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Novel roles of the renal angiotensin-converting enzyme

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Abstract

The observation that all components of the renin angiotensin system (RAS) are expressed in the kidney and the fact that intratubular angiotensin (Ang) II levels greatly exceed the plasma concentration suggest that the synthesis of renal Ang II occurs independently of the circulating RAS. One of the main components of this so-called intrarenal RAS is angiotensin-converting enzyme (ACE). Although the role of ACE in renal disease is demonstrated by the therapeutic effectiveness of ACE inhibitors in treating several conditions, the exact contribution of intrarenal versus systemic ACE in renal disease remains unknown. Using genetically modified mouse models, our group demonstrated that renal ACE plays a key role in the development of several forms of hypertension. Specifically, although ACE is expressed in different cell types within the kidney, its expression in renal proximal tubular cells is essential for the development of high blood pressure. Besides hypertension, ACE is involved in several other renal diseases such as diabetic kidney disease, or acute kidney injury even when blood pressure is normal. In addition, studies suggest that ACE might mediate at least part of its effect through mechanisms that are independent of the Ang I conversion into Ang II and involve other substrates such as N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), Ang-(1–7), and bradykinin, among others. In this review, we summarize the recent advances in understanding the contribution of intrarenal ACE to different pathological conditions and provide insight into the many roles of ACE besides the well-known synthesis of Ang II.

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CONFLICT OF INTEREST

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INTRODUCTION

The classical view of the renin angiotensin system (RAS) as a systemic proteolytic cascade leading to the synthesis of circulating angiotensin II (Ang II) has changed substantially in the last few decades thanks to the discovery of a local RAS in several tissues including the kidneys.[1] The intrarenal expression of all RAS components and the observation that intratubular Ang II levels greatly exceed the plasma concentration suggest that the synthesis of renal Ang II occurs independently of the circulating RAS.[2] Besides the juxtaglomerular apparatus, renin is abundantly expressed in the distal nephron, mainly by principal cells of the connecting tubules and collecting duct.[3,4] In terms of angiotensinogen, the liver appears as the main source of this protein in the kidney. However, research demonstrated that angiotensinogen can also be synthesized in the proximal tubule and can be secreted to the tubular lumen, playing a potential role in intratubular Ang II synthesis.[5] Angiotensin-converting enzyme (ACE) is also widely expressed throughout the nephron including the glomerular endothelium, mesangial cells, podocytes,[6] and the brush border of the proximal tubule, its highest site of expression in the kidney.[7] The Ang II type 1 (AT1) receptor is predominantly expressed in the proximal tubule brush-border and basolateral membranes. However, it can also be observed in other nephron segments such as distal tubules, and cortical and medullary collecting ducts. AT1 receptor is also found in cortical blood vessels and in the glomerulus, specifically in mesangial cells and podocytes.[8] Taken together, these findings demonstrate that the kidney has all the required components for a fully functional local RAS.

The role of ACE in cardiovascular-related diseases is underscored by the therapeutic effectiveness of ACE inhibitors in treating several conditions, such as high blood pressure, heart failure, and halting the kidney damage associated with hypertension and diabetes.[9] However, these studies fail to determine the exact contribution of intrarenal versus systemic ACE during the progression of cardiovascular disease and have led to persistent questions about the relative physiologic importance of the systemic versus the local generation of Ang II within kidney. Furthermore, ACE is a dipeptidyl peptidase with two independent catalytic sites that can cleave a wide repertoire of substrates with distinct biological effects. Although the beneficial effects of ACE inhibitors were classically associated with the inhibition of Ang II formation, ACE can process other peptides including bradykinin, Ang-(1–7), and the anti-inflammatory tetrapeptide AcSDKP, among others. Thus, the exact contribution of Ang II-independent effects of ACE together with the clinical relevance of local versus systemic ACE to the progression of cardiovascular disease are a matter of continuous research. This review summarizes the recent advances in understanding the contribution of intrarenal ACE to different pathological conditions and provides insight into the many roles of ACE besides the well-known synthesis of Ang II.

