

Another conundrum to concentrate on?

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IN THE MID-1980s, THE PIONEERING work of Mario R. Capecchi, Sir Martin J. Evans, and Oliver Smithies (jointly awarded The Nobel Prize in Physiology or Medicine 2007) led to the development of gene knockout mice (e.g., Refs. 8 and 13). The use of gene knockout and transgenic mouse models has added essential information to our understanding of renal physiology, including the molecular mechanisms underlying urinary concentration and dilution. Multiple mouse models (currently over 75 listed in PubMed) exist where deletion of various renal transporters or receptors has resulted in defective renal water handling or urinary concentrating defects. These include aquaporins, urea transporters, ion transporters and channels (NHE3, NKCC2, NCC, ENaC, ROMK, CIC-K1), G protein-coupled receptors (type 2 vasopressin receptor, prostaglandin receptors, endothelin receptors, angiotensin II receptors), and various signaling molecules (summarized in Ref. 6). Several of these mouse models with increased urine volume, expectedly, arise from deletion of proteins that are regulated by the antidiuretic hormone arginine vasopressin (AVP), e.g., aquaporins (11) and urea transporters (5), thus confirming the essential downstream molecular targets of AVP and their role in renal water handling. However, other models with concentrating defects arise from deletion of genes that have not been predicted to play any specific role in water balance, e.g., deletion of integrin $\alpha 1$ (a transmembrane receptor for extracellular matrix components) results in increased urine output and reduced urine osmolality (9).

In an issue of the *American Journal of Physiology-Renal Physiology* (4), another mouse model is reported with a urinary concentrating defect. Evans et al. (4) examined the renal water handling abilities in mice in which they had genetically deleted 11 β -hydroxysteroid dehydrogenase type 2 (11 β HSD2), which is expressed with mineralocorticoid receptors (MR) in aldosterone target tissues and protects the receptor from activation by glucocorticoids. Acute pharmacological inhibition of 11 β HSD2 has previously been shown to promote the reabsorption of sodium and water (e.g., (3)). In contrast, chronic administration of 11 β HSD2 inhibitors increases urine flow rate (7), and patients with apparent mineralocorticoid excess (AME) resulting from inactivating mutations in 11 β HSD2 suffer from sustained polyuria (12). In line with these observations, the 11 β HSD2 knockout mice displayed a severe and progressive “polyuric/polydipsic phenotype,” which was apparent in mice of 2 mo of age and progressed in older mice; confirming an essential role of 11 β HSD2 in renal water handling. The majority of previously published knockout mice with altered renal water handling can be divided into two groups: those in which water balance appears to be selectively compromised as a result of disruption of expression of essential proteins and

those that result in water balance abnormalities that are associated with broader systemic effects or due in part to a destructive effect of the gene deletion on renal structure (6). Indeed, >75% of articles reporting gene knockouts with concentrating defects also report alterations in renal structure. Thus the observation of Evans et al. (4) that the polyuria in 11 β HSD2 knockout mice occurs before any structural abnormalities suggests that the phenotype is not of developmental origin or related to altered renal morphology.

Therefore, what is the basis for the concentrating defect in these mice? One can postulate that, similar to previous mouse models with genetic deletion of the components of the renin-angiotensin-aldosterone system (RAAS) and urinary concentrating defects, the observed polyuria in 11 β HSD2 knockout mice is multifactorial (6). However, unlike other “RAAS knockouts” that tend to have impaired sodium handling and natriuresis, 11 β HSD2-deficient animals have decreased fractional excretion of sodium at birth that normalizes during adulthood when the polyuria is established (2). Although the authors provide potential explanations for the observed polyuria, namely, a V1aR-mediated blunting of AVP’s antidiuretic effects or an alteration of 11 β HSD2-mediated access to the glucocorticoid receptor (e.g., Ref. 1) leading to changes in glucocorticoid-regulated levels of urea transporters (e.g., Ref. 10), the actual mechanism responsible for the polyuria remains unknown. Thus, similar to other models of diabetes insipidus, renal physiologists are left with “another conundrum to concentrate on.”

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: R.A.F. drafted manuscript; R.A.F. edited and revised manuscript; R.A.F. approved final version of manuscript.

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