Complex vascular bundles, thick ascending limbs, and aquaporins: wringing out the outer medulla

Thomas L. Pallone
Department of Medicine, Division of Nephrology, University of Maryland School of Medicine, Baltimore, Maryland
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Despite its small mass, the renal inner medulla plays a pivotal role in homeostasis. It adjusts the solute, water, and proton content of the final urine to match the excretory needs of the organism. The large glomerular filtrate is reabsorbed by highflow, low-gradient processing in the proximal nephron along with key transport steps that occur within the outer medulla. In combination, they protect the inner medulla from the need to process large tubular and vascular volume flows. In a recent issue of the American Journal of Physiology-Renal Physiology, Ren and colleagues (9) provide important insights into the anatomic relationships that underlie the ability of the outer medulla to participate in that scheme.

Hemisection of the kidney reveals cortical, outer medullary, and inner medullary zonation. The outer medulla is subdivided into the outer stripe and inner stripe. The inner stripe is further divided into vascular bundles and the interbundle region (1, 3, 8). Counterflow of blood epitomizes vascular bundle function; ascending vasa recta (AVR) lie adjacent to descending vasa recta (DVR) to accommodate efficient exchange of solutes and water between them. The “simple” vascular bundle exemplified by rabbit and humans contains only DVR and AVR. The “complex” vascular bundle of highly concentrating rodents incorporates descending thin limbs of short-looped nephrons to a degree that varies with individual species. In mice, descending limbs of short loops migrate within vascular bundles and lie adjacent to peripheral vasa recta. DVR endothelia and red blood cells (RBCs) express aquaporin (AQP)-1 water channels and urea transporter (UT)-B so that their equilibration occurs by a combination of solute influx and solute-free water removal (6, 7). DVR and AVR are not simply diffusive countercurrent exchangers. AVR shunt any water osmotically withdrawn across DVR endothelia back to the cortex. In all species, AQP-1-expressing descending thin limbs of long-looped nephrons and AQP-2-expressing collecting ducts are excluded to the interbundle region.

Ren and colleagues (9) generated three-dimensional reconstructions of tubules and vessels of the murine outer medulla by digitizing serial sections and tracing the structures from the midlevel of the inner stripe toward the cortex and inner medulla. Proper identification was assured by noting the origins and terminations of thin-walled tubules and vessels. In addition, immunostaining for AQP-1 was performed to localize its expression by DVR endothelia and descending limbs of long-looped nephrons. It is noteworthy that AQP-1-expressing structures in vascular bundles (DVR and RBCs) and the interbundle region (i.e., thin descending limbs of long loops) lie near thick ascending limbs. They found that thick ascending limbs of long-looped nephrons surround the vascular bundle at its border and sometimes migrate into the vascular bundle periphery. Other features were also confirmed by the investigators. DVR arise solely from juxtamedullary efferent arterioles. Periglomerular origins of DVR were not found. DVR in the vascular bundle center perfuse the inner medulla, whereas those on the periphery give rise to the capillary plexus of the interbundle region. All AVR from the inner medulla return to the cortex via vascular bundles, and AVR do not form by coalescence of the interbundle capillary plexus. An effective summary of their findings is shown in Fig. 9 of their article (9). What are the physiological correlates of these tortured tubular-vascular relationships?

AVR and the interbundle capillary plexus have fenestrated endothelia. Measurements of their transport characteristics have been few and none, respectively. AVR show high diffusive permeability to hydrophilic solutes and high hydraulic conductivity to water (5, 7). Thus, slight elevations of interstitial pressure should drive convective water flux and, by solvent drag, hydrophilic solutes into the AVR lumen unopposed by molecular sieving. The same reasoning applies to the interbundle capillary plexus. An obvious difference between AVR and the interbundle plexus is that the former engages in countercurrent transport, whereas the latter, due to spatially chaotic anastomoses, cannot. In any case, both AVR and the interbundle capillary plexus provide low-resistance conduits for outer medullary reabsorbate to be returned to the cortex and systemic circulation without presenting it to the inner medulla.

It is reasonable to surmise that reabsorption of NaCl by thick ascending limbs both dilutes its lumen and generates a locally hypertonic interstitium so that some combination of water reabsorption and/or NaCl secretion may be induced in neighboring structures. Stated another way, NaCl can diffuse down its gradient into adjacent lumens and/or become diluted by driving osmotic water efflux from neighbors that express AQP-1s. Within vascular bundles, DVR endothelia and RBCs express AQP-1, so that vicinal deposition of hypertonic NaCl, whether by active transport (from thick ascending limbs) or diffusive efflux (from AVR), may concentrate DVR contents en route to the inner medulla. DVR are variably NaCl permeable (7), so that some of the load of NaCl from the thick ascending limbs might well diffuse into the DVR lumen even as water efflux concomitantly occurs across endothelial AQP-1. Hence, combined diffusive NaCl influx and molecular sieving by AQP-1 concentrates DVR plasma and reduces vascular flow to the inner medulla. Possibly, this coils an energetic spring to prepare for the final removal of water from inner medullary collecting duct. Outside vascular bundles in the interbundle region, the deposition of NaCl near descending thin limbs of long looped nephrons by thick ascending limbs favors the osmotic removal of water, again across AQP-1, hence reducing...
fluid delivery by long-looped thin descending limbs to the inner medulla. The hypertonic removal of water across AQP-2 in outer medullary collecting duct achieves a similar end (4). Taken together, juxtaposition of thick ascending limbs and AQP-expressing structures in the outer medulla probably serves to remove water and reduce overall volume delivery to the inner medulla. “Wringing out” the luminal flow of all descending structures prepares for the maximization of interstitial osmolality and final adjustments of inner medullary collecting duct urine.

Another plausible purpose of thick ascending limb-DVR juxtaposition might be to accommodate the diffusion of paracrine signaling molecules (7). For example, the generation of nitric oxide by endothelia might inhibit Na+/H+ reabsorption to favor “pressure natriuresis” and decrease O2 consumption by thick ascending limbs. Conversely, paracrine vasodilators from thick ascending limbs may dilate DVR to increase O2 delivery. Such adaptations may offset the medullary hypoxia that inescapably arises from countercurrent exchange.

Finally, not to be neglected, urea is transported by UT-A and UT-B carriers (2, 10). As with AQP-1, UT-B localizes to DVR endothelia and RBCs. Hence, in the vascular bundle center, urea can readily recycle to the inner medulla by countercurrent exchange. On the vascular bundle periphery, facilitated diffusion of urea from AVR into descending thin limbs of short nephrons via UT-A2 might compete with vascular exchange to partially recycle urea to the medulla via the distal nephron and collecting duct. Conversely, if active secretion of urea occurs in pars recta, an outwardly directed urea gradient might favor subsequent efflux (10) whereupon urea could recycle to the inner medulla via DVR and RBCs.

Nearly 400 years after the discovery of the renal corpuscle by Marcello Malphigi and 150 years after the definition of the loop by Jacob Henle, we revisit microanatomy (8, 9) so that highly resolved spatial definitions of tubular-vascular relationships can combine with details of molecular physiology and mathematical modeling to advance our understanding of the kidney. We may soon be able to explain to our children how the inner medulla concentrates urine!

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