ROLE OF RENAL ACE IN DISEASE

High blood pressure

Experimental and clinical evidence have demonstrated that the kidney plays a central role in blood pressure regulation.[10] Seminal studies by Dr. Guyton outlined the hypothesis in which the kidney rapidly increases urinary sodium excretion in response to elevations in blood

pressure, the so-called ‘pressure natriuresis’, reducing body fluid volume and returning blood pressure to normal. Defects in this renal excretory function were predicted to result in the development of hypertension.[11] Clinical evidence supporting an essential role of the kidney in hypertension came from studies showing that hypertensive patients transplanted with a kidney from normotensive donors normalized their blood pressure.[12] Further experimental data demonstrated that a kidney transplant from a hypertensive donor rodent caused hypertension in a recipient normotensive control.[13] The role of the intrarenal RAS in blood pressure regulation was demonstrated with elegant studies by Drs. Crowley and Coffman.[14] They showed that mice transplanted with kidneys from AT1 receptor knock-out donors were protected against Ang II-induced hypertension despite normal expression of AT1 receptors in all other tissues.[14] Indeed, the specific elimination of AT1A receptors from the kidney proximal tubular epithelium using a Cre-loxP technology attenuated hypertension despite fully preserving Ang II-dependent vasoconstrictor responses.[15] These studies were complemented by experiments showing that the proximal tubule is a source of intrarenal RAS components such as angiotensinogen and Ang II and they might play a key role in blood pressure regulation.[1] Even more important, studies in humans demonstrated that urinary angiotensinogen is increased in hypertensive patients.[16]

The contribution of intrarenal ACE to normal kidney development and hypertension has also been widely studied. Our laboratory has generated different genetically modified mouse models in which renal ACE was nearly or completely abolished while preserving ACE expression in other tissues. A mouse strain termed ACE 3/3 expresses ACE under the control of the albumin promoter. These mice display ACE expression predominantly in hepatocytes while renal ACE is roughly 10–15% of wildtype levels.[17] In ACE 10/10 mice, ACE expression is under the control of the c-fms promoter resulting in ACE only made by myelomonocytic cells while renal ACE levels are negligible.[18] Both ACE 3/3 and ACE 10/10 mice have normal circulating levels of ACE, normal basal blood pressure and renal development, and a preserved ability to concentrate urine despite no or minimal renal ACE expression. A completely different phenotype was observed in ACE 9/9 mice. Here, ACE is only expressed by renal tubular epithelial cells resulting in renal ACE levels equivalent to wild-type with almost undetectable ACE in plasma or extrarenal tissues. These mice have low blood pressure and impaired kidney development compatible with low perfusion pressure.[19] These studies suggested that systemic ACE, rather than intrarenal ACE, is essential to maintain basal blood pressure and normal kidney development. The sole expression of ACE in the kidney, in the absence of systemic ACE, fails to maintain the hemodynamic homeostasis.

Although intrarenal ACE does not contribute to basal blood pressure regulation and proper kidney development, it plays an important role in the establishment of different forms of hypertension. Using the same mouse models described above, our group evaluated the contribution of renal versus systemic ACE to different forms of experimental hypertension. In ACE 9/9 mice, where ACE is solely expressed in tubular cells, despite having low blood pressure and abnormal renal development, a chronic Ang I infusion increased kidney Ang II levels, enhanced the rate of urinary Ang II excretion, and resulted in hypertension. Contrarily, in ACE 10/10 mice, the absence of kidney ACE substantially blunted the hypertension induced by Ang II infusion or L-NAME.[20,21] Similarly, ACE 3/3 mice, in

which ACE was marginally expressed in the kidney, were protected from L-NAME-induced hypertension.[21] Further analysis using a model of salt sensitivity induced by renal injury revealed that mice lacking renal ACE expression did not develop hypertension in response to a high sodium intake despite having similar renal injury as wild-type controls.[22] Consistently, the absence of renal ACE, even in the presence of normal systemic ACE, was associated with no intrarenal Ang II accumulation, preserved glomerular filtration rate and lower activation of key sodium transporters and channels along the nephron such as Na^+/K^+ 2 Cl^- cotransporter isoform 2 (NKCC2), Na^+/Cl^- cotransporter (NCC) and epithelial Na^+ channel (ENaC). The reduction of these transporters promoted an enhanced natriuretic response, and consequently, the absence of blood pressure elevation in response to several hypertensive stimuli. Taken together, current data support the concept that systemic and renal ACE roles are non-redundant. While systemic ACE is related to basal blood pressure regulation and proper kidney development, renal ACE seems to be associated with the pathophysiology of hypertension.

