Water, Water Everywhere: A New Cause and a New Treatment for Nephrogenic Diabetes Insipidus

Jeff M. Sands
Renal Division, Department of Medicine and Department of Physiology, Emory University School of Medicine, Atlanta, Georgia

Diabetes insipidus is a rare condition in which patients produce very large quantities of dilute urine. In the most severe forms, patients can produce 1 L urine every 1 hour 24 h/d, 7 d/wk, and 365 d/yr and must drink a comparable amount of water to avoid severe dehydration. Diabetes insipidus can be either central, resulting from failure of the posterior pituitary to make or secrete vasopressin (also called antidiuretic hormone), or nephrogenic, resulting from failure of the kidney to respond to vasopressin (reviewed in ref. 1). There are good therapies available for central diabetes insipidus, such as giving desmopressin to replace the missing hormone. However, there are no good therapies for nephrogenic diabetes insipidus (NDI). NDI can result from genetic abnormalities, such as mutations in the V2-vasopressin receptor (V2R) or the aquaporin-2 (AQP2) water channel, or acquired causes, such as chronic lithium therapy. Two recent publications in the Journal of the American Society of Nephrology (JASN) have provided important advances in our understanding of NDI: identification of a previously unknown genetic cause of NDI2 and a new therapy for lithium-induced NDI.3

Congenital NDI is a rare condition. Mutations in the V2R are responsible for about 90% of patients with congenital NDI, and they have an X-linked pattern of inheritance (reviewed in ref. 1). In approximately 10% of patients, congenital NDI follows an autosomal recessive or dominant pattern of inheritance. Although the majority of these patients have mutations in AQP2, approximately 2% do not, and the genetic cause of NDI in these patients is unknown. In their recent JASN paper, Mamenko et al.2 identify a previously unknown mutation that causes NDI and in so doing, also elucidate a novel role for intracellular calcium (Ca\(^{2+}\)) in water reabsorption.

Mamenko et al.2 discovered that an animal model, the SHR-A3 rat, has disrupted store-operated calcium entry (SOCE) and a urinary concentrating defect.3 SOCE is a mechanism by which extracellular signals can lead to a prolonged elevation of intracellular Ca\(^{2+}\). Mamenko et al.2 showed that the SHR-A3 rat has a novel truncating mutation in the gene encoding stromal interaction molecule 1 (STIM1), which is the endoplasmic reticulum Ca\(^{2+}\) sensor that triggers SOCE. Mamenko et al.2 used whole-genome sequencing to uncover this novel mutation in the STIM1 gene. Mamenko et al.2 made this discovery using a clever approach: they crossed SHR-A3 rats with a very closely related rat, the SHR-B2. The SHR-B2 rat shares 87% of its genome with the SHR-A3 rat but lacks the STIM1 mutation present in the SHR-A3 rat. Mamenko et al.2 found a significant relationship between the inheritance of the STIM1 SHR-A3 mutation allele and the production of dilute urine.

In addition to finding the mutation, Mamenko et al.2 performed physiologic studies to show that the STIM1 mutation present in SHR-A3 rats resulted in increased urine volume, polydipsia, hypertonic plasma, and impaired urinary concentrating ability accompanied by elevated vasopressin levels (i.e., NDI). Mamenko et al.2 used split–open collecting ducts from SHR-A3 rats and found decreased basal intracellular Ca\(^{2+}\) levels and a major defect in SOCE, which results in a failure of vasopressin to induce a sustained intracellular Ca\(^{2+}\) mobilization in SHR-A3 rat collecting ducts. This led to a reduction in AQP2 protein abundance and an increase in the intracellular retention of AQP2, thereby resulting in less AQP2 in the apical plasma membrane where it is needed to reabsorb water in collecting ducts from SHR-A3 rats. Mamenko et al.2 used cultured cells to show that STIM1 knockdown reduces SOCE and basal intracellular Ca\(^{2+}\) levels and prevents vasopressin-mediated translocation of AQP2 to the plasma membrane. Thus, Mamenko et al.2 identified a novel genetic mutation and a novel physiologic mechanism for NDI through SOCE and STIM1 and elucidated an important role for Ca\(^{2+}\) signaling in the urinary concentrating mechanism.2

