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Physiology and pathophysiology of the plasminogen system in kidney

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Abbreviations

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<th>Abbreviation</th>
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<tr>
<td>α2-AP</td>
<td>Alpha2-antiplasmin</td>
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<td>Plg</td>
<td>Plasminogen</td>
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<td>PA</td>
<td>Plasminogen activator</td>
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<td>PAI</td>
<td>Plasminogen activator inhibitor</td>
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<td>PAR</td>
<td>Protease activated receptor</td>
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<td>tPA</td>
<td>Tissue-type plasminogen activator</td>
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<td>uPA</td>
<td>Urokinase-type plasminogen activator</td>
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<td>uPAR</td>
<td>Urokinase-type plasminogen activator receptor</td>
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<td>suPAR</td>
<td>Soluble urokinase-type plasminogen activator receptor</td>
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Abstract

The plasminogen system is important for fibrinolysis in addition to tissue remodeling and inflammation with significance for kidney disease. The system consists of the circulating zymogen plasminogen and the tissue- and urokinase-type activators tPA and uPA, expressed in glomeruli, endothelium and tubular epithelium, respectively, and the inhibitors α2-antiplasmin and plasminogen activator inhibitor-type1, PAI-1. Plasminogen is activated by surface receptors, some with renal expression: uPAR, Plg-RKT and tPA, most evident in the endothelium. Plasmin may exert effects through protease-activated receptors, PARs, expressed in kidney. Deletion of plasminogen system component genes confers no major developmental or renal phenotypes in normal mice. In glomerular injury and renal interstitial fibrosis, deletion of various components, notably plg, uPA, PAI and uPAR is associated with protection suggesting a disease promoting effect of plasmin in some cases exerted through PAR1 receptor activation. Plasminogen and uPA are aberrantly filtrated across the glomerular barrier in proteinuria and plasminogen is activated in the tubular fluid. In tubular fluid, plasmin may activate proteolytically the epithelial sodium channel ENaC and inhibit the apical calcium transporter TRPV5, which could explain impaired sodium excretion and enhanced calcium excretion in proteinuria. Amiloride, a potassium-sparing diuretic, inhibits urokinase and plasmin activation in tubular fluid and uPAR expression in vitro, which highlights new indications for an old drug. Protease inhibitors lowered blood pressure and antagonized fibrosis in salt sensitive Dahl rats. Current knowledge indicates that the plasminogen system aggravates renal disease by direct and indirect hypertensive effects and is a promising target to antagonize disease progression.
**Introduction** Chronic kidney disease (CKD) affects 10-15% of the population and prevalence is increasing due to increased life expectancy and increased prevalence of diabetes, hypertension and atherosclerosis [24]. CKD is associated with increased risk of hypertension, cardiovascular disease and metabolic bone disease. Multiple mechanisms have been implicated in the development and progression of CKD. Proteinuria is a hallmark of CKD and predicts a poor renal outcome and increased risk of cardiovascular morbidity and mortality. The mechanistic coupling between proteinuria and kidney disease progression is not well established. The plasminogen system has been shown to promote pathological processes in the kidneys. The scope of the present review is to briefly highlight and discuss causal involvement of the plasmin system in glomerular, interstitial and intratubular effects associated with physiology and kidney disease. By the plasminogen system we define the key enzyme plasminogen, its activators, inhibitors and receptors.