ACE in the kidney is made by different cell types including podocytes, mesangial cells, endothelial cells, and in large amounts by tubular epithelium. The exact locus of renal ACE involved in hypertension was analyzed using an *in vivo* silencing RNA approach to generate a mouse model in which ACE was specifically removed from renal tubular epithelial cells while preserving its expression in all other renal and extrarenal locations, the it-ACE mice.[23] These mice were protected against the development of salt-sensitive hypertension in the context of renal inflammation showing, in unequivocal terms, that renal tubular ACE plays a pivotal role in hypertension. Further confirmation of these findings was obtained using the opposite mouse model in which renal ACE was only expressed in renal tubules while absent in all other renal cell types, the ACE 3/9 mice. These mice developed salt sensitivity similarly to wild-type mice.[23] Thus, although ACE is ubiquitously expressed in the body, these data indicate that tubular epithelial ACE and not ACE expression by renal endothelium, lung, brain, or plasma is obligatory for the induction of salt sensitive-hypertension during renal injury.

Diabetic kidney disease.

Both clinical and experimental data have widely demonstrated that ACE inhibition and AT1 receptor blockers protect against renal disease in both type 1 and type 2 diabetic patients. Indeed, these drugs are considered the most effective therapeutic approaches to slow down the progression of diabetic nephropathy even in normotensive patients.[24,25] However, whether the effect of ACE inhibitors is produced through the inhibition of the systemic or the intrarenal ACE remains unknown. The observation that whole kidney Ang II levels in diabetes can increase, decrease, or even remain unchanged during the progression of diabetic nephropathy,[26–32] suggests that the regulation of the renal RAS during diabetes might be more complicated than generally appreciated. The expression of renal ACE has been evaluated in several animal models of diabetic kidney disease.[33] Although most reports agree that total kidney ACE is decreased during diabetic nephropathy,[34–36] there is actually a redistribution of ACE in the diabetic kidney. In db/db mice, a model of type 2 diabetes and obesity, Ye and coworkers observed that the expression of ACE was greatly increased in glomerular endothelial cells while its expression in the brush border of the proximal tubule

was less intense compared to control mice. According to the authors, the overexpression of ACE in the glomerulus might lead to an excessive glomerular Ang II accumulation that predisposed to glomerular damage and albuminuria.[37] A similar ACE expression pattern was observed using streptozotocin-induced diabetes, a model of type 1 diabetes.[35,38] For example, Tikellis and co-workers observed higher glomerular ACE and lower tubular ACE expression levels 24 weeks after inducing diabetes with streptozotocin. This overexpression of glomerular ACE might result in elevated urine levels of ACE. Indeed, mice with streptozotocin-induced diabetes and humans with type 1 diabetes-associated kidney disease displayed increased urine concentrations of several RAS components including ACE.[39] On the other hand, recently published studies performed in Akita mice, an autosomal dominant model of spontaneous type 1 diabetes showed higher expression of ACE in tubular epithelial cells compared to wild-type.[40] In total, published work indicates that the renal ACE expression pattern is altered during diabetes resulting in changes of total kidney ACE.

