B–E). Plasma UII and URP concentrations in control mice were ~2 ng/mL and 36 ng/L, respectively. By contrast, the levels of UII and URP in the plasma of STZ-treated mice were 5 ng/mL and 43 ng/L, respectively, indicating that STZ treatment increased mouse plasma UII and URP levels by ~60 and 16 %, respectively (Fig. 3A and C). Similarly, urinary UII and URP in STZ-treated mice increased by ~77% and 54 %, respectively, compared with the control (Fig. 3B and D).

Real-time imaging of cell growth kinetics over 96 h showed that UII and URP time-dependently increased GMC growth (Fig. 4A and B). Increases in proliferation stimulated by UII and URP started ~18 h post-treatment (Fig. 4A). However, UII caused more significant GMC proliferation from 30 to 96 h (Fig. 4B). UT antagonist urantide reversed both UII- and URP-induced GMC proliferation (Fig. 4A and B). Type IV collagen production was increased in GMCs treated with UII and URP, respectively. However, UII evoked a more significant type IV collagen increase compared with URP (Fig. 4C). UII- and URP-induced rise in type IV collagen levels was inhibited by urantide (Fig. 4C), suggesting that, like UII, URP-induced UT activation promotes ECM protein synthesis by GMCs.

The high structural homology suggests potential cross-reactivity between UII and URP antibodies (Forty and Ashton, 2013). Hence, the immunological assays may indicate the contribution of both peptides (Forty and Ashton, 2013). However, the manufacturers of the UII and URP antibodies and ELISA kits (supplemental file) used in this study indicated the absence of cross-reactivity between the respective antibodies. Also, the increase in plasma and urinary concentrations of UII in the diabetic mice were higher than those of URP. The respective UII and URP primers (supplemental file) used for the qPCR are unique to their intended target and, hence, differentiate the mRNA expression levels of the peptides. The results from qPCR indicated increases in both peptides in the diabetic mice.

Both UII and URP promote GMC proliferation and ECM protein production. However, at the same concentration, UII is more potent than URP in inducing GMC growth and ECM accumulation. Activation of UT receptors by both UII and URP may contribute to DKD.

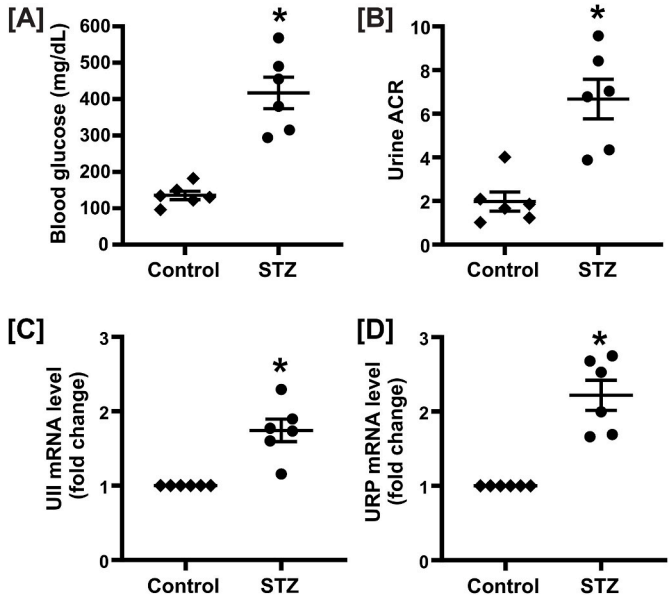

Fig. 1. A and B: Blood glucose levels and urine albumin/creatinine ratio (ACR) in control and STZ-treated mice. **C and D:** mRNA expression levels of UII and URP in control and STZ-treated mice. *P < 0.05 vs. control. Urine ACR was calculated by dividing albumin concentration (in μg/mL) by creatinine concentration (in mg/dL).

UII and URP directly activated somatostatin receptor subtypes sst2 and sst5, which triggered intracellular Ca^{2+} elevation and proliferation in CHO–K1 cells stably expressing sst2 and sst5 (Malagon et al., 2008). Whether UII and URP activate somatostatin receptors in native kidney cells of normal or diabetic animals is unclear but requires further investigation.

Palosuran, an orally active UT antagonist, improved kidney function in diabetic rats (Clozel et al., 2006), but results from human studies on the potential use of palosuran for kidney protection in diabetes were inconclusive (Sidharta et al., 2009; Sidharta et al., 2006; Vogt et al., 2010).

