REVIEW

The role of the renin-angiotensin system in pediatric kidney diseases and neonatal development

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Abstract : The local renal renin-angiotensin system (RAS) is regulated independently of the systemic RAS. The renal RAS not only regulates blood pressure and hemodynamics but also plays an important role in the kidney disease development. Many studies have shown that the of angiotensinogen urinary excretion rate is a specific index of the intrarenal RAS activation. Moreover, urinary angiotensinogen (AGT) levels reflect the intrarenal RAS status associated with hypertension, chronic kidney disease, and diabetic nephropathy. In addition, urinary AGT is a novel biomarker of intrarenal RAS activation during neonatal kidney development. Furthermore, angiotensin-converting enzyme 2 and the (pro)renin receptor have recently been identified as new components of the RAS that have novel functions in kidney diseases and development. This review summarizes the current knowledge on intrarenal RAS activation in the context of pathological and physiological processes in children. J. Med. Invest. 72 : 241-244, August, 2025

Keywords **:** *Renin-angiotensin system, pediatric kidney disease, neonatal development*

INTRODUCTION

The renin-angiotensin system (RAS) is pivotal in regulating blood pressure and fluid/electrolyte balance (1). The systemic RAS is primarily controlled via renin production by juxtaglomerular cells in the kidney, which acts on angiotensinogen (AGT) produced by the liver to initiate a tightly regulated enzymatic cascade that regulates the production of angiotensin II (Ang II) (2). Local activation of intrarenal RAS is involved in the pathogenesis of hypertension and kidney injury, as well as in kidney development (3). Recent studies have reported that the progression of proteinuria and kidney tissue damage are associated with intrarenal RAS activation (1, 4, 5). Furthermore, angiotensin-converting enzyme 2 (ACE2) and (pro)renin receptor ((P)RR) contribute to kidney diseases development (Figure 1) (6, 7). In this review, we explored recent findings pertaining to the involvement of the intrarenal RAS in the progression of renal diseases.

INTRARENAL RAS ACTIVATION

The renal RAS is unique in that all necessary components to generate intrarenal Ang II are present along the nephrons in both the interstitial and intratubular components (8). There is substantial evidence that the major fraction of Ang II present in renal tissues is generated from AGT and subsequently delivered to the kidney, as well as from AGT produced by proximal tubule cells (8). Furthermore, Ang I delivered to the kidneys can be converted to Ang II (8). Renin has also been detected in cultured proximal tubular cells (9). Additionally, the brush border membrane of proximal human kidney tubules expresses abundant levels of ACE mRNA and protein (8). ACE has been detected in both proximal and distal tubular fluids, with higher concentrations observed in the proximal tubular fluid (8). Therefore, all major components required to generate Ang II are expressed in kidneys (4). It is difficult to clearly distinguish the influences of intrarenal RAS from that of circulating Ang II (5). Nevertheless, there are circumstances in which the intrarenal and circulating RAS achieve concordance, such as variations in salt intake (5). In other situations, alterations in intrarenal RAS are not mirrored by changes in systemic renin and Ang II levels, as observed in certain types of hypertension and diabetes mellitus (5). Although every organ system in the body contains elements of RAS, the kidney contains every component of RAS, with compartmentalization in the nephron and intestinal networks ; additionally, intracellular accumulation of Ang II has been observed in the kidney (8). Thus, the kidneys are unique regarding the tissue concentrations of Ang II, which are much higher than the concentrations delivered to this organ by arterial blood flow (1).

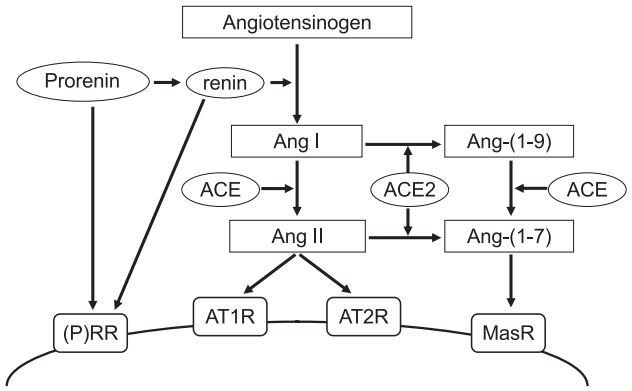

Figure 1. The renin-angiotensin system cascade.
Ang, angiotensin ; ACE, angiotensin converting enzyme ; (P)RR, (pro) renin receptor ; AT1R, angiotensin type 1 receptor ; AT2R, angiotensin type 2 receptor ; MasR, Mas receptor.

Received for publication December 8, 2023 ; accepted March 4, 2025.