The paper in JASN by de Groot et al.3 addressed a different aspect of NDI: a new therapeutic approach to lithium-induced NDI. Lithium is used to treat manic depressive illness (reviewed in ref. 4). Lithium enters cells by substituting for sodium on several transport proteins that normally transport sodium. However, the pathways for transporting lithium out of cells are more limited, resulting in intracellular lithium accumulation. Lithium inhibits adenylyl cyclase in the collecting duct. Vasopressin, through the V2R, activates adenylyl cyclase, stimulates cAMP production, and activates protein

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Correspondence: Dr. Jeff M. Sands, Emory University School of Medicine, Renal Division, 1639 Pierce Drive, NE, WMB Room 338, Atlanta, GA 30322. Email: jsands@emory.edu

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kinase A, which in turn, phosphorylates both AQP2 and the urea transporter-A1 and increases their apical plasma membrane accumulation (reviewed in ref. 5). Thus, by inhibiting the adenylyl cyclase-cAMP-protein kinase A signal transduction pathway, lithium disrupts the activation of vasopressin-sensitive transport proteins in the collecting duct, which results in polyuria and NDI. In addition, chronic lithium therapy decreases both AQP2 and urea transporter-A1 protein abundance, further contributing to NDI.6,7

Conventional therapy for lithium-induced NDI includes thiazide diuretics, amiloride, and a very low–sodium (0.5 g) diet. A nonsteroideal anti–inflammatory drug may be added, but nonsteroideal anti–inflammatory drugs can be nephrotoxic. Amiloride inhibits the epithelial sodium channel. Lithium enters collecting duct cells via the epithelial sodium channel, so amiloride may be able to reduce intracellular lithium accumulation.8 Thiazides inhibit the sodium-chloride cotransporter (NCC) in the distal convoluted tubule. The beneficial effect of thiazides has been attributed to a hypovolemia-induced activation of the renin-angiotensin-aldosterone system and a compensatory increase of sodium and water reabsorption in the proximal tubule, thereby decreasing distal delivery and the amount of tubular fluid available to become urine. However, thiazides also reduce the poluria of lithium-induced NDI in mice lacking NCC, which indicates that the beneficial effect of thiazides is independent of NCC.9 Thiazides are derived from carbonic anhydrase (CA) inhibitors,10 raising the possibility that their beneficial effect in lithium-induced NDI may be related to inhibition of CA.

de Groot et al.3 tested this hypothesis directly in lithium-treated mice by comparing acetazolamide with thiazide/amiloride therapy. de Groot et al.3 found that, in mice with lithium-induced NDI, treatment with either acetazolamide or thiazide/amiloride resulted in a similar reduction of polyuria, increase in urine osmolality, and increase in AQP2 protein abundance. However, the side effects of the two treatment regimens were different. The thiazide/amiloride–treated mice developed hyponatremia, hyperkalemia, hypercalcemia, metabolic acidosis, and increased serum lithium concentrations, similar to the side effects observed in patients. These side effects were not observed in the acetazolamide–treated mice with lithium-induced NDI. de Groot et al.3 also found that acetazolamide treatment of mice with lithium-induced NDI reduces inulin clearance, reduces the cortical expression of the sodium/hydrogen exchanger 3, and reduces the increase in urinary prostaglandin E2 observed in mice with lithium-induced NDI.

de Groot et al.3 concluded that the reduction in polyuria after acetazolamide treatment was partially caused by a tubular-glomerular feedback response and reduced GFR. In addition, de Groot et al.3 concluded that the tubular-glomerular feedback response and/or a direct effect on collecting duct principal or intercalated cells may be responsible for the reduction in urinary prostaglandin E2 levels in mice with lithium-induced NDI and treated with acetazolamide and that this contributes to the amelioration of the lithium-induced NDI.

Thus, de Groot et al.3 made the novel observation that acetazolamide, by inhibiting CA, attenuates lithium-induced NDI in mice similar to thiazide/amiloride but with fewer adverse side effects. This study establishes the basis for a future clinical trial to determine if acetazolamide would be effective in treating people with lithium-induced NDI with equal efficacy but fewer side effects than thiazide/amiloride.

Together, these two papers in JASN provide important and novel insight into the pathogenesis and potential therapy for NDI. They also emphasize the importance of fundamental research in renal physiology for providing novel insights that can serve as the inspiration and foundation of future translational or clinical studies to advance the treatment of NDI specifically and renal disease in general.

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DISCLOSURES

None.

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