The ins and outs of angiotensin processing within the kidney

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The kidney is a key target for the diverse components of the renin-angiotensin-aldosterone system that include prorenin/renin, angiotensin II (ANG II), ANG-(2–8) (ANG III), ANG-(1–7), ANG-(3–8), ANG-(1–9), and aldosterone (2, 3, 6, 10). The kidney also comprises an intrinsic renin-angiotensin system (RAS) particularly within the proximal tubule epithelium capable of producing bioactive peptides to activate their respective receptors (R) in a paracrine or autocrine manner (2, 6, 10). Currently, the renal RAS can be functionally partitioned into at least two arms based on the distinct processing enzymes and receptors that comprise the ANG II-AT1 and the ANG-(1–7)-AT7/MasR axes (2, 3, 7, 10, 14). In general, these two pathways exhibit opposing effects in the kidney and may antagonize the actions of one another (2, 3). Within the tubular system of the kidney, ANG II stimulates the AT1 receptor to activate oxidative stress, and stimulates cellular phosphatases to inhibit mitogen-activated kinase pathways such as chymase to form ANG II. An ANG-(1–7) endopeptidase (TOP) to process ANG I to ANG-(1–7) or ACE-independent (non-ACE) pathways may markedly alter the functional signature of the RAS (2). ACE2 efficiently metabolizes ANG II to ANG-(1–7) and may markedly alter the functional signature of the RAS (2). ACE2 is a monocarboxypeptidase that does not continue to metabolize ANG-(1–7) due to the COOH-terminal proline; however, ACE hydrolyzes the Ile5-His6 bond of ANG-(1–7) to form ANG-(1–5) (2). ACE inhibitors increase circulating levels of ANG-(1–7) by preventing the rapid metabolism of the peptide, as well as shifting the processing of ANG I to ANG-(1–7) by the endopeptidase nephrilysin (NEP) (2, 13, 14). All three enzymes are classified as metalloproteinases.

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with membrane-anchoring domains that orient their active sites on the extracellular cell surface to process substrates within the glomerular filtrate, interstitial fluid, cerebrospinal fluid (CSF), or the blood (Fig. 1). These peptidases comprise the extracellular pathway for the formation of ANG II and ANG-(1–7) to subsequently bind to AT₁R or AT₂R on the cell surface and activate various signaling pathways (Fig. 1). ACE, ACE2, and NEP also contribute to the metabolism of both peptides to either inactive forms or, in the case of ANG-(1–7), a metabolite that functionally opposes the ANG II-AT₁R axis (2, 13).

In addition to the extracellular processing of peptides, there is compelling evidence for the intracellular expression of both ANG II and ANG-(1–7) in the kidney and other tissues (1–8). The tissue expression of angiotensins may indeed lead to their subsequent release into the extracellular space; however, evidence of intracellular AT₁R, AT₂R, and AT₇R may portend for their systemic distribution, as has been noted in the brain (3). Although additional characterization of the ANG-(1–7) endopeptidase regarding the enzyme’s specificity and regulation is warranted, therapeutic approaches that target both intracellular and extracellular pathways to enhance the “ANG-(1–7) to ANG II tone” that include reduced metabolism of ANG-(1–7) may provide additional renoprotection in diabetes, hypertension, and fetal programming events.

REFERENCES

Perspectives and Significance
Functional partitioning of the RAS is facilitated in part through multiple peptidase pathways that occur downstream from the initial processing of angiotensinogen by renin and likely reflects their discrete cellular localization and relative affinities for peptides. Fetal glucocorticoid exposure is one example of in utero programming events that remarkably influence the RAS in adults through altered expression of distinct peptidase components in the kidney, circulation, and brain (3). Although additional characterization of the ANG-(1–7) endopeptidase regarding the enzyme’s specificity and regulation is warranted, therapeutic approaches that target both intracellular and extracellular pathways to enhance the “ANG-(1–7) to ANG II tone” that include reduced metabolism of ANG-(1–7) may provide additional renoprotection in diabetes, hypertension, and fetal programming events.

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DISCLOSURES
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AUTHOR CONTRIBUTIONS
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