An insight into the role of glomerular versus tubular ACE in the development of diabetic kidney disease was obtained by our group using two genetically modified mice previously described: the it-ACE mice, which make endothelial ACE but lack ACE expression by renal tubular epithelium, and ACE 3/9 mice, which lack endothelial ACE but only express renal ACE in tubular epithelial cells. The absence of endothelial ACE prevented glomerular hyperfiltration and reduced endothelial injury in diabetic ACE 3/9 mice. However, these mice developed tubular injury and albuminuria that were similar to what was observed in diabetic wild-type mice. In diabetic it-ACE mice, despite having hyperfiltration, the absence of renal tubular ACE greatly reduced tubulointerstitial injury and albuminuria compared with diabetic wild-type.[41] These findings demonstrate that endothelial ACE is a central regulator of the glomerular filtration rate while tubular ACE is a key player in the development of tubular injury and albuminuria. Since proximal tubules can reabsorb a substantial amount of filtered albumin, albuminuria reflects the balance between glomerular filtration and tubular uptake of albumin.[42–44] Eriguchi concluded that, during diabetic kidney disease, ACE expression in tubular epithelium upsets this balance and promotes albumin loss.[41]

Acute and chronic kidney disease.

Acute kidney injury (AKI) is a major cause of long-term chronic kidney disease.[45–48] In the majority of cases, the prerequisite for AKI is renal ischemia and reperfusion that induces oxidative stress, promotes inflammation and activates the RAS resulting in renal dysfunction.[49] There is a strong link between intrarenal ACE and AKI. In an ischemia/reperfusion-induced AKI model, increased renal ACE levels were associated with elevated intrarenal Ang II levels and injury markers such as interleukin 6 and TGF-β.[50] Further studies showed that captopril or enalapril treatment prevented renal parenchyma lesions in a model of ischemia reperfusion injury.[51] The physiologic actions of ACE in the development of AKI are also influenced by genetic variants that regulate its plasma and tissue levels.[52,53] These variants of the ACE gene, known as insertion/deletion (I/D) polymorphisms, have been associated with a vulnerability to develop AKI. Isbir and coworkers found a significant association between the ACE D–allele and increased risk of postoperative AKI after coronary artery bypass grafting.[54] Contrary to this, other groups found that the I/I genotype

is associated with an increased risk for AKI and the progression to end-stage renal disease.[55] Thus, current association studies are unable to provide definitive evidence linking ACE genetic variations to AKI.[56]

The intrarenal RAS was also shown to play an important role in the pathogenesis of chronic kidney disease (CKD), in large measure, thanks to experimental studies conducted in the 1980s.[57] CKD has been associated with activation of the intrarenal RAS as both ACE inhibitors and AT1 receptor blockers provide protection against progressive loss of renal function.[58–60] An inappropriate stimulation of the intrarenal ACE has been implicated in a variety of animal models of renal disease as an initial response to hypoperfusion and an important driver of disease progression. Studies in Sprague-Dawley rats exposed to chronic normobaric hypoxia showed increased ACE staining in proximal tubules.[61] Furthermore, renal levels of ACE were increased in other animal models of CKD such as the 5/6 nephrectomy and the 2-kidney, 1 clip-hypertension model highlighting the central role of intrarenal ACE in the occurrence of many forms of CKD.[62,63] To date, the use of ACE inhibitors and AT1 receptor blockers remain the cornerstone therapy for amelioration of albuminuria and renal disease progression. However, a recent study in adult kidney transplant recipients with proteinuria showed that ramipril treatment failed to significantly reduce serum creatinine, and the progression to end-stage renal disease or death compared to the placebo group.[64] Thus, although the concept of intrarenal RAS in renal disease has been well established, a number of issues still need to be resolved as current therapies are still inadequate. Defining the functional role of intrarenal ACE and the identification of additional components of the RAS are expected to offer new therapeutic perspectives for the treatment of cardiovascular and renal disease.