**Localization and significance of the plasminogen system in the healthy kidney.** The zymogen plasminogen is synthesized by the liver and circulates in plasma at concentrations of 1-5 µmol/L [89] [127]. The activation of plasminogen requires surface tethering, which facilitates highly localized effects such as intravascular fibrinolysis [8,9] and promotion of wound healing [64]. Activation of plasminogen is achieved by two main physiological plasminogen activators (PA), tissue-type (t)PA and urokinase-type (u)PA, which cleave the single activation site of plasminogen [91]. Tissue type PA is synthesized by endothelial cells particularly in renal glomeruli [97,117]. Urokinase-type PA is the “fibrin-independent” activator [40,46] [60] with low affinity to fibrin [7]. uPA mRNA is observed along both proximal tubule and loop of Henle epithelium [97] while immunoreactivity is more widespread in human kidney likely reflecting the presence in tubular fluid and association with cell surfaces [117]. uPA is secreted as a catalytically inactive single-chain precursor, pro-uPA [13,76,122]. Active uPA and pro-uPA binds to a specific cell surface receptor uPAR (45-55kDa). The uPA activator/receptor, uPAR, is a glycosylphosphatidylinositol (GPI) membrane anchored receptor [12,84,93], which also mediates protease-independent effects, including cell adhesion and migration [87,26]. uPA and uPAR are expressed in collecting duct principal cells, with regulation by vasopressin and EGF [83], and uPAR has been associated with glomerular mesangial cells, resident fibroblasts and invading inflammatory cells [115,94,74,1,123,101,117,27,103]. uPAR exists in a soluble
form [111,84] which is generated by proteolytic cleavage of the transmembrane domain or cleavage of the GPI anchor [47]. The soluble form is detectable in plasma and urine and is an established biomarker that predicts cancer, cardiovascular disease, mortality and diabetes complications [82,110,34]. In addition to the PAs, plasminogen binds to different cell surface molecules, i.e. annexin A2 S100A10-complex, Plg-RKT, amphoterin and members of the β2 integrins collectively termed plasminogen receptors which promote plasmin generation on the cell surface and facilitate proteolysis, cell migration and activation of signaling pathways [38]. Human podocytes express uPA and the three plasminogen receptors uPAR, tPA, and Plg-RKT [88,6]. The Plg-RKT has been found on the cell surface in close proximity with the uPAR receptor. The colocalization of Plg-RKT and uPAR allows plasminogen and uPA to be close and facilitate plasminogen activation.

Inhibition of the plasmin(ogen) system occurs by specific endogenous PA inhibitors (PAIs) and at the level of plasmin by α2-antiplasmin (AP). The circulating PAIs, type 1 and 2 (PAI-1 and PAI-2) [14,21,22] [105,62] are serpin class proteinase inhibitors. Patients with PAI-1 deficiency exhibit frequent bleedings [35], while hyperactive PAI-1 has been associated with increased risk for coronary artery disease and myocardial infarction [10,52,121]. In healthy kidney, no glomerular expression of PAI-1 is detected [30]. The expression of PAI-1 is stimulated by renin-angiotensin-aldosterone system and exhibit circadian variation in plasma [5,69]. Increased circulating PAI-1 has been observed in pathophysiological conditions with relation to kidney e.g. diabetes [25,99,65], fibrosis [63,37], inflammation, metabolic and ischemic disease [78,17] and PAI-1 synthesis is elevated in the chronically injured kidney [30,68]. Thus PAI-1 is clearly associated with disease states both systemically and locally. Alpha 2-AP inhibits plasmin [59] on the fibrin clot or as plasmin-antiplasmin complex in the circulation. Hereditary α2-AP deficiency promotes bleeding and increased levels accelerate thrombosis. α2-AP is synthesized in hepatocytes and is abundantly expressed in the kidneys [70]. Deletion of α2-AP and double knockout of α2-AP and PAI-1 was associated with increased endogenous fibrinolytic capacity but conveyed no major spontaneous renal or systemic phenotype and did not affect viability or fertility [29,59,79]. Thus it is clear that absence of endogenous restraints on plasmin activity is not associated with renal malformation, injury or impaired kidney function.
per se. Collectively, components of the plasminogen system, especially tPA and uPA-uPAR are expressed in the normal kidney.

