Urea Transporter Inhibitors: En Route to New Diuretics

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Summary

A selective urea transporter UT-A1 inhibitor would be a novel type of diuretic, likely with less undesirable side-effects than conventional diuretics since it acts on the last portion of the nephron. Esteva-Font et al. (2013) develop such an inhibitor by using a clever high-throughput screening assay, and document its selectivity.

Diuretics are commonly used to treat conditions associated with volume overload, such as congestive heart failure, cirrhosis, and nephrotic syndrome. Diuretics are also a mainstay for the treatment of hypertension. Currently used diuretics act by inhibiting sodium transport in different segments of the kidney tubule (figure 1). The loop diuretics, such as furosemide and others in this class, act by inhibiting the Na-K-2Cl co-transporter, NKCC2, in the thick ascending limb of the loop of Henle. This segment is responsible for 25% of sodium reabsorption, making them powerful diuretics. The thiazide diuretics act by inhibiting the Na-CI co-transporter in the distal convoluted tubule, which is responsible for 5% of sodium reabsorption. Diuretics such as amiloride, triamterene, or spironolactone, act by inhibiting sodium reabsorption in the collecting duct, either by inhibiting the epithelial sodium channel (ENaC) or the mineralocorticoid receptor. These diuretics are less potent in terms of inducing a natriuresis, but have the benefit of causing less kaliuresis. In patients with hard to treat volume overload, diuretics with different mechanisms of action, and which act on different nephron segments, are often combined. These various medications lead to an effective natriuresis and diuresis, but they can cause undesired electrolyte abnormalities.

In this issue of Chemistry and Biology, Verkman and colleagues report on the development of a very clever high-throughput screening assay to identify small molecule inhibitors of the urea transporter UT-A1 (Esteva-Font, et al., 2013). They transfected UT-A1-MDCK cells (Fröhlich, et al., 2004) with the aquaporin-1 (AQP1) water channel to ensure that these cells have a much higher water permeability than urea permeability, thereby permitting them to develop a screen based upon changes in cell volume in response to an imposed urea gradient. Transfecting AQP1 into the UT-A1-MDCK cells was key to creating an appropriate cell system for high throughput screening. They then transfected the cells with a chloride-sensing, genetically encoded fluorescent protein, so that they could use a change in fluorescence in their screening assay. The innovative creation of UT-A1-MDCK cells transfected with AQP1 and the fluorescent protein resulted in a cell line that was amenable
to high throughput screening, and was critical to the successful identification of small molecule inhibitors of UT-A1.

The existence of urea transporter proteins in the inner medullary collecting duct (IMCD), which is where UT-A1 is expressed, was initially proposed in 1987(Sands, et al., 1987). The SLC14A family of urea transporters has two major subgroups, designated UT-A (SLC14A2) and UT-B (SLC14A1) (reviewed in (Klein, et al., 2012; Klein, et al., 2011). The UT-A urea transporters consist of 6 distinct isoforms, 3 of which are located primarily in the kidney medulla (figure 1). UT-A1, which is the focus of the current study, and UT-A3 are expressed in the IMCD. The IMCD is the last nephron segment through which tubular fluid (urine) passes before entering the ureter. UT-A2 is expressed in the thin descending limb of the loop of Henle. UT-B1 is expressed in descending vasa recta and red blood cells. Urine concentrating ability, and hence the ability to conserve water, is reduced in genetically engineered mice lacking UT-A1/UT-A3, UT-A2, UT-B1, or UT-A2 and UT-B1 (reviewed in (Klein, et al., 2012; Klein, et al., 2011). Thus, an inhibitor of any of these urea transporters may result in a diuresis.

Urea plays a critical role in the urinary concentrating mechanism and in the maintenance of water balance (reviewed in (Sands and Layton, 2013; Sands, et al., 2011)). Protein-deprivation or a low-protein diet reduces maximal urine concentrating ability, and hence the ability to conserve water, and is restored by urea infusion. As mentioned above, mice with genetic knock-out of both IMCD urea transporters, UT-A1 and UT-A3, have a urine concentrating defect. The polyuria in these mice results from the absence of urea transport in their IMCD(Fenton, et al., 2004).

Here, Verkman and colleagues report a selective inhibitor of the UT-A1 urea transporter, as well as a UT-A1/UT-B1 non-selective inhibitor(Esteva-Font, et al., 2013). While an inhibitor of UT-B1 that is metabolically stable and works at nanomolar potency has been reported previously (Anderson, et al., 2012; Yao, et al., 2012), this study is, to best of my knowledge, the first to report a UT-A1 selective inhibitor. Further development and in vivo testing of this intriguing compound would be quite exciting. Although future studies in animals will be needed to assess the ability of UT-A1 inhibitors to induce and sustain a diuresis, it seems likely that UT-A1 inhibitors will be effective. A UT-A1 inhibitor is particularly attractive as a drug target since having a diuretic that works by inhibiting urea transport in the last nephron segment offers the exciting possibility that it will have less undesirable side-effects on electrolytes than the conventional diuretics that inhibit sodium transport in the thick ascending limb or distal convoluted tubule. In addition, a UT-A1 inhibitor would have a different mechanism of action from other diuretics, and be the first diuretic to act in the IMCD. This opens the possibility for combination therapy with other diuretics, in addition to mono-therapy with a UT-A1 inhibitor.

Acknowledgments

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Reference List


Figure 1.
Diagram of the loop of Henle, distal convoluted tubule, and collecting duct showing the names and location of the major sodium (Na-K-2Cl co-transporter NKCC2, Na-Cl co-transporter NCC), water (aquaporins AQP2-AQP4), and urea transport (urea transporter UT-A1, UT-A2, and UT-A3) proteins. Loop diuretics act by inhibiting sodium transport by NKCC2. Thiazide diuretics act by inhibiting sodium transport by NCC. The newly identified urea transporter inhibitor may act as a diuretic by inhibiting UT-A1.