Coping with nephron loss:

Transport at a price

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Running title: Transport at a price

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The adaptive response to unilateral nephrectomy is hypertrophy and enhanced function within the remaining kidney. This basic observation has been known for over a century, and has attracted investigative tools of every era to delineate the specific changes in mass and function, and to try to identify the signals that drive this process. By the end of the micropuncture era, we knew that hypertrophy began promptly after the reduction in renal mass, that blood flow and glomerular filtration increased in the remaining kidney (with proportionally greater blood flow), and that tubules were larger and transported more, both proximally and distally (4). Translational significance of these observations was keenly appreciated at the start of the transplantation era, to the apparent benefit of kidney donors (8). The plot thickens with the realization that nephron loss also occurs on a microscopic scale with forms of nephritis or tubule injury, and that remaining nephrons hypertrophy, with both enhanced filtration and tubule function (5). Unfortunately, in many if not most cases, there is limited survival for these remaining nephrons, and renal failure progresses even when the initial insult has long passed. In this context, a “chronic hypoxia hypothesis” emerged, in which increased glomerular filtration leads to increased tubular work, exacerbating local medullary hypoxia, thus producing local scarring and further nephron damage (1). This view has attracted attention of those interested in energy sensing mechanisms within the kidney (3), although testing of the hypoxia hypothesis is experimentally challenging, if not intractable. Nevertheless, the scheme has stoked fears within the transplant community, that the enhanced senescence that is recognized at the nephron level, might also be taking place at the whole kidney level in the donor population, albeit at a slower time scale.
Against this background, Layton et al. (6) provide a mathematical model of tubular function and oxygen utilization within the hypertrophied kidney. The work starts from a comprehensive simulation of rat nephrons (7), and then incorporates a variety of anatomical and functional observations to inform modification of tubular dimensions and transporter densities. Transport by this model kidney is shown especially well in their figure 6, which displays cumulative nephron flows of volume, Na⁺, K⁺, and Cl⁻, in relation to baseline two-kidney flows of these substances. As a consequence of glomerulotubular balance, initial and end-proximal tubule flows are in the same proportion as baseline. In the absence of flow-dependent transport in the loop of Henle and distal convoluted tubule, Na⁺ and Cl⁻ reabsorptive fluxes there do not ramp up with delivery, so that the collecting ducts receive what had been baseline flows. In this model, connecting segment K⁺ secretion is not especially susceptible to increased Na⁺ delivery, so that collecting duct K⁺ delivery is well below baseline. However, fewer collecting ducts receive the same fluid flow as baseline, producing faster fluid velocity, and this reduces medullary K⁺ reabsorption, so that K⁺ excretion is also back to baseline. Excretion rates of model and baseline appear in their table 3, and the congruence is good, except for titratable acid. Complementing segmental Na⁺ transport rates, the authors compute local oxygen consumption, and find that with their predicted pattern of early and late nephron transport, there is little change in overall metabolic efficiency of the hypertrophied kidney, i.e. the ratio of oxygen utilization to Na⁺ reabsorption is maintained.

From the perspective of modeling kidney function, this work of Layton et al. (6) provides a portal from which one may go on to examine the hypoxia hypothesis of nephron loss. One important detail of this model, beyond the rescaled tubules, is the selection of boundary conditions (systemic solute concentrations) that reflect the azotemia and
acidosis of renal insufficiency. In this paper, however, the authors were reluctant to represent the altered hormonal signals commonly encountered in renal clinic, i.e. elevations of parathyroid hormone (PTH), aldosterone, and natriuretic peptide. It is likely that inclusion of high PTH will restore titratable acid excretion to baseline. More importantly, the present model computes only oxygen utilization requirements, and fineses the issue of oxygen delivery and diffusion between vessels and tubules; specifically the hypoxia of the “chronic hypoxia” hypothesis remains to be addressed. Layton and Edwards and their coworkers are sensitive to this issue, and have used a medullary model to estimate baseline medullary oxygen tension (2). Furthermore, their collaborators have provided a secure view of vascular and tubular architecture (9), although their measurements have not yet extended to the distortions, which accompany the scarring of chronic renal disease. Expansion of this model to address medullary oxygen supply to hypertrophied tubules will immediately bump up against the experimental reality of how little is known about the magnitude of medullary blood flow in the conditions considered here. Plausible arguments can be made for either increases or decreases in local pO2. Nevertheless, because medullary oxygen is in limited supply, it does make sense that the thick ascending limb does not show the load-dependent increases in NaCl reabsorption that we see in proximal tubules of the hypertrophied kidney. It is encouraging to see these workers take up the task of simulating kidney metabolism in the context of a comprehensive model of transport. As the calculations mature, one hopes that they may motivate experimental investigation into an hypothesis of immense translational significance.

Acknowledgement

This investigation was supported by Public Health Service Grant R01-DK-29857 from
References


