Critical Role of Urea in the Urine-Concentrating Mechanism

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The ability to produce concentrated or dilute urine allows people to vary water excretion to match water intake, thereby maintaining a nearly constant blood plasma osmolality. This is accomplished in the renal medulla through the combined actions of several transport proteins in the loops of Henle, collecting ducts, and vasculature and the complex but unique spacial relationship that these structures have to each other. In the outer medulla, active NaCl reabsorption by the Na-K-2Cl co-transporter in the thick ascending limb provides NaCl to increase the medullary osmolality and, at the same time, to dilute the fluid in the lumen of the thick ascending limb. Osmolality continues to increase in the inner medulla, but the mechanism for the concentrating effect remains controversial. The most widely accepted mechanism remains the passive reabsorption of NaCl, in excess of solute secretion, from the thin ascending limb (1,2), although the “passive mechanism” hypothesis is not universally accepted.

Several studies showed that maximal urine-concentrating ability is decreased in protein-deprived animals and humans and is restored by urea infusion (3–10). These findings led to the generally accepted concept that urea plays a critical role in the urine-concentrating mechanism in the inner medulla. Two urea transporter genes have been cloned: The UT-A (Scl14A2) gene encodes six protein and nine cDNA isoforms; the UT-B (Scl14A1) gene encodes a single isoform (reviewed in references [11,12]). In recent years, several laboratories created mice in which specific urea transporters were genetically knocked out and used them to test long-standing hypotheses regarding urea’s role in the urine-concentrating mechanism. In this issue of the Journal of the American Society of Nephrology, Fenton and Knepper provide a scholarly review of this important area of investigation (13). As they discuss in their review, all urea transporter knockout mice—UT-A1/UT-A3 (14,15), UT-A2 (16), and UT-B (17–19)—have urine-concentrating defects. The urea transporter knockout mice support the concept that any hypothesis regarding the mechanism by which the inner medulla concentrates urine needs to include an effect that is derived from urea and a role for urea transporters and, indeed, seemingly support the architectural features of the passive mechanism hypothesis.

As also discussed in their review (13), Fenton and Knepper used their UT-A1/UT-A3 knockout mice to test three classic concepts regarding the role of urea in the concentrating mechanism: (1) The Berliner hypothesis that the role of urea transporters in the inner medullary collecting duct is to prevent a urea-induced osmotic diuresis (20), (2) the Gamble phenomena that there is “an economy of water in renal function referable to urea” (4), (3) and the passive mechanism hypothesis as proposed by Kokko and Rector and by Stephenson (1,2). These hypotheses are not mutually exclusive, so it is possible that they all contribute to urinary concentration. Fenton and Knepper interpret their findings (in their UT-A1/UT-A3 knockout mice) to support the first two concepts (Berliner and Gamble) but not the third (Kokko/Rector and Stephenson) (14,15,21).

In their review (13) but not in their original publications (14,15), Fenton and Knepper conclude that the absence of the inner medullary collecting duct urea transporters UT-A1 and UT-A3 does not prevent the concentration of NaCl in the inner medulla, contrary to what would be predicted from the passive mechanism as proposed by Kokko and Rector and by Stephenson (1,2). Although authors generally have more poetic license in reviews than in original manuscripts, some caution should be exercised before reaching this conclusion that goes beyond the original publication. Fenton and Knepper’s elegant studies clearly show that inner medullary tissue urea content was reduced markedly after water restriction in the UT-A1/UT-A3 knockout mice (14,15). They did not detect a measurable difference in NaCl content at two different levels of the inner medulla between water-restricted UT-A1/UT-A3 knockout mice and wild-type mice (14,15), which is inconsistent with the predictions of the passive mechanism hypothesis (1,2) and the basis for drawing their stronger conclusion in the review. However, the failure to detect a measurable difference in NaCl content may have resulted from an unavoidable study design limitation: The need to make measurements using the whole papilla. NaCl concentrations progressively rise to their highest values near the very tip of the papilla. It simply is not possible to make thin enough sections of the papilla with enough tissue to measure NaCl content, especially in a mouse. Therefore, the averaging of tissue from the entire papilla may have masked any increase at the papillary tip and prevented the detection of a measurable difference in NaCl content in the water-restricted UT-A1/UT-A3 knockout mice. If a decrease in NaCl content had been detected in the UT-A1/UT-A3 knockout mice, then that would have been very strong evidence in support of the passive mechanism. However, the lack of supporting evidence is not the same as evidence disproving the passive mechanism.
Where does this leave us 35 yr after the initial publication of the passive mechanism hypothesis (1,2)? It remains the most widely accepted hypothesis to explain how the inner medulla concentrates urine. There are experimental studies that support it but also studies, including the UT-A1/UT-A3 knockout mouse studies (14,15), that do not. Recently, Layton et al. (22) proposed two hypotheses that are closely related to the passive mechanism and were motivated by recent experimental findings by Pannabecker et al. (23,24). Layton et al. performed computer simulations for both hypotheses and found that the predicted urine osmolalities were consistent with urine from moderately antidiuretic rats. These simulations are a significant advance because many earlier computer simulations had been unable to generate comparably high urine osmolalities. Additional work, both experimental and theoretical, needs to be performed to unravel fully the mystery of how the inner medulla concentrates urine.

What impact do these findings have for the clinical nephrologist? Until another hypothesis is put forward to explain the concentrating mechanism in the inner medulla, the passive mechanism hypothesis remains a very useful model, both clinically and for educating fellows, residents, and medical students. As mentioned, any hypothesis regarding the mechanism by which the inner medulla concentrates urine needs to include an effect that is derived from urea, and the passive mechanism hypothesis does so. It also provides an explanation for the clinical observations in protein-deprived people. Last, as nicely discussed by Fenton and Knepper, the demonstration that genetic knockout of urea transporter proteins results in reduction of urine-concentrating ability suggests that development of agents that inhibit these transporters could be clinically useful as novel diuretic or aquaretic agents.

Disclosures
None.

References