3. Urotensin II system gene polymorphism and the risk of diabetes in humans

Although findings vary, UII gene polymorphism has been reported to be associated with the risk of diabetes in humans. UII gene rs228648 polymorphisms in Han Chinese with type 2 diabetes have been reported (Sun et al., 2002; Zhu et al., 2002). UII and/or UT gene polymorphisms have also been associated with genetic susceptibility to gestational diabetes, essential hypertension, and insulin resistance in the Chinese population (Ong et al., 2006; Tan et al., 2006; Wu et al., 2007; Yi et al., 2006). However, a subgroup analysis reported by Zhao and colleagues suggested a significant association of rs228648 polymorphism with a decreased risk of diabetes in the Chinese but an increased risk in the European population (Zhao et al., 2018). Wenyi and colleagues showed that, unlike the T21M, S89N polymorphism in the UII gene is associated with developing type 2 diabetes and insulin sensitivity in adult Japanese patients surveyed (Wenyi et al., 2003). Studies by Suzuki and colleagues supported the findings that the allele frequency of 89 N is higher in Japanese type 2 diabetic patients (Suzuki et al., 2004). However, two polymorphisms in the non-coding region of the UT gene were unchanged in diabetic Japanese patients compared with the control non-diabetic Japanese (Suzuki et al., 2004). Other populations with reported associations between UII gene polymorphisms and diabetes include India, Spain, and Turkey (Kumar et al., 2020; Okumus et al., 2012; Sáez et al., 2011). The relationship between polymorphism in the URP gene and diabetes remains unclear. Whether specific ethnicity is a factor in single nucleotide polymorphism in UII gene in diabetes requires further investigation. Genetic variations in these genes and their association with increased susceptibility to different causes of CKD need additional delineation.

4. Urotensin II system in hypertensive nephropathy

The kidney plays a central role in long-term blood pressure control by regulating extracellular fluid volume and renal perfusion pressure (Guyton, 1961; Guyton et al., 1972). Hence, kidney dysfunction can result in heightened sympathetic nervous system activity, increased renin-angiotensin-aldosterone system, and volume expansion (Martínez-Maldonado, 1998; Wadei and Textor, 2012). Changes in the production of vasoactive mediators in the kidneys can contribute to the orchestration of events that increase peripheral resistance and, hence, high blood pressure (Martínez-Maldonado, 1998; Wadei and Textor, 2012). By altering vascular resistance, changes in vascular smooth muscle, endothelial, and perivascular neuron signaling contribute to the pathophysiological mechanisms of hypertension (Touyz et al., 2018). Uncontrolled blood pressure can dysregulate preglomerular microvessels, alter intrinsic renal autoregulation, and promote glomerular capillary barotrauma, leading to progressive nephrosclerosis and CKD (Bidani et al., 2009; Freedman et al., 1995).

Hypertension is a major risk factor for CKD (Garofalo et al., 2016; Lee et al., 2022). Hypertensive nephropathy ranks as the second most

