Role of renal tissue angiotensin II in proximal tubule function

William J. Welch
Department of Medicine, Georgetown University, Washington, District of Columbia

THE RENIN-ANGIOTENSIN SYSTEM (RAS) in the kidney has been studied extensively, both in its regulation of systemic function and within the kidney. Evidence that the components of the RAS are produced and function locally suggests that it can also exert paracrine control of renal function. The rate-limiting step for the formation of the biologically active octapeptide angiotensin II (ANG II) is the enzymatic conversion of angiotensin I by angiotensin-converting enzyme (ACE), which occurs primarily in the systemic circulation. However, ACE has been localized in the kidney, including the proximal tubule (PT) (1), suggesting intrarenal production and action of the RAS. ANG II produced in the PT could have both tubular and vascular consequences, influencing solute and fluid reabsorption and altering flow to the loop of Henle, thus affecting tubuloglomerular feedback (TGF) control of afferent arteriole resistance. To distinguish the systemic vs. the PT actions of ANG II, in this issue of American Journal of Physiology-Renal Physiology Hashimoto et al. (7) have used a tissue-specific, gene-deficient mouse to study the effects of the RAS in the PT. ACE has been selectively deleted from all tissues in a genetically engineered mouse, the ACE 2/2 mouse. However, the accompanying low blood pressure in this strain complicates renal functional studies. This issue has been addressed by the generation of a second ACE-deficient mouse (ACE 1/3), in which tissue ACE is deleted but ACE is selectively expressed in the liver (5). This unique model is able to maintain sufficient plasma levels of ACE and subsequently normal blood pressure. By using this creative strategy, renal function can be studied during the absence of renal ACE, with and without normal renal perfusion pressure.

Part of the rationale of this study was, in fact, to determine whether the absence of tissue ANG II, particularly in the PT, led to chronic loss of fluid volume and the observed hypertension in this ACE-deficient mouse. However, there were no differences in PT absorption in both ACE knockout mice, suggesting that the hypotension is not due to volume depletion associated with loss of PT function.

These experiments assessed single-nephron function by renal micropuncture methods. Free-flow collections were made in the late PT to characterize absorption and, in separate mice, late PTs were perfused to stimulate the macula densa along with the simultaneous measurement of proximal stop-flow pressure to estimate TGF. These classic in vivo techniques provide the most direct analyses of renal segmental function and remain state-of-the-art. The execution of these methods in mice is technically more difficult than in the rat, which reflects the paucity of reports in mice. This is remarkable considering the number of genetic models targeting renal function and the growth of mouse physiology. However, the information provided in this study could not have been obtained in vivo without the two specialized approaches to this problem: genetic engineering and renal micropuncture. This study is an example of the continuing value of micropuncture in understanding single-nephron function, especially in new genetically engineered models.

The novel information gained in genetically altered mice must be balanced by concerns of developmental compensation. Some of those concerns are demonstrated in this study as well. TGF was absent in the ACE 1/3 strain, yet GFR was not different from that in wild-type control mice. This is the fourth null mouse model in which basal TGF is absent and the GFR is normal: angiotensin type 1 receptors (4, 8); adenosine type 1 receptors (2, 6, 9); 5’-ecto-nucleotidase (3); and ACE (10). In each study, the relative roles of these systems have been reasonably assigned, but the uniformity of effects on TGF is surprising. These multiple observations may point to the redundancy of the control of GFR, since several genes apparently regulate TGF, but GFR is maintained regardless of the loss of each. It may also demonstrate the complex interaction of ANG II acting via the angiotensin type 1 receptor and adenosine acting on the adenosine type 1 receptor in the control of TGF. Alternatively, the regulatory role of TGF during the chronic loss of key hormonal elements may be diminished. Additional studies in tissue-specific gene-deletion models will be useful in addressing this dilemma.

This novel mouse model of tissue ACE deletion with the maintenance of blood pressure should be valuable in future studies on understanding the function of renal epithelial ANG II. The role of ANG II generated in the PT and acting downstream on AT receptors, specifically in the macula densa, may also be examined in this model. This study by Hashimoto et al. (7) provides a significant advancement in understanding the intrarenal effects of the RAS.

REFERENCES