**Plasminogen system and the glomerular filtration barrier in physiology and kidney disease** In particular two renal diseases affecting the glomerular filtration have been in focus in relation to the plasminogen system (Table 1); crescentic glomerulonephritis/focal segmental glomerulosclerosis (FSGS) with fibrin depositions and diabetic nephropathy. Physiological glomerular filtration is based upon 3 barriers that are composed of a fenestrated endothelium, the glomerular basement membrane (GBM) and the podocytes. The GBM is composed of specific extracellular matrix proteins on to which the podocytes attach through their cell-matrix adhesion receptors, e.g. integrins, which is of importance for the physiological integrity of the filtration barrier [95]. In FSGS, podocytes are targeted and damage to the cytoskeleton ultimately leads to podocyte detachment from the GBM and massive proteinuria [100]. Mutations underlying certain forms of FSGS have been identified in few cases. Many of the patients experience rapid recurrence after kidney transplantation, suggesting a circulating factor is responsible for FSGS in these cases. The soluble form of the urokinase plasminogen receptor (suPAR) has been suggested as a circulating permeability factor, and Wei et al. (2011) found elevated plasma levels of suPAR in 2/3 of patients with primary FSGS [119]. Soluble uPAR correlates directly with degree of proteinuria [102] and with faster decline in kidney function [44]. The GPI-anchored form of uPAR is associated with the glomerular endothelium and podocytes [120]. uPAR is dispensable for a normal renal filtration barrier, but podocyte-specific knockout of uPAR rendered mice resistant to LPS-induced proteinuria [120]. Soluble uPAR and GPI-anchored uPAR promote cell motility through activation of αvβ3 integrin in podocytes [119,120], which related directly with the foot process effacement and indicated that (s)uPAR is mechanistically involved in the pathogenesis of FSGS. In relation to uPAR it is interesting, that patients treated with the potassium-sparing diuretic amiloride have a lower degree of proteinuria [3,80]. Amiloride is an off-target competitive inhibitor of uPA [114] and inhibits the expression of human urokinase receptor [118]. In cultures of human podocytes, amiloride, but not the ENaC inhibitor triamterene, inhibited the expression of uPAR, indicating that non-ENaC targets are important [124]. PAI-1 displayed low expression in healthy kidney but in a mouse model of glomerular injury, PAI-1
was expressed in glomerular endothelium and in later stages also in capillaries and podocytes [55]. PAI-1 was associated with glomeruli in chronic allograft nephropathy in humans [90] and PAI-1 deletion was renoprotective in various murine diabetes models [75,23] and, of note, the pro-inflammatory cytokine TGFβ was lowered in renal tissue. In human and rat, AT1 receptor antagonists lowered PAI-1[98] [61]. The PAI-1 inhibitor TM5484 ameliorated proteinuria [55]. PAI-1/uPA complexes induced cell detachment through endocytosis of β1 integrin, a process that could be blocked by an anti-uPAR antibody [55]. β1 integrin expression by podocytes is crucial for the structural integrity of the glomerular filter [86]. Together, data indicate that glomerular expression of PAI-1 is associated with injury and inflammation and that PAI-1 promotes podocyte damage. Podocytes express several receptors for plasminogen e.g. uPAR, tPA and Plg-RKT [88,6]. In a mouse model of crescentic glomerulonephritis, the involvement of plasminogen in glomerular pathology appears protective since deletion of plg and in particular tPA exacerbated glomerular injury, while uPA and uPAR appeared of minor significance [54]. On the other hand, pharmacologic inhibition of plasminogen activation by epsilon-aminocaproic acid (EACA) reduced proteinuria in a rat model of nephritis [48] and, in vitro, direct incubation of podocytes with plasminogen at a physiological plasma concentration led to EACA-sensitive increased oxidative stress and podocyte apoptosis [88]. Thus, the actions of the plasminogen system in glomerular disease are not clearly pro- or anti-fibrotic. Effects of e.g. PAI-1 could be direct and independent of plasmin activation or related to potential confounding effects of PAI-1 on blood pressure or inflammation. Moreover, PARs could be involved since plasma from patients with FSGS displayed serine and/or cysteine protease activity with ability to activate podocyte migration in vitro [42]. PARs 1-3 are expressed in podocytes and knockdown of PAR1 led to inhibition of the signaling by plasma [42]. This indicated that dysregulated plasma protease activity could be an important contributor to FSGS, but whether this is due to increased plasma protease or reduced inhibitor levels are still not understood. In summary, the urokinase/plasminogen system has no documented role in the physiological development and maintenance of the normal glomerular filtration barrier; however, the system accelerates podocyte injury. uPAR and PAI-1 affects integrin signaling in podocytes and measures to inhibit uPAR/PAI-1 have shown beneficial effects on the degree of proteinuria.
Urokinase-plasminogen effects in the renal interstitium in acute and chronic renal disease