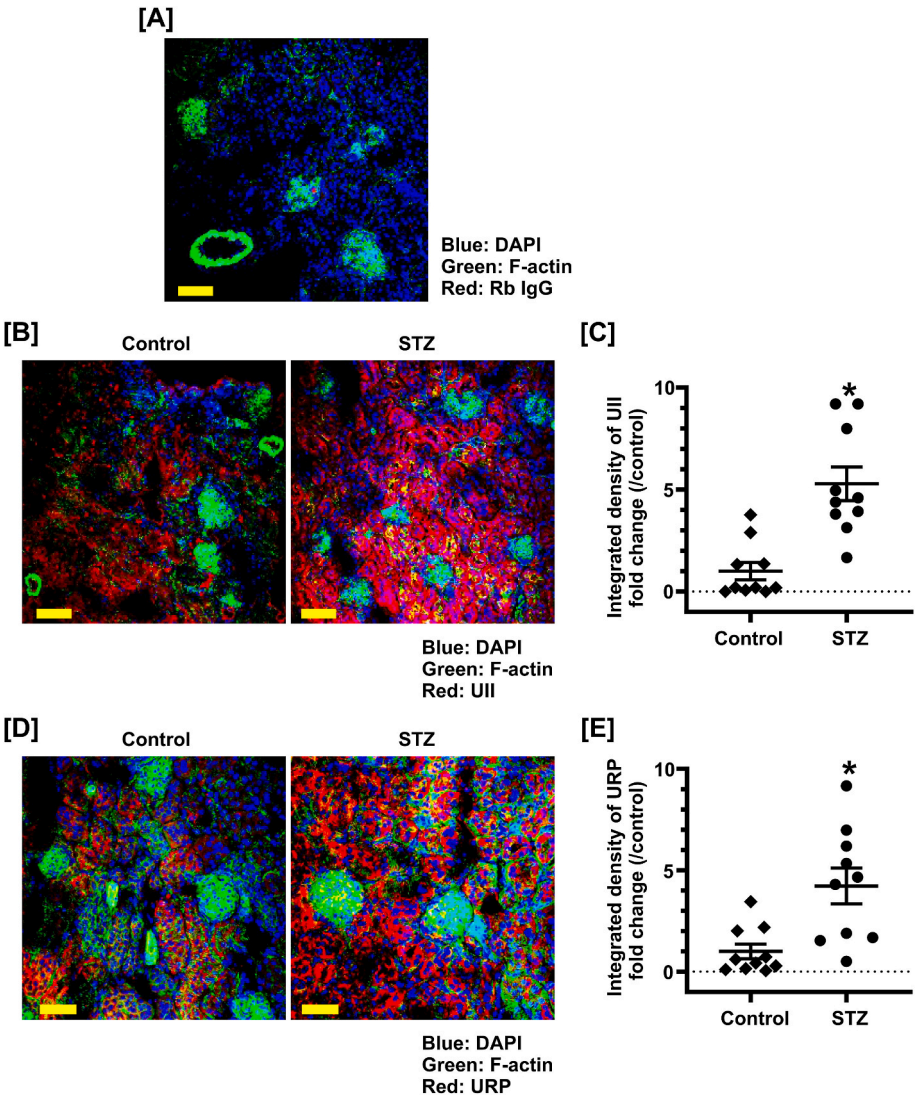

Fig. 2. Confocal microscopy images of mouse kidney slices immunostained with **A:** normal rabbit (Rb) IgG (negative control), UII (**B**), and URP (**D**). **C and E:** plots of mean fluorescence intensity in control and STZ-treated mouse kidney sections immunostained for UII and URP. Sections were counterstained with ActinGreen 488 (F-actin) reagent and mounted with a medium containing DAPI nuclear stain. *P < 0.05 vs. control (n = 10 imaging fields from 5 mice, each). Scale bar = 50 μm.

prevalent cause of progressive CKD, trailing only behind diabetes (Griffin, 2017). One in four people with hypertension develop kidney failure, and importantly, hypertension is both a cause as well as a consequence of CKD (Garofalo et al., 2016; Reynolds et al., 2007). Hypertension and type 2 diabetes frequently coexist. Individuals with prediabetes and prehypertension often demonstrate insulin resistance and face a higher likelihood of developing diabetes (Tsimihodimos et al., 2018). Furthermore, hypertension is prevalent among individuals with diabetes compared to those without the condition (Tsimihodimos et al., 2018).

The contribution of the UII system to hypertension is highlighted in studies showing increased expression of UII, URP, and UT in hypertensive SHR. UII, UT, and/or URP mRNA expression levels were upregulated in the kidneys of hypertensive SHR compared with normotensive WKY rats (Abdel-Razik et al., 2008; Mori et al., 2009; Shi et al., 2008; Song et al., 2006). UII and UT mRNA expression levels were upregulated in the heart of SHR compared with age-matched WKY rats (Hirose et al., 2009). URP and UT expression levels were also found to be increased in the aorta of the SHR (Hirose et al., 2009). The expression levels of URP and UT were increased in the remnant kidney of rats subjected to 5/6 nephrectomy compared with sham-operated controls (Mori et al., 2009). Progressive CKD induced by a 5/6 subtotal nephrectomy also increased immunoreactive UII and UT staining in the kidneys of male Spraque-Dawley rats (Eyre et al., 2019). UT antagonists, SB611812, delayed the increase in systolic blood pressure and kidney injury in the rats (Eyre et al., 2019). However, the circulating and urinary levels and vascular effects of UII and URP in hypertension are complicated, with several studies reporting contrasting findings.

Urinary UII concentration was significantly higher in hypertensive patients with kidney disease than in normotensive patients with kidney disease (Matsushita et al., 2001). Patients with elevated urinary β2-microglobulin, signifying renal tubular disorders and membranous nephropathy (Jotwani et al., 2020; Reichert et al., 1995), exhibited higher urinary UII than healthy and hypertensive individuals (Matsushita et al., 2001). In a cross-sectional case-control study, the plasma concentration of UII was higher in hypertensive outpatient individuals than in normotensive controls (Cheung et al., 2004). However, the data did not correlate with kidney function or diabetes (Cheung et al., 2004). Peng and colleagues also reported higher plasma UII levels in newly diagnosed hypertensive patients than in normotensive controls, an association independent of nitric oxide metabolites (Peng et al., 2013). Serum UII levels are higher in patients with non-dipper than in those with dipper hypertension (Erbay et al., 2013). Plasma UII is also higher in patients with preeclampsia-eclampsia (Balat et al., 2005). However,

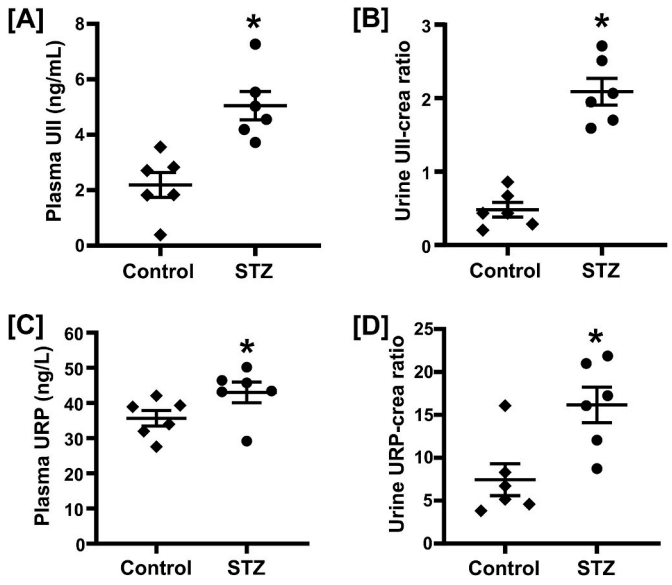

Fig. 3. A-D: Plasma and urine concentrations of UII and URP in control and STZ-treated mice. *P < 0.05 vs. control. The urine UII- and URP- creatinine (crea) ratio was determined by dividing UII and URP concentrations by respective creatinine concentrations.

