Reciprocal effect of angiotensin II in collecting duct renin synthesis

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ACTIVATION OF THE RENIN-ANGIOTENSIN system (RAS) plays a central role in the regulation of hypertension and sodium homeostasis. Angiotensin II (ANG II) is the most potent biologically active peptide that possesses pleiotropic functions to increase renal vascular resistance, cardiac contractility, aldosterone production, and enhanced sodium absorption in renal tubules, leading to elevated arterial blood pressure. Apart from the classic RAS pathway, there is growing evidence that there is a locally activated RAS pathway in the kidney which may, for instance, contribute to hypertension and chronic kidney disease (2, 6). The concept of intrarenal RAS evolved, in part, with the discovery of unexpectedly high levels of ANG II in the kidney, which could not simply be explained from equilibrating effects of circulating ANG II in plasma (9). In addition, various RAS components were found in specific nephron segments (12), suggesting local generation of ANG II which might be regulated differently or independently of classic RAS-mediated ANG II production (6). Thus current evidence indicates that the kidney has all of the RAS components that are necessary to generate ANG II and can do so independently of the classic RAS system. It has been speculated that persistent intrarenal RAS activation may lead to inappropriate salt retention and lead to elevated blood pressure.

In the classic RAS pathway, renin is secreted from the juxtaglomerular (JG) cells and activates the RAS cascade by cleaving angiotensinogen that is made and released by the liver, with subsequent generation of ANG II through the angiotensin-converting enzyme. However, renin is also seen in all renal nephron segments, except the loop of Henle (12). Renin, synthesized in the collecting duct (CD), may amplify intrarenal RAS activity and independently play a role in regulating blood pressure (11). For example, CD renin secreted into the distal lumen can cleave angiotensinogen released from proximal tubules and subsequently increase ANG II (8). This increase in intratubular ANG II can directly stimulate the epithelial sodium channel (ENaC) to reabsorb sodium, which may lead to inappropriate salt retention (14). In addition, an increase in ANG II contributes to a positive feedback cycle to further stimulate CD renin synthesis that perpetuates intrarenal RAS activation (10, 11). Regulation of both the classic and intrarenal RAS pathways include cAMP-dependent renin gene transcription, while activation of protein kinase C (PKC)/Ca2+ pathways inhibits renin synthesis in JG cells (3). ANG II is an important stimulus for renin synthesis in both JG cells and in CDs but they have distinct mechanisms of action. For example, stimulating JG cells with ANG II inhibits renin secretion (5), but the action of ANG II in CD renin production appears to have an opposite effect (10). The exact mechanism for this reciprocal ANG II-mediated CD renin upregulation has not been fully established, but it appears to involve the PKC pathway (4a).

In the current article, Gonzalez and coworkers (4) further characterize potential mechanisms for ANG II regulation of renin expression in the CD. As they previously described (4a), they confirmed that ANG II stimulates renin expression in a PKC-dependent manner but also demonstrated that subsequent activation of protein kinase A (PKA) and adenylyl cyclase 6 (AC6) are involved in renin synthesis. This is contradictory to studies which have shown that increased PKC/Ca2+ suppresses AC6 activity (1). However, at least in M-1 CD cells, treatment with ANG II appears to upregulate cAMP/CREB phosphorylation and stimulates renin synthesis in a PKC-dependent manner, since a PKC inhibitor (calphostin C) and PKA inhibitor (H89) both attenuated this signaling pathway. The PKC inhibitor not only blunted ANG II-mediated cAMP activation but similarly inhibited forskolin (increased cAMP production), or a phosphodiesterase inhibitor (suppressed cAMP degradation) induced increased cAMP. In addition, knockdown of PKCα (dominant isoform in the CD) and possibly AC6 in M-1 cells appears to attenuate ANG II-mediated upregulation of renin. These results convincingly show the involvement of PKC (likely PKCα) in ANG II-mediated CREB/cAMP activation. Although previously demonstrated in inner medullary CD cell lines (4a), it is not clear from this study, whether stimulating M1 cells with ANG II directly increased intracellular Ca2+ and thus led to activation of the PKCα enzyme. Moreover, the mechanism of how PKC activation subsequently upregulated the cAMP/CREB in the CD remains unknown.

Nonetheless, ANG II-mediated signaling via PKC and the CREB phosphorylation/cAMP pathway in the CD is clearly distinct from the response in JG cells. There remains some uncertainty regarding the issue that increased PKC/Ca2+ suppresses AC6 activity in other cell types (1). This apparent contradiction should be addressed in future studies. One unique aspect of the CD is that it helps to control homeostasis by regulating both salt and water reabsorption. In this unique cell type, ANG II could conceivably elevate cAMP, which would stimulate vasopressin signaling pathways and lead to aquaporin-2-induced water transport. ANG II directly stimulates ENaC (7, 14), suggesting that high ANG II would lead to coordinated increased salt and water reabsorption. This would make sense, since ANG II levels are elevated during conditions such as hemorrhage or volume depletion. In addition, these findings may have an implication in polycystic kidney disease. This is because intrarenal RAS and vasopressin/cAMP are both upregulated in this disease and identified as potential therapeutic targets, respectively (13), but whether these two components have mutual interactions are yet largely unknown.

GRANTS

T. Saigusa is supported by grants from National Institute of Diabetes and Digestive and Kidney Diseases (K08DK106465) and the Dialysis Clinic, Inc. (Nashville, TN).
DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: T.S. drafted manuscript; T.S. edited and revised manuscript; T.S. approved final version of manuscript.

REFERENCES