Both acute tubulo-interstitial injury and chronic interstitial (Table 2) changes involve the plasminogen system. Thus, uPAR was elevated in kidney graft patients with rejection compared to non-rejection patients and uPAR was associated with lymphocytes and epithelial cells in biopsies from graft patients [92]. In experimental models of ischemia-reperfusion and allograft nephropathy, uPAR deficiency protected against ischemia injury and uPA–uPAR were upregulated after ischemia and allograft transplantation; also here uPAR⁻/⁻ allografts displayed better function. Functional studies showed that endothelial uPAR was necessary for adhesion and migration of leukocytes and for ischemia-induced apoptosis [39]. Thus, uPAR contributes to injury associated with acute inflammation in kidney transplantation and post ischemia reperfusion. In the chronic setting, interstitial fibrosis is characterized by infiltration of macrophages and expansion of extracellular matrix proteins such as collagen and laminin. Mice deficient in PAI-1 were protected against renal and pulmonary fibrosis [77,33] and an anti-PAI-1 antibody increased matrix degradation in human cultured mesangial cells [11]. The data imply either a direct pro-fibrotic effect of PAI-1 or, that excess plasminogen system activity is protective against kidney fibrosis. The matrix turnover rate is an important feature of fibrogenesis and plasmin was hypothesized to exert protection against fibrosis through its proteolytic effect on matrix proteins and its ability to activate matrix metalloproteases (MMP) [71]. Mild spontaneous fibrosis in lungs and liver was accelerated in mice with deletion of plasminogen (plg⁻/⁻) [109,85]. Mice lacking uPAR exhibited accelerated renal fibrosis consistent with the view that active plasmin attenuated renal fibrosis [126]. However, an anti-fibrotic effect of plasmin was challenged by the observation that plg⁻/⁻ mice with unilateral ureter obstruction (UOO) had reduced collagen and macrophage accumulation in the kidney compared to their littermate controls (plg⁺/⁺) [31,125]. Indirect evidence from mice with double knockout of plasmin inhibitors α2-AP and PAI-1 supported that plasmin promotes perivascular lymphocyte infiltration [79]. Latent sequestered pro-fibrotic transforming growth factor-β (TGF-β) was higher in plg⁻/⁻ kidneys compared to plg⁺/⁺ [125] compatible with the known activating ability of plasmin on TGF-β [66]. Epithelial-to-mesenchymal transition (EMT) was reduced in plasminogen deficient mice and the addition of plasmin to cultures of murine tubular epithelial cells was followed by a
phenotypic transition to fibroblast-like cells inhibited by protease-activated receptor-1 (PAR-1) silencing RNA and by an anti-PAR-1 signaling peptide [125]. PAR-1 activation by plasmin is followed by signal transduction via p44/42 extracellular signal-regulated kinases (ERK)/mitogen-activated protein kinase (MAPK) pathways and it was shown that ERK kinase inhibitor UO126 also inhibited the transition to fibroblast-like cells. [125]. These independent findings demonstrated that plasmin exerted a direct pro-fibrotic action and that PAI-1’s pro-fibrotic effect probably is exerted independently of plasmin activity. It is possible that the pro-fibrotic effect of both PAI-1 and plasmin is due to their common effect; activation of TGF-β.