Debiec and colleagues did not find an association between genetic variation in the UII system and blood pressure or estimated GFR in Caucasians (Debiec et al., 2013). The authors also demonstrated in a gene expression analysis of approximately 100 human kidneys that UII, URP, and UT gene expression levels were not upregulated in hypertensive compared with normotensive patients, suggesting that kidney UII system may not be involved in the control of human blood pressure or kidney function (Debiec et al., 2013). However, the levels of UII or URP in the blood or urine of the patients were not quantified. It is also unclear if the patients in this study had CKD of any stage. More studies are needed to make convincing conclusions on the contribution of the UII system to hypertensive nephropathy in humans.

UII can act on the central nervous system to regulate blood pressure. Whereas microinjection of UII into the A1 area of the brainstem decreased blood pressure and heart rate, its injection into the paraventricular or arcuate nucleus of the hypothalamus raised blood pressure and heart rate (Lu et al., 2002). Lin and colleagues reported that in contrast to intravenous injection, which causes a depressor effect, intracerebroventricular (ICV) injection of UII in rats increased the arterial pressure and heart rate via sympathetic activation (Lin et al., 2003). ICV administration of UII has also been shown to cause a more pronounced pressor reaction in SHR when contrasted with that observed in WKY rats (Lin et al., 2003). UII injection into the rostral ventrolateral medulla significantly elevated blood pressure, heart rate, and renal sympathetic nerve activity (Cao et al., 2020). Central injection of eel URP and UII increased blood pressure in Japanese eels (Nobata et al., 2011). Additional studies have also shown that central administration of UII to rats increased brown adipose tissue and adrenal sympathetic nerve activity (Watson et al. 2008; Yasuda et al., 2012). In summary, these findings suggest that central actions of UII exert distinct cardiovascular effects, depending on the brain region, with sympathoexcitation being important in mediating UII-induced increase in blood pressure and heart rate.

Bolus injections of dogfish UII, but not goby UII into the celiac artery of dogfish, increased arterial pressure via the sympathetic system (Hazon et al., 1993; Platzack et al., 1998). Intra-arterial injection of trout UII in rainbow trout produced a dose-dependent increase in arterial blood pressure (Le Mevel et al., 1996). Aortic injection of eel URP and UII increased blood pressure in Japanese eels (Nobata et al., 2011). However, bolus injections of frog urotensin II (100 nmol/kg) into the left systemic arch of bullfrogs did not alter arterial blood pressure (Yano et al., 1995). Human UII also increased arterial pressure elevation in mice (Nishi et al., 2019; Tandon et al., 2020). However, Gardiner and colleagues reported a biphasic response of mean arterial pressure (MAP) to a bolus intravenous injection of human UII in conscious SHR and Sprague-Dawley rats, an initial decrease followed by a modest increase (Gardiner et al., 2004). Human UII infusion increased MAP in conscious, chronically instrumented rats (Gardiner et al., 2006). In anesthetized SHR and WKY rats, intravenous injection of human UII decreased MAP (Gendron et al., 2005). Several other studies have also supported the depressor effect of acute UII or URP administration in rats (Hassan et al., 2003; Ovcharenko et al., 2006; Song et al., 2006; Sugo et al., 2003; Trebicka et al., 2008). Bolus intravenous injection of human UII to anesthetized cats markedly increased the MAP and systemic vascular resistance without altering heart rate or stroke volume (Behm et al., 2004). We have reported that bolus injection of human UII via intrarenal artery dose-dependently increased MAP in anesthetized and mechanically ventilated neonatal pigs, an effect attenuated by pharmacological inhibition of UT, phospholipase C, and inositol 1,4,5 trisphosphate receptors(Soni and Adebiyi, 2013). Our findings suggested the involvement of renal vascular smooth muscle cell UT (Soni and Adebiyi, 2013). The pressor effect of UII in the piglets may also be mediated by peripheral sympathoexcitation, as our unpublished data indicate that UT is expressed in the perivascular renal sympathetic nerve and that infusion of human UII stimulates norepinephrine production in the pigs (Figs. 5 and 6). In anesthetized non-human primates, human UII caused a modest reduction in blood pressure, increased total peripheral resistance, and significantly decreased cardiac output (Ames et al., 1999). Zhu and colleagues reported that intravenous bolus injection of human UII decreased MAP and total peripheral resistance and caused circulatory collapse in cynomolgus monkeys (Zhu et al., 2004). A pilot study showed that infusion of human UII via the brachial artery into healthy male volunteers did not alter arterial pressure (Wilkinson et al., 2002). In another human study, a dose-ramped brachial artery infusion of UII and urantide (UT antagonist) to healthy volunteers and patients with a history of cardiovascular disease (angina, myocardial infarction, stroke, transient ischemic attack, or peripheral vascular disease) significantly increased systolic and mean arterial blood pressure (Cheriyan et al., 2009). The authors concluded that these changes are unlikely caused by UII action on UT, but rather due to infusion time (Cheriyan et al., 2009). These studies suggest that species, pathological conditions, and route of administration influence UII system expression and function in relation to blood pressure. Further investigations into the role of the UII system in hypertension in the setting of various CKD stages are needed to provide more insights into the activities of the urotensin II system in hypertensive nephropathy.