ANGIOTENSIN II-INDEPENDENT ROLES OF ACE

AcSDKP

One of the most intriguing aspects of ACE lies in its structure. ACE is composed of a single polypeptide that forms two similar but not identical domains, the C- and the N-domain. Both domains bind zinc and are catalytically active, but they have different biochemical properties and substrate preferences.[65] Besides Ang I, ACE can process a wide diversity of substrates such as bradykinin, and other small peptide hormones, including neurotensin, substance P, enkephalins, N-formyl-Met-Leu-Phe, N-acetyl Ser-Asp-Lys-Pro (AcSDKP) and Ang-(1–7).[65] However, the catalytic activity varies between each domain. For example, the K_{cat} for the conversion of Ang I into Ang II is three times higher for the C-domain compared to the N-domain.[66] Using animals with point mutations that inactivate either the C- or the N-domain, known as CKO and NKO mice respectively, it was demonstrated that under basal conditions most of the *in vivo* Ang II generation is mediated through the C-domain.[67] Although the N-domain is also capable of producing Ang II, it requires supraphysiological levels of renin and Ang I to reach normal Ang II concentration in the plasma.[67] The question that arises from these observations is why would ACE conserve the N-domain during evolution. The obvious answer is that the N-domain might mediate the conversion of other physiologically relevant peptides besides Ang I. In fact, there are peptides that are exclusively degraded by the N-domain such as Ang-(1–7) or the tetrapeptide AcSDKP. AcSDKP is an

immunomodulatory and pro-angiogenic peptide mainly released from its precursor thymosin β4 via enzymatic hydrolysis involving meprin-α and prolyl-oligopeptidase.[68] Substantial amount of research has demonstrated that treatment with AcSDKP has anti-fibrotic and anti-inflammatory properties in the heart, lung, brain, and kidneys.[68] For example, studies showed that AcSDKP treatment in Zucker obese rats fed a high salt diet prevented renal damage by reducing inflammation, fibrosis, and systolic blood pressure.[69] AcSDKP also ameliorated kidney disease in both type 1 and type 2 diabetic mice.[70] Because its degradation is mediated through the ACE N-domain, in NKO mice, the plasma concentration of AcSDKP is 7-fold higher and the urinary levels are 3-fold higher than wild-types.[41,71] Recently published studies showed that NKO mice made diabetic through streptozotocin have lower kidney injury and inflammation, improved renal function and an enhanced sodium excretory response when challenged with an acute sodium load compared to equally treated wild-type mice.[41] Further analysis revealed that the beneficial phenotype of NKO mice was mediated through the accumulation of AcSDKP and it was independent from Ang II variations and blood pressure regulation.[41]

Angiotensin-(1–7)

The heptapeptide Ang-(1–7) is also degraded by the ACE N-domain to form the inactive fragment Ang-(1–5). Seminal studies by Drs. Chappell and Ferrario demonstrated that the treatment with ACE inhibitors augment Ang-(1–7) levels both in the circulation and the kidney.[72,73] Ang-(1–7) is a biologically active peptide that has been described as a natural counterbalance to the physiological actions of Ang II within the RAS. In the kidney, Ang-(1–7) is mostly produced in the proximal tubule and typically reaches concentrations that are comparable to those observed for Ang II.[74] The balance between these two peptides is regulated through angiotensin-converting enzyme 2 (ACE2) which converts Ang II into Ang-(1–7).[75] It has been shown that Ang-(1–7) exerts renoprotective effects in several experimental settings of kidney disease, including hypertension, diabetic nephropathy, glomerulonephritis, tubulointerstitial fibrosis, pre-eclampsia, and acute kidney injury.[76] The G-coupled Mas receptor has been classically described as the main mediator of renal Ang-(1–7) effect as it is abundantly expressed in the kidney.[77] However, these findings have been challenged by Gaidarov and co-workers showing no clear interaction between Ang-(1–7) and the Mas receptor.[78]

Bradykinin

Bradykinin is degraded by both ACE domains. Indeed, the affinity of ACE is higher for bradykinin than for Ang I. A large body of evidence has demonstrated numerous cardiovascular benefits associated with bradykinin both at the systemic and renal levels.[79] Bradykinin has been shown to decrease blood pressure and, under normal conditions, it maintains the physiologic hemodynamic homeostasis by counterbalancing the deleterious effects of Ang II.[80] In line with these findings, mice lacking the bradykinin B2 receptor display salt sensitivity, significant renovascular resistance and decreased renal blood flow.[81] Indeed, studies performed by Dr. Danser's group suggest an interaction between bradykinin and Ang-(1–7). Authors proposed that the blood pressure-lowering effects of Ang-(1–7) appear to be largely bradykinin-dependent, and most likely reflect its capacity to potentiate bradykinin due to the fact that Ang-(1–7) might act as an ACE inhibitor.[82]