**Intratubular activation and luminal effects of the plasminogen system on renal epithelial electrolyte transport** In urine from healthy persons, plasmin(ogen) can be shown by sensitive mass spectrometry [73] while plasminogen often falls below detection limit by conventional ELISA and western blotting analyses, e.g. [15,16,107]. Glomerular filtration of plasminogen with a molecular weight of ~90 kDa is normally restricted by the filtration barrier. In pathophysiological settings with filtration barrier defects e.g. diabetic nephropathy [2], preeclampsia [18,19,15] and nephrotic syndrome [116,4], however, plasminogen is aberrantly filtered and, in nephrotic syndrome patients, it was the dominant serine protease recovered from urine [107]. Activation of plasminogen occurs luminally between Bowman’s space and final urine and is likely confined to surfaces that bind plasminogen and uPA. The exact site(s) have not been defined [67,43,58,57]. The activation of plasminogen was inhibited by amiloride [106,107], indicating that uPA facilitates the activation [80,106] Consistent with its tubular expression in healthy kidney, uPA was detectable in urine from healthy persons [50,104], while proteinuria/albuminuria was associated with increased urinary levels in experimental nephrosis and in patients with diabetes and nephrotic syndrome [106,2]. Both uPA and plasmin were present in active form in urine from patients with proteinuria of various etiologies [81,107,106]. Plasmin and uPA are activators of ENaC [81,107,51,20] through proteolysis of the extracellular domain within the γ-subunit leading to increased open probability of the channel [81]. Urine samples from patients diagnosed with proteinuria e.g. preeclampsia [15], diabetic nephropathy [36], type-2 diabetes [2], congestive heart failure [128] and nephrotic syndrome [4,107] activated amiloride- and anti-
plasmin/protease-sensitive inward current in single collecting ducts cells *in vitro*, which was mimicked by pure plasmin. Thus, plasmin-mediated stimulation of ENaC could promote sodium and water retention in proteinuric diseases *in vivo* and predicts sensitivity to the K⁺-sparing diuretic amiloride in hypertension/volume retention-associated proteinuria. Amiloride was as effective in mobilizing edema as furosemide in pediatric nephrotic patients [28] and has shown additive effects in resistant hypertensives with diabetes [3,80]; in low renin resistant hypertensives [32]; and in African Americans with hypertension [96].

The *in vitro* activation of ENaC by plasmin was dependent of prostasin [108] which is a glycosylphosphatidylinositol anchored protease [113] associated with principal cells of the collecting ducts [108] that activates ENaC [113]. Plasmin also affects the epithelial Ca²⁺ channel, TRPV5 [121]. TRPV5 is mainly expressed in the distal convoluted tubule and connecting tubules of the nephron, where it functions as a key player in regulation of Ca²⁺ balance by establishing a constitutively open apical entry for transcellular Ca²⁺ reabsorption. Urinary plasmin inhibits TRPV5 through activation of PAR-1 and subsequent PKC-mediated phosphorylation of the S144 residue of TRPV5, resulting in decreased channel pore size and reduced open probability [112]. This could explain the nephrocalcinosis associated with nephrotic range proteinuria. In summary, plasmin and uPA concentrations in urine from patients with proteinuria are sufficient to cause ENaC activation *in vitro* and administration of amiloride reduced hypertension and mobilized Na⁺ in proteinuric patients. Intratubular anti-plasmin and anti-protease therapy should be further elucidated as new targets to control hypertension and for organ protection.