5. Urotensin II system in glomerulonephritis

Glomerulonephritis (GN) comprises several derangements that promote inflammation and injury of the kidney glomeruli. GN can occur suddenly and is often associated with infections, such as streptococcal glomerulonephritis (Kanjanabuch et al., 2009; Mohammad and Baracco, 2020). Chronic GN develops slowly over time and can result from various underlying conditions, including autoimmune diseases, diabetes, or recurrent episodes of acute GN (Hricik et al., 1998). Standardized classification of GN based on causal immune processes is divided into five groups (Sethi and Fervenza, 2019): 1) immune complex-mediated (e.g., IgA nephropathy and lupus nephritis), 2) antineutrophil cytoplasmic antibody-associated (e.g., pauci-immune necrotizing crescentic GN), 3) anti-glomerular basement membrane (Goodpasture disease), 4) monoclonal immunoglobulin-mediated (proliferative GN with monoclonal immunoglobulin deposits), and 5) C3 glomerulopathy (electron-dense intramembranous deposits within the glomerular basement membrane, mesangium, and subendothelial

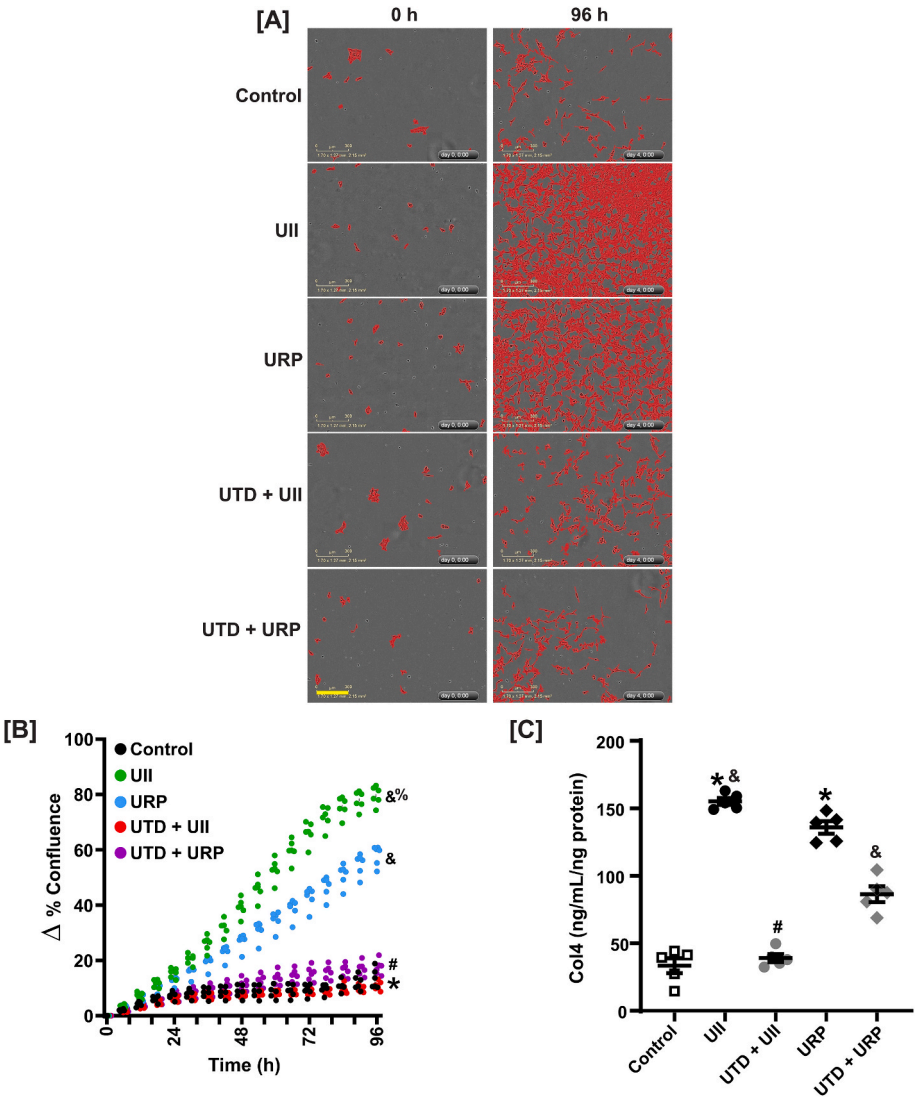

Fig. 4. **A:** Phase contrast images demonstrating cell density in control, UII (10 nM)-, URP (10 nM)-, urantide (UTD; 10 nM) + UII-, and UTD + URP-treated mouse GMCs. Scale bar = 300 μm. **B:** Cell growth curves summarizing the time-dependent proliferative effect of UII and URP and reversal by UTD in mouse GMCs (n = 6 each): $^{\&}P < 0.05$ vs. control (18–96 h); $^{\%}P < 0.05$ vs. URP (30–96 h); $^{\#}P < 0.05$ vs. URP (18–96 h); $^{*}P < 0.05$ vs. UII (18–96 h). **C:** Type IV collagen (Col 4) levels (normalized to protein concentrations) in mouse GMCs that were treated with UII (10 nM), URP (10 nM), urantide (UTD; 10 nM) + UII, and UTD + URP: $^{*}P < 0.05$ vs. control; $^{\#}P < 0.05$ vs. UII; $^{\&}P < 0.05$ vs. URP.

region).

Individuals with GN exhibit varying proteinuria, hematuria, edema, hypertension, mesangial proliferation, glomerular scarring, and interstitial fibrosis (Mookerje et al., 2001). GN is a common cause of CKD in adults and children and often results in kidney replacement therapy (Harambat et al., 2012; Hricik et al., 1998; Wetmore et al., 2016). Evidence suggests that UII and UT are found in the glomerulus (Adebiyi, 2014; Balat et al., 2007; Shenouda et al., 2002; Soni and Adebiyi, 2017). Studies on the association between the UII system and glomerular diseases are