Both experimental and clinical approaches have shown that ACE inhibitor therapy not only reduces Ang II synthesis, but it is often associated with increased plasma and tissue levels of AcSDKP, Ang-(1–7) and bradykinin.[68,73,79] Thus, besides reducing Ang II synthesis, at least part of the beneficial cardiovascular and renal effects of ACE inhibitors might be due to the accumulation of these biologically active peptides. Along this line, although ACE inhibitor treatment may acutely lower circulating Ang II, clinical evidence demonstrated that, in a subset of patients chronically treated with ACE inhibitors, plasma Ang II and aldosterone concentrations returned to baseline levels.[83]

Immune function

Studies performed by our group in the last decade have broadened the current knowledge of ACE by demonstrating its role in several physiological processes related to immunity and metabolism. However, the ACE-related substrates and/or products involved in these processes have yet to be identified. One of the most fascinating effects of ACE is its ability to increase the immune effectiveness of myelomonocytic cells. Two mouse lines genetically modified to overexpress ACE in macrophages or neutrophils demonstrated an enhanced immune response that conferred increased resistance to melanoma, methicillin-resistant *Staphylococcus aureus*, and *Listeria monocytogenes* infections.[18,84,85] This somewhat agrees with a population based cohort study showing that chronic treatment with ACE inhibitors is associated with an increased risk of lung cancer.[86] Although the mechanism behind these observations is not known, recently published data revealed that ACE overexpression in myeloid cells increases oxidative metabolism and cellular ATP.[87] Using mass spectrometry and chemical analysis, ACE over expressing macrophages and neutrophils displayed increased cellular ATP and Krebs cycle intermediates including citrate, isocitrate, succinate, and malate. This might be part of a mechanistic explanation to the increased immune response demonstrated by these cells.[87] Even more important, the phenotype of ACE overexpressing cells depends on the ACE C-domain catalytic activity, but it is completely independent of Ang II.[87] Our group also investigated the role of macrophages overexpressing ACE in atherosclerosis.[88] For this, ApoE-knockout (KO) mice were bred with ACE 10/10 mice such that the ApoE-KO animals overexpressed ACE in macrophages. These mice were then subjected to the DOCA salt model. After 8 weeks of treatment there was significantly less atherosclerosis, reduced vascular wall inflammation and remodeling in mice over expressing ACE in macrophages compared to controls. This protective phenotype was largely because of an increased ability of these macrophages to resolve the inflammatory challenge of elevated lipids.[88] Whether renal ACE has any role in controlling the metabolism and the immune response in the kidney remains largely unexplored, but it represents a new area of research that will further expand our knowledge about the many roles of ACE in the kidney.

CONCLUDING REMARKS

Since its discovery by Dr. Leonard T. Skeggs Jr. in 1956,[89] ACE has been the target of extensive research. The observation that ACE is expressed in several tissues and cell types and the description of the so-called local RAS has further extended the complexity of this spectacular proteolytic system. When it comes to blood pressure regulation, the therapeutic

effectiveness of ACE inhibitors leaves no doubt about the role of ACE in hypertension. However, ACE is involved in several other renal diseases such as diabetic kidney disease, or acute kidney injury even when blood pressure is normal. Moreover, current research has demonstrated that ACE inhibition might involve more than just a reduction in Ang II synthesis. Other peptides such as AcSDKP, Ang-(1–7), bradykinin, or even peptides still unknown, might play a role in the beneficial effects of ACE pharmacological inhibition. Understanding the very complex functions of ACE in the kidney may confer a clinical advantage to design more specific, effective and safe drugs for treating hypertension and other renal diseases.

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Table 1 -

Description and characterization of mouse models with genetic changes to the ACE gene:

Mutation	Genotype	Description	Distribution of ACE	BP	Renal Development	Reference
Wild type	wt/wt	Two normal ACE alleles	Vascular endothelium, kidney, gut, brain, plasma, testis	Normal	Normal	
ACE 1	1/1	Null for all ACE	No ACE	Low	Medullar and papillary dysplasia	90 91