**The plasminogen system and renal hemodynamics** Direct effects of urokinase-plasminogen on hemodynamic regulation have not been shown in the renal vascular bed. Protease-activated receptors 1 and 2 have been shown to affect renin secretion and renal vascular resistance in isolated perfused kidneys suggesting that e.g. plasmin could exert effects [45]. Little is known about systemic cardiovascular parameters in mice with global deletion in plasminogen, tPA and PAI-1 while uPA⁻/⁻ mice had lower baseline blood pressure compared to wild type mice and aortic rings from uPA⁻/⁻ mice revealed an attenuated contractile response when exposed to phenylephrine [72]. In isolated aortic rings from rats, addition of uPA enhanced phenylephrine-induced vasoconstriction [41]. In agreement, uPAR⁻/⁻ mice showed no phenotype.
The lower arterial blood pressure and the impaired vascular contractility were reversed when mouse- and human uPA were added [72]. This potential tonic contribution to blood pressure regulation by uPA needs confirmation. Several studies have shown that deletion of different components of the plg-system is protective in experimental atherosclerosis mouse model [56,49]. The protection is generally ascribed to attenuated inflammation but with lack of data on the confounding effect of blood pressure. PAI-1 deficient mice are protected against vascular changes that follow hypertension in a setting where long-term NOS inhibition is known to induce perivascular fibrosis and hypertension in mice [53].

**Summary and conclusion**

The plasminogen system resides in the kidneys through expression of plg activators and receptors in glomerular podocytes, vascular endothelium and tubular epithelium. Whereas the system has little impact on normal kidney development, function and structure, it is involved in pathophysiology of glomerular injury, tubulo-interstitial injury/fibrosis and proteinuria-associated disturbances in electrolyte handling. In particular, glomerular PAI-1 and uPA-uPAR promotes glomerular injury and are associated with invading inflammatory cells in the interstitium which contribute to injury. Plasminogen itself is pro-fibrotic in mouse models of renal injury. In proteinuria, aberrant filtration of plasminogen system components, uPA and plg, leads to intratubular plasmin activation with potential adverse effects on renal Na\(^+\) and Ca\(^{2+}\) handling through ENaC and TRPV5 that promote hypertension and nephrocalcinosis. Amiloride, an ENaC inhibitor, is an off-target blocker of urine uPA activity and renal uPAR expression. Amiloride has together with general protease inhibitors shown renal protective effects in both experimental animals and human settings.

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**Conflict of Interest:** The authors declare that they have no conflict of interest.
REFERENCES:


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Table 1: The effects of the plasminogen system on the glomerular filtration barrier

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<th>Effect of knockout</th>
<th>Effect of inhibition</th>
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<tr>
<td><strong>Plasminogen</strong></td>
<td>Exacerbation of glomerular injury after anti–mouse GBM globulin injection [72]</td>
<td>Inhibition of plasminogen activation reduces proteinuria in rat nephritis model [80], and podocytes <em>in vitro</em> [36]</td>
</tr>
<tr>
<td><strong>uPAR</strong></td>
<td>Podocyte-knockout protective LPS-induced proteinuria [66]</td>
<td>Amiloride inhibits uPAR expression in podocytes and reduced proteinuria in two different model of glomerular injury [71]</td>
</tr>
<tr>
<td><strong>PAI-1</strong></td>
<td>Protective in diabetes models [75,76]</td>
<td>Reduces proteinuria [73]</td>
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Table 2: The effects of the plasminogen system on the chronic interstitial fibrosis

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<th><em>In vitro</em> effects</th>
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<td><strong>Plasminogen</strong></td>
<td>Protective against fibrosis in unilateral ureter obstruction model[94]</td>
<td>Induces transition of tubular epithelial to fibroblast-like cells [95]</td>
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<tr>
<td><strong>uPAR</strong></td>
<td>Accelerated renal fibrosis in obstructive nephropathy [89]</td>
<td></td>
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<tr>
<td><strong>PAI-1</strong></td>
<td>Protective against renal fibrosis after ureteral obstruction [85]</td>
<td>anti-PAI-1 antibody increases matrix degradation in cultured mesengial cells [87]</td>
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