A radical approach to balancing the tides of tubular flow

Paul M. O'Connor
Department of Physiology, Georgia Regents University, Augusta, Georgia

HOMER SMITH POSTULATED the modern day glomerulus to have evolved as a mechanism to rapidly remove water from the body (13). Smith describes the evolution of the mammalian glomerulus in terms of its function as a high-pressure filter, powered by the beating heart, that separates water from other constituents of the plasma, chiefly plasma proteins and cells (13). The extreme pressures needed to efficiently separate water from plasma electrolytes, however (essentially reverse osmosis), are many orders of magnitude greater that what can be achieved by the heart. Therefore, it is postulated that the tubular nephron evolved side-by-side with the glomerulus to reabsorb almost all of the electrolytes that could not be efficiently separated from water during filtration (13). Our kidneys match electrolyte reabsorption closely to glomerular filtration rate, only allowing a small fraction (equivalent of the net addition of these added to the body each day) to pass into the urine. Reabsorption of these critical electrolytes is a monumental task that, if not tightly regulated, would result in fluid and electrolyte disorders and/or disturbances in pH.

Tubular luminal flow in the renal nephron is not constant. Luminal flow rate varies acutely in response to changes in glomerular hemodynamics, peristalsis of the renal pelvis, and/or changes in upstream fluid reabsorption. Furthermore, chronic increases in luminal flow are observed in disease states including hypertension and diabetes. Aligning with the role of the tubular nephron to prevent wasting of filtered electrolytes, increases in luminal flow are associated with enhanced Na reabsorption at major reabsorptive sites along the nephron (3, 4, 11). Given the potential for disturbances in such pathways to result in fluid and electrolyte disorders, it is important to understand the cellular mechanisms through which individual nephron segments “sense” changes in flow and “respond” appropriately by altering transport rates.

In an issue of the American Journal of Physiology-Renal Physiology, Hong and Garvin (5) describe a novel mechanism through which Na+/H+ exchanger 3 (NHE3) activity in the thick ascending limb of the loop of Henle is matched to tubular flow rate. Under normal conditions, the thick ascending limb is responsible for ~25–30% of the reabsorption of filtered Na. This segment of the nephron is also responsible for producing the hypertonic NaCl gradient in the renal medulla, which is critical for the formation of concentrated urine. Na reabsorption in the thick ascending limb occurs by both trans- and para-cellular pathways, with the major apical membrane transporters responsible for trans-cellular uptake of Na being Na-K-Cl cotransporter 2 (NKCC2) and NHE3. In addition to the uptake of Na, NHE3 is also involved in the reabsorption of filtered bicarbonate which occurs secondary to the movement of protons into the luminal fluid in exchange for Na. Increasing luminal flow rates has previously been observed to stimulate the formation of the free radical superoxide (O2−) in isolated thick ascending limb (1, 6). While Garvin and colleagues (8, 9) demonstrated that endogenous O2− acts on a number of key transporters in the thick ascending limb to promote Na reabsorption, it was unclear whether endogenous O2− levels, stimulated by flow, were capable of activating Na transport and thereby matching reabsorption to tubular flow. The current manuscript by Hong and Garvin addresses this issue and is an important step toward understanding flow-regulated NaHCO3 reabsorption in the thick ascending limb, as it demonstrates for the first time that endogenous levels of O2−, stimulated by physiologically relevant increases in luminal flow rate, are capable of activating NHE3 activity via PKCα/β1(5).

Identification of this regulatory pathway is potentially important in our understanding of the pathogenesis of kidney disease. Garvin and colleagues previously identified the NADPH oxidase isoform NOX4 as the source of flow-stimulated O2− in thick ascending limb (7), and renal medullary oxidative stress attributed to augmented NADPH oxidase activity is associated with the development of hypertension in rats (2). While it has been proposed that hemodynamic changes are responsible for the development of hypertension in response to elevated medullary reactive oxygen species (ROS) production (2), the current study by Hong and Garvin suggests that enhanced tubular transport is likely to occur in such states. In addition to activation of Na and bicarbonate reabsorption by NHE3, O2− is also likely to activate NKCC2 in the thick ascending limb (8), further enhancing NaCl reabsorption by this segment. It is easy to speculate that such mechanisms may be important in the development of disease following high-salt feeding where tubular flow rates are increased, particularly in models susceptible to the development of renal injury and hypertension, such as the Dahl salt-sensitive rat. As the final regulation of renal NaCl excretion is thought to occur primarily in medullary segments of the nephron, whether flow-stimulated increases in tubular transport in the thick ascending limb alone are capable of mediating the development of hypertension remains unclear. Dysregulation of these pathways could also potentially promote medullary hypoxia, secondary to the increased demand for oxygen that accompanies greater tubular reabsorption of Na (12). This outcome would be consistent with the relative medullary hypoxia observed in some patients (14). Further research is required to determine the impact of these pathways toward the development of disease.

A major question arising from this work is “how the thick ascending limb senses changes in flow and respond by increasing O2− production?”. The exact cellular localization of the NADPH isoforms responsible for flow-mediated O2− production within thick ascending limbs remains unclear, although previous studies utilizing dihydroethidium to assess the rate of O2− production in response to changes in flow suggest that much of the O2− produced is localized within the cell. It is unclear how intracellular NOX4 may sense changes in flow. One possibility involves mitochondrial-derived H2O2, driven by increased tubular work, activating NADPH oxidase via
thick ascending limb segment senses increases in tubular flow.

Hong and Garvin (5) detail a novel mechanism whereby the
response to flow appear to be important questions for future
research. Interestingly, the current study by Hong and Garvin indicates that exogenous (presumably extracellular) and flow-stimulated endogenous O$_2^-$ (demonstrated to be dependent on NOX4) produces essentially the same effect to promote NHE3 activity (5), suggesting the location of O$_2^-$ formation may not be critical. Determining the biophysical stimuli responsible for enhanced NADPH oxidase activity in response to tubular flow would appear to be an interesting area of future research.

In summary, balancing tubular flow rate with the reabsorption of electrolytes is a critical function of the kidney. In an issue of the American Journal of Physiology-Renal Physiology, Hong and Garvin (5) detail a novel mechanism whereby the thick ascending limb segment senses increases in tubular flow and responds with increased O$_2^-$ production, activation of PKCα/β1, and stimulation of NHE3 activity. These data greatly enhance our understanding of how the thick ascending limb balances tubular flow with reabsorption of critical electrolytes Na and HCO$_3^-$. While the cellular pathways linking tubular flow to reabsorption in the thick ascending limb are becoming clearer, much remains unknown. In particular, the role of these pathways in disease states as well as the biophysical mechanisms promoting activation of NADPH oxidase in response to flow appear to be important questions for future research.

GRANTS

P. M. O’Connor received funding from the American Heart Association 10SDG4150061 and National Institutes of Health Grant DK099548.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: P.M.O. drafted manuscript; P.M.O. edited and revised manuscript; P.M.O. approved final version of manuscript.

REFERENCES