sparse. However, findings by Dr. Balat and colleagues have reported the presence of UII in the plasma and urine of children with minimal change nephrotic syndrome (Balat et al., 2005). Although the urinary concentration of UII was significantly higher in relapse than in remission, the UII level in the plasma was decreased during relapse than in remission (Balat et al., 2005). These changes were not associated with other kidney-related clinical findings, including blood pressure, number of relapses, serum creatinine and hematological parameters, proteinuria, and GFR (Balat et al., 2005). Hence, the authors concluded that UII changes in the plasma and urine may not have any significant implications in pediatric minimal change nephrotic syndrome (Balat et al., 2005).

Dr. Balat's group has also reported increased immunostaining of UII in the glomerular basement membrane, mesangium, Bowman capsule, and tubules of kidney biopsy sections from children with glomerular diseases, including membranoproliferative glomerulonephritis, membranous nephropathy, IgA nephropathy, and focal segmental glomerulosclerosis (Balat, 2010; Balat and Büyükçelik, 2012; Balat et al., 2007). The systolic and diastolic blood pressure in patients with membranoproliferative glomerulonephritis correlated with mesangial and endothelial UII immunostaining (Balat et al., 2007). A gene expression study by Woo and colleagues demonstrated that UII was upregulated ~ 3-fold in adult patients with IgA nephropathy (Woo et al., 2010). Associations between Thr21Met, but not Ser89Asn polymorphism of the UII gene and the risk factor for the development of systemic sclerosis (autoimmune chronic fibrotic disorder) and Behcet's disease (a vasculitis or chronic inflammation disorder) have been described (Kamal et al., 2022; Oztuzcu et al., 2013; Pehlivan et al., 2012). As indicated above, individuals with systemic lupus erythematosus disease (SLE) are at a higher risk of glomerulonephritis and CKD. A 2011 report demonstrated elevated circulating UII levels in adult patients with SLE

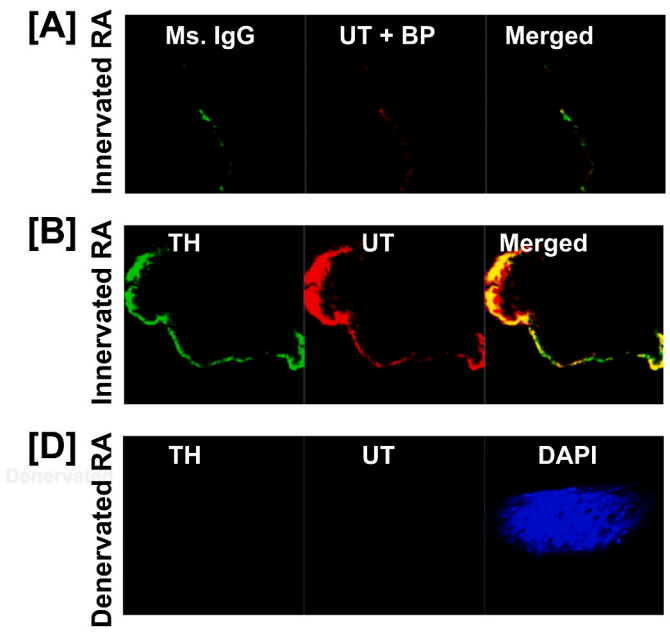

Fig. 5. Immunostaining of neonatal renal perivascular nerves indicating: **A:** negative staining for mouse (Ms.) IgG, and UT + UT blocking peptide (BP; negative controls). **B:** UT colocalizes with tyrosine hydroxylase (TH, a sympathetic nerve marker). **C:** colocalization between UT and TH is absent in denervated neonatal pig renal arteries (RA).