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ACE2 IN PEDIATRIC KIDNEY DISEASES

ACE2 is an ACE homolog that regulates ACE activity (10). ACE2 cleaves Ang I into Ang-(1-9) and Ang II into the vasodilator peptide Ang-(1-7) (10). Ang-(1-7) is a biologically active peptide that binds to the Mas receptor to expert opposing effects on Ang II (11). Although many studies have reported the protective role of Ang-(1-7) in the prevention of Ang II activity, it has been shown that Ang-(1-7) stimulates growth factor expression and cell proliferation (12). Furthermore, coronavirus disease 2019 (COVID-19) interfaces with the RAS through ACE2, which functions as a receptor for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (13). The interaction between SARS-CoV-2 and ACE2 has been suggested as a potential factor in infectivity (13).

Recently, we demonstrated that ACE2 expression is increased in the kidney of patients with pediatric IgA nephropathy and is accompanied by mesangial hypercellularity (14). Furthermore, we clarified that intrarenal RAS activation was suppressed in pediatric patients with IgA nephropathy treated with RAS blockade (15). In a future study, we aim to measure urinary ACE2 levels following RAS blockade and evaluate the expression of ACE2 in kidney tissue to test the hypothesis that ACE2 is associated with kidney damage in pediatric IgA nephropathy (16). On the other hand, urinary and glomerular ACE2 expression levels at the second biopsy were lower than those at the first biopsy in patients with pediatric IgA nephropathy (16). Furthermore, urinary ACE2 levels were positively correlated with urinary protein levels, mesangial hypercellularity, and ACE2 expression levels in kidney tissue (16). These data suggest that measuring urinary ACE2 levels may be useful for assessing glomerular damage in pediatric patients with IgA nephropathy (16).

The loss of ACE2 functionality has been suggested to be critical COVID-19 pathophysiology (17). Several studies have suggested that RAS inhibitors increase ACE2 expression, raising concerns regarding their safety in patients with COVID-19 (13). However, sufficient data from human studies are not available ; furthermore, continuation of RAS inhibitors is recommended because its abrupt withdrawal may result in clinical instability and adverse health outcomes in high-risk patients (13). Our current findings suggest that ACE2 in the kidney is crucial for glomerular damage in pediatric IgA nephropathy ; however, it is difficult to determine whether ACE2 drives the activity of IgA nephropathy.

URINARY AGT IN DEVELOPMENT AND PEDIATRIC CHRONIC KIDNEY DISEASE

Recent studies have demonstrated the contribution of RAS to the mammalian kidney development (18, 19). Many studies have established the importance of an intact RAS cascade during renal development using both pharmacological inhibition and genetic deletions that affect various RAS components. Prenatal insults likely result in renal injury via the disturbance of RAS and other factors necessary for normal kidney development (19). Our previous study demonstrated that urinary AGT levels at birth were significantly higher in preterm neonates than in full-term neonates, suggesting that intrarenal RAS was activated during kidney development (20). Another study reported that urinary AGT could be an efficient tool for screening renal dysfunction after discharge from the neonatal intensive care unit (21). However, urinary AGT excretion and renal AGT expression associated with the pathophysiology of kidney injury have not been extensively studied in humans, more so in neonates. We demonstrated that urinary AGT levels were decreased during the first year of life and were significantly higher in neonates than in children (22). In addition, urinary AGT levels at birth and 1 year later were inversely correlated with cystatin C-based eGFR measured 1 year after birth (22). These results, in addition to those of our previous investigations, suggest that neonatal urinary AGT is a prognostically significant biomarker of renal dysfunction later in life.

In addition to RAS activation, the activation and infiltration of monocytes/macrophages into kidney tissues and fibrosis are involved in kidney injury progression (23). Recently, the degree of macrophage infiltration into the renal region was evaluated by measuring CD68 expression, a surface marker of macrophages, in renal glomeruli and by measuring the urinary concentration of monocyte chemoattractant protein-1 (MCP-1), which is a monocyte chemoattractant (24-27). In addition, it was suggested that RAS activation induced CD68-positive macrophages and promoted crescent formation in a rat model of crescentic glomerulonephritis (28). Therefore, we examined the relationship between RAS activation and childhood chronic glomerulonephritis (29). Urinary AGT levels were positively correlated with urinary protein levels, mesangial hypercellularity, crescentic glomeruli ratio, and expression levels of AGT and CD68 in the glomeruli. Moreover, urinary MCP-1 levels positively correlated with urinary protein levels, mesangial hypercellularity, crescentic glomeruli ratio, and AGT and CD68 expression levels in the glomeruli. We also demonstrated that urinary AGT and MCP-1 levels, and renal AGT and CD68 expression were decreased in pediatric patients with chronic glomerulonephritis treated with immunosuppressive therapy. These observations further corroborate that urinary AGT can act as a novel biomarker of intrarenal RAS activation ; additionally. MCP-1 is a useful marker for monitoring changes in intraglomerular macrophage infiltrate levels associated with glomerular injury in pediatric patients with chronic glomerulonephritis (29).

