Alternative renin regulatory pathways and the NKCC1 isoform

William H. Beierwaltes
Hypertension and Vascular Research Division, Henry Ford Hospital and Health Sciences Center, Detroit, Michigan

THE MACULA DENSA IS ONE OF the classic regulatory pathways that control the release of renin from the juxtaglomerular cells (11). It senses the distal luminal NaCl concentration in the thick ascending limb and sends a signal to increase renin secretion in response to sustained decreases in distal NaCl delivery. In 1968–1969, shortly after the development and availability of loop diuretics, investigators began reporting their ability to stimulate renin secretion in humans (10), rats (1), rabbits (9), and dogs (13). It was generally thought that the diuretic-induced diuresis resulted in decreased plasma volume and therefore stimulation of the renal baroreceptor and sympathetic nervous system, and that prolonged natriuresis would ultimately lead to stimulation of renin secretion by the juxtaglomerular (JG) cells (7). We now appreciate that these diuretics act through inhibition of the (furosemide-sensitive) Na\(^+-\)K\(^+-\)2Cl\(^-\) cotransporter (NKCC2) in the macula densa (11), likely resulting in activation of a cascade that involves stimulation of cyclooxygenase-2 (5) in the macula densa, resulting in the formation of PGE\(_2\), which interacts with the adjacent JG cells (12) to stimulate adenylate cyclase, and formation of the potent second messenger for renin, cAMP. Each of these components seems to be discretely located within this pathway, including the unique expression of NKCC2 within the apical membrane of the thick ascending limb and macula densa (14). Thus the anatomic localization of the NCC2 isoform to the macula densa leads predictably to the dogma that it is solely responsible for initiating the cascade. However, as the study by Castrop et al. (2) suggests, things are not always as simple as we would like to think. While the NKCC2 isoform is located in the macula densa, loop diuretics are not selective enough to discriminate between the two isoforms of the cotransporter. Thus these authors decided to examine the possible role of the NKCC1 isoform as a partial mediator of the renin response to loop diuretics. In the absence of isoform-selective drugs, the development of an NKCC1 knockout mouse (3, 8) provided a unique opportunity to test their novel hypothesis. The NKCC1 isoform of this member of the cation cotransporter superfamily is widely distributed in secretory epithelia and generally thought to be involved in controlling cellular volume, often coordinating with other cellular ionic pumps, as well as chloride excretion (4). In the kidney, the NKCC1 isoform has been reported to exist in cortical locations near the JG cells, including the afferent arterioles and the glomerular and extraglomerular mesangium (3), where it could easily respond to changes in plasma or even distal tubular salt composition.

Castrop et al. (2) report that basal circulating renin levels were increased in the NKCC1 knockouts, as were renin mRNA and the percentage of microdissected afferent arterioles that stained for renin or renin recruitment. Furosemide inhibition of NKCC cotransport in vivo stimulated renin in both strains of mice; however, in a primary culture of isolated JG cells, only those from wild-type mice (with NKCC1 intact) showed a 10% increase in membrane capacitance, and therefore, by implication, a stimulus for renin in response to furosemide could be mediated by NKCC1 on the JG cells (something not previously demonstrated). With the chronic absence of NKCC1 in the knockouts, every parameter of renin (plasma renin concentration, mRNA, histological distribution, in vitro stimulation) seemed to be exaggerated, suggesting that in the knockouts some tonic suppression of renin had been deleted. Thus while the authors’ initial hypothesis that NKCC1 could also mediate the classic macula densa pathway was not supported, they do reveal an important modulating effect of this transporter on the process of renin regulation. Their observations represent a new and unexpected pathway that may influence renin secretion.

As exciting and provocative as this observation is, some cautions are in order. First, the remarkable technology of gene deletion is not without its limitations. These mice often adapt by developing redundant or back-up systems to compensate for the lost expression. Importantly, systemic blood pressure in NKCC1 knockouts may be lower (8), which could lead to chronic stimulation of renin through the renal baroreceptor, independently of a direct effect of NKCC1 on the JG cell. This provides a certain irony, as it would support the original hypothesis of the 1960s that the effect of loop diuretics on renin was secondary to some degree of volume depletion influencing the renal baroreceptor (7). As pointed out by Castrop et al. (2), “these in vivo experiments do not permit a clear distinction between direct and indirect consequences of the NKCC1 null mutation on the renin-angiotensin system.” However, the combination of data from these in vivo studies and their primary cultures of isolated JG cells from both wild-type and knockout mice supports their conclusion that there may be a tonic influence of the cotransporter. Ultimately, the NKCC1 isoform is rather ubiquitous, and thus its deletion may have important consequences, perhaps even uncovering various aspects of its involvement in renal function including chloride excretion (3), renal vascular resistance, and renal perfusion (8). The final answers to the question of how NKCC1 modulates renal function and specifically renin secretion will probably involve various direct and indirect signals under different conditions. The resolution of this question will unfold because of the novel model, not even dreamed of in the 1960s when this journey began, and the unorthodox thinking of these investigators who are willing to test ideas that confront and challenge convention.

REFERENCES