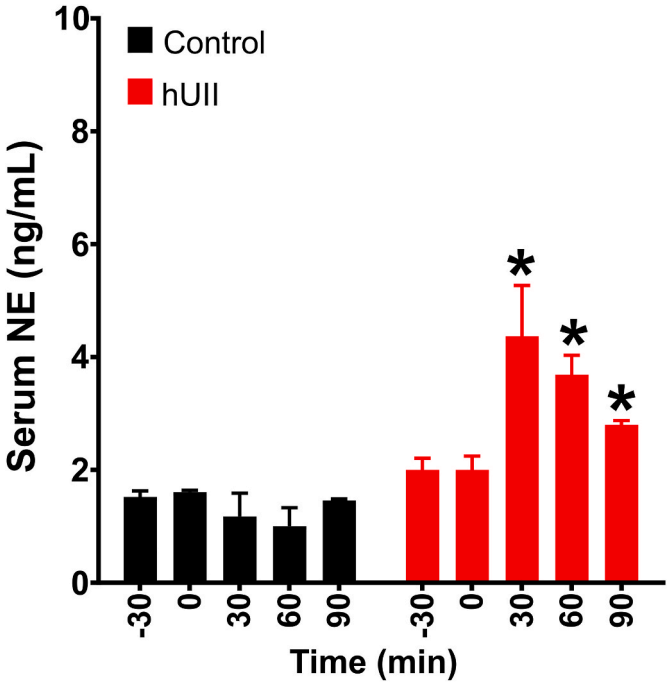

Fig. 6. Intrarenal artery infusion of UII (100 ng/kg/min) elevates serum norepinephrine (NE) concentration in neonatal pigs n = 3; *P < 0.05 vs. control (saline).

(Buyukhatipoglu et al., 2011). However, whether this observation correlates with significant glomerular injury is unclear.

UII(Adebiyi, 2014; Soni and Adebiyi, 2017) and URP (this manuscript) promote mesangial cell proliferation. Given its role in initiating and promoting inflammatory diseases, UII has been described as an inflammatory cytokine (Sun and Liu, 2019). UT inhibition and ablation of UII after an apolipoprotein E knockout attenuated serum cytokine levels (You et al., 2012). Proinflammatory cytokines increased UT receptor mRNA expression in human peripheral blood mononuclear cells (Segain et al., 2007). Lipopolysaccharide stimulated the UII system to activate migration and increase cytokine gene levels in frog leukocytes (Tomiyama et al., 2015). Other studies have reported the proinflammatory action of the UII system in cells and circulation (Clavier et al., 2020; Liu et al., 2015; Rex et al., 2022; Sun and Liu, 2019). UII also stimulates fibrosis in various tissues, including the heart, liver, and kidney (Kemp et al., 2009; Liang et al., 2021; Liu et al., 2009; Tian et al., 2008a; Zhang et al., 2007). Although the pathophysiological relationships between the UII system and the mechanisms of glomerulonephritis are unresolved, its proinflammatory, pro-fibrotic, and pro-proliferation activity may contribute to glomerular diseases and CKD (Balat and Büyükçelik, 2012).

6. Urotensin II system as a potential therapeutic target in CKD

The volume of evidence linking the UII system and CKD has grown rapidly in the past two decades, highlighting the UII system as a possible new therapeutic target. Because increased UII, URP, and UT levels adversely impact diabetes- and hypertension-related CKD, UT antagonism should, in theory, slow or reverse the progression of CKD. Palosuran, an orally active UT antagonist, mitigated the decline in GFR and renal blood flow in type 1 diabetic rats (Clozel et al., 2006). However, findings from human trials evaluating palosuran's efficacy in safeguarding the kidneys of individuals with diabetes yielded inconclusive results. (Sidharta et al., 2009; Sidharta et al., 2006; Vogt et al., 2010). Oral palosuran reduced 24-h albumin excretion in type 2 diabetic patients with microalbuminuric nephropathy (Sidharta et al., 2006). On the contrary, in hypertensive type 2 diabetic patients, palosuran did not affect albuminuria, GFR, or renal plasma flow (Vogt et al., 2010). Palosuran also failed to affect insulin response to hyperglycemic glucose clamp in type 2 diabetic patients (Sidharta et al., 2009). Adding to this complexity, palosuran can act on receptors of somatostatin (Malagon et al., 2008), which is part of the superfamily of genes that also encode URP and UII (Tostivint et al., 2006). UT displays structural resemblances to somatostatin 2 and 4 receptor subtypes (Marchese et al., 1995), and receptor cross-activation by UII and URP on somatostatin receptors and vice versa has been reported (Malagon et al., 2008). In addition, the diminished affinity of palosuran for UT within intact cells and tissues implies that it may not serve as an ideal UT antagonist. (Behm et al., 2008).