(P)RR IN GLOMERULONEPHRITIS

(P)RR was identified as a single transmembrane receptor encoded by the *ATP6AP2* gene that acts by enhancing tissue RAS by binding to its ligands renin and/or prorenin (30, 31). This receptor plays important roles in various pathways, such as RAS, mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), and Wnt/β-catenin pathways, that are involved in a wide range of physiological and pathological processes (32). The tissue RAS in the kidney has several pathophysiological functions, not only in blood pressure regulation but also in regulating renal cell growth and glomerulosclerosis, which can lead to the development of renal fibrosis (33). Previous studies have shown that RAS blockades has beneficial effects in various renal diseases, which are often considerably more significant than its suppressive effects on blood pressure (5).

The development of renin inhibitors has provided an opportunity to evaluate the effects of direct renin inhibition (DRI) as another method of RAS blockade. Currently, aliskiren is the main available inhibitor (34). Direct administration of aliskiren to the kidneys using a collagen matrix was shown to mitigate anti-Thy 1.1 antibody-induced glomerulonephritis (35). In addition, the treatment of mesangioproliferative glomerulonephritis in rats with aliskiren reduced or prevented marked proteinuria and albuminuria due to intrarenal RAS activation (36). Our previous studies showed that RAS blockades have beneficial effects in various glomerulonephritis models, which are often considerably more significant than the suppressive effects of RAS on blood pressure (37, 1, 33). However, our current knowledge regarding the effects of direct renin inhibitors (DRIs) for glomerulonephritis

and its mechanisms of action is limited. Therefore, we focused on the potential role of (P)RR in the progression of crescentic glomerulonephritis in rats.

Treatment with DRIs reduces glomerular crescent formation and prevents proteinuria, accompanied by suppressed macrophage infiltration (38). In addition, (P)RR expression in the glomeruli was markedly increased in nephritic rats, which was suppressed by DRI treatment (38). We observed that prorenin significantly enhanced cell proliferation and treatment with PD98059 and (P)RR siRNA transfection abrogated this change in cultured parietal epithelial cells (PECs) (38). Notably, treatment of cultured PECs with prorenin induced ERK1/2 phosphorylation, which was inhibited by transfection of (P)RR siRNA. These results suggest that ERK1/2 phosphorylation in PECs by prorenin enhances cell proliferation via (P)RRE, which is associated with crescent formation during glomerulonephritis progression. DRIs did not inhibit cell proliferation or ERK1/2 phosphorylation in cultured PECs treated with prorenin, suggesting that DRIs failed to block prorenin binding to (P)RR in PECs. Furthermore, cultured mesangial cells (MCs) stimulated with prorenin-induced MCP-1 mRNA, and (P)RR siRNA transfection inhibited this augmentation (38). Additionally, Wnt4 siRNA transfection and selective β-catenin pharmacological antagonist XAV939 treatment blocked MCP-1 expression in cultured MCs stimulated by prorenin (38). Taken together, these data indicate that prorenin binds (P)RR and induces MCP-1 expression via Wnt/β-catenin signal activation, leading to glomerular crescent formation in rats.

CONCLUSION

To understand of the role of RAS in pediatric kidney diseases and neonatal kidney development, we must focus on intrarenal RAS activation. Novel mechanisms regarding RAS activation in the kidneys of pediatric patients and their role in pediatric kidney development will further help in this endeavor. Thus, targeted research to improve our understanding of these aspects are required. Given our current knowledge, researchers must act to bridge these gaps in our understanding to protect pediatric kidney health.

CONFLICT OF INTEREST

None.

ACKNOWLEDGEMENTS

The author acknowledges the critical discussion and/or excellent technical assistance from Shoji Kagami, Ryuji Nakagawa, Shuji Kondo, Maki Shimizu, Masanori Takamatsu, Kenichi Suga, Sato Matuura, Yukiko Kinoshita, Natsuko Kishi, Takashi Nagai, Masashi Suzue, Miki Shono, Keisuke Fujioka, Ariunbold Jamba, Tomoki Hattori, Yuki Sakaki, Naomi Okamoto, Chizuko Yamamoto (Tokushima University Graduate School). These studies were supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

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