Proximal tubule water transport-lessons from aquaporin knockout mice

Michel Baum1,2 and Raymond Quigley1

1Department of Pediatrics and 2Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas

THE PROXIMAL TUBULE REABSORBS essentially all the filtered organic solutes, most of the filtered phosphate, 80% of the filtered bicarbonate, and 60% of the filtered sodium chloride. Approximately 70% of the filtered water is also reabsorbed by this segment. Despite these very high rates of proximal tubule solute transport, the osmolality of the luminal fluid decreases by only 5 mosmol/kgH2O from Bowman’s space to the end of the proximal tubule accessible by micropuncture (3). Furthermore, the luminal osmolality was found to be 7.5 mosmol/kgH2O lower than that in the peritubular plasma in Munich-Wistar rats (3). This luminal hypotonicity provides the driving force for water reabsorption in the proximal tubule. The fact that there is only a very small decrease in luminal osmolality is consistent with a very high diffusional water permeability in this nephron segment (10).

Despite much debate, physiological studies showed that the vast majority of water is transported across the proximal tubule cell and not across the paracellular pathway (1, 8, 10). The mechanism for this high rate of tranacellular water flow was elusive until the cloning of aquaporin-1 (9), which was found to be expressed in high abundance on the apical and basolateral membranes of the proximal tubule and also in the thin descending limb (7). Since these seminal observations, a family of aquaporins has been cloned. At least seven aquaporin isoforms are expressed in the kidney, and each different nephron segment has a unique aquaporin isoform expression (6). In addition to aquaporin-1, aquaporin-7 is also expressed on the proximal tubule but only on the apical membrane of the distal portion of the proximal straight tubule, the S3 segment.

The role of aquaporin-1 in mediating proximal tubule water transport has been delineated by elegant studies by Schnerrmann, Verkman, and co-workers (11). Aquaporin-1 null mice have an ~50% lower rate of proximal tubule volume absorption measured in vivo and in vitro than do wild-type mice (11). These data indicate that water permeability can be a limiting factor in proximal tubule solute transport. These mice also have a lower brush-border membrane vesicle osmotic water permeability compared with wild-type mice (4). In addition, aquaporin-1 null mice had an 80% reduction in transepithelial water permeability consistent with most of water movement occurring transepithelially via aquaporin-1 (11). Aquaporin-1 null mice generate a higher proximal tubule transepithelial osmotic gradient despite the lower rates of volume reabsorption, indicating that the nearly isotonic reabsorption of proximal tubular fluid is largely due to water movement through aquaporin-1 (13).

Aquaporin-1 null mice have polydipsia and polyuria and an impaired concentrating ability despite the fact that the collecting duct expresses the vasopressin-responsive aquaporin-2 on the apical membrane and aquaporins-3 and -4 are present on the basolateral membrane (5, 11). The impaired concentrating mechanism in aquaporin-1 null mice is probably not secondary to an increased solute load from impaired proximal tubule transport flooding the distal nephron as tubular glomerular feedback decreases single-nephron GFR in these mice (11) but is most likely the result of an inability to maximally form a hypertonic medulla due to the lack of aquaporin-1 in the thin descending limb.

The study by Sohara et al. (12) examined the importance of aquaporin-7 in water and glycerol transport using aquaporin-7 knockout mice. Aquaporin-7, unlike aquaporin-1, also facilitates glycerol as well as water transport. Brush-border membrane vesicles from the outer medulla, which includes the S3 proximal tubule, of aquaporin-7 knockout mice had only a 10% reduction in osmotic water permeability. Thus even in the late proximal straight tubule, aquaporin-1 appeared to be the channel responsible for most water transport. Furthermore, unlike aquaporin-1 knockout mice (4), aquaporin-7 null mice did not have a reduction in urinary concentrating ability. Rather than assume that aquaporin-7 had no significant role in proximal tubule water reabsorption, the authors generated an aquaporin1/aquaporin-7 double-knockout mouse. They found that brush-border membrane vesicles from the outer medulla of double-knockout mice had a lower osmotic permeability than that of aquaporin-1 knockout mice. Furthermore, the double-knockout mouse had a greater impairment in urinary concentrating ability compared with the aquaporin-1 knockout mouse, indicating that the normal urinary concentrating ability in the aquaporin-7 knockout was due to compensation by aquaporin-1 and that aquaporin-7 does indeed play an important role in proximal straight tubule water reabsorption.

Aquaporin-7 is an aquaglyceroporin, and aquaporin-7 null mice have marked urinary excretion of glycerol, a compound almost undetectable in the urine of wild-type mice. This is not the only aquaporin that increases glycerol permeability (2, 14), but aquaporin-7 renal distribution makes it potentially clinically important. The late proximal straight tubule, because of its high metabolic rate and limited oxygen supply, is prone to hypoxic-ischemic injury. These authors demonstrate in two models of acute renal failure, cisplatin nephrotoxicity and ischemia, that there is glyceroluria. Thus urinary glycerol may be an important biomarker that may be of use clinically as a harbinger of tubular injury. This could lead to early diagnosis of acute tubular injury following trauma and surgery and potentially affect treatment of patients.

REFERENCES

Address for reprint requests and other correspondence: M. Baum, Dept. of Pediatrics, UT Southwestern Medical Ctr., 5323 Harry Hines Blvd., Dallas, TX 75235-9063 (Michel.Baum@UTSouthwestern.edu).