In a comparative study, a UII antagonist, DS37001789, was more potent and highly efficient in lowering UII-induced hypertension than palosuran (Nishi et al., 2019). This novel UII antagonist DS37001789, provided renal protection against hypertension and diabetes-induced kidney disease (Nishi et al., 2019). Another potent, orally long-acting UT antagonist, SAR101099, reduced albuminuria in STZ-induced diabetic and stroke-prone spontaneously hypertensive rats (Marie-Laure et al., 2020). However, no human studies of these drugs have been reported to date.

The effective application of UT antagonists in clinical scenarios has not been realized. Challenges such as the absence of readily accessible highly selective UT antagonists, contrasting UT physiological functions, and the widespread presence of the UII system across various organ systems are obstacles yet to be overcome.

7. Unexplored roles of urotensin II system in CKD

Clinical staging of diabetic nephropathy depends on the degree of proteinuria, with more significant protein loss in urine signifying advanced stages of nephropathy (Gross et al., 2005). Similarly, macroalbuminuria is an important prognostic marker of CKD progression in hypertensive nephropathy (Udani et al., 2011). Urinary protein loss is proportionate to the degree of damage to the glomerular filtration barrier, which retains macromolecules like proteins within the vascular

compartment of renal glomeruli. Therefore, the prevalence of proteinuria in CKD implies that the activation of the UII system associated with CKD might significantly impact the constituents of the glomerular filtration barrier. The glomerular filtration barrier comprises a layer of fenestrated endothelium, podocytes - the highly specialized epithelial cells, and the glomerular basement membrane (Arif and Nihalani, 2013). Therefore, the role of the UII system on the glomerular capillary, glomerular basement membrane, and podocytes might be an exciting area that remains unexplored.

Another potential target of UII, which is important in the context of DKD, is the pancreas. Evidence indicates that UII is present in pancreatic tissue extracts (Silvestre et al., 2004) and significantly lowers glucose-induced insulin secretion by beta cells (Marco et al., 2008; Silvestre et al., 2004, 2009). The insulinostatic effect of UII on the pancreas is reversed by UT antagonists, palosuran and urantide (Marco et al., 2008). UII also caused insulin resistance and reduced insulin-mediated glucose transport in mouse skeletal muscle (Wang et al., 2009, 2013), a major factor in the pathogenesis of type 2 diabetes. Urantide ameliorates UII-induced insulin resistance (Wang et al., 2013). In addition to beta cells and skeletal muscle insulin resistance, UII's diabetogenic actions could also be mediated by pancreatic alpha cells. A recent publication from our lab showed that UT gene deletion protects against DKD in STZ-induced type 1 diabetic mice (Peixoto-Neves et al., 2022). UT KO reversed hyperglucagonemia, mitigating hyperglycemia and its effects on kidneys (Peixoto-Neves et al., 2022).

Two prevalent contributors to CKD, namely diabetes and hypertension, manifest as disorders affecting multiple systems and organs. The expression of UII and UT encompasses various cell types and organs, posing a challenge for research focusing on specific cells or organs. Conducting experiments on whole animals using pharmacological agents inevitably triggers the activation or inhibition of receptors at multiple sites. At the same time, global knockout mouse models result in a widespread loss of function in UII/UT genes. Consequently, there is a need for animal models featuring cell-specific, conditional knockout of UII/UT to gain insights into the specific role of the UII system in individual cells. This approach might also help understand the apparent differential effect of UII on blood vessels, as the final physiological action could be the sum of UT activation on different cell types, including smooth muscle cells, endothelial cells, and autonomic neurons. In addition, the solution to the conundrum of UII and URP physiological actions might also lie in the presence of multiple UT isoforms activating signal transduction pathways with opposing effects.

8. Conclusion

Research indicating the connection between the UII system and CKD pathophysiology hints at possible therapeutic avenues, but additional efforts are required. Conducting in-depth mechanistic studies on targeted pharmacological UT antagonism and genetic ablation in conditions like glomerulonephritis (GN), diabetic kidney disease (DKD), and hypertensive nephropathy will offer further understanding of the UT system's involvement in CKD. Moreover, acquiring comprehensive human clinical data is crucial to elucidate the role of the UII system in managing CKD.

CRediT authorship contribution statement

Conception and design: AA and RG. Data acquisition and analysis: AA, HS, RRL, and KAJ. Writing of the manuscript: OSM, PK, AA, and RG. Approval of manuscript: all authors.

Declaration of competing interest

The authors declared that they have no conflicts of interest in this work.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crphys.2024.100126.

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