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Harnessing Transporters to Clear Uremic Toxins

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The constancy of the *milieu intérieur* described by Claude Bernard is an absolute prerequisite for the health of the organism. The primacy of the kidney in whole organism homeostasis is best exemplified by the disturbance in the composition and amount of body fluid and solute when this organ fails to function. In simplistic terms, one can envision renal failure as the inability to remove what should be excreted and inability to add what should be added to the body. The inability to excrete the appropriate amount of water and various solutes is well studied and serves as a marker in clinical practice to evaluate the degree of dysfunction and adequacy of therapy. There are also many additional substances that are not properly excreted in renal failure, the accumulation of which contributes to the uremic state, but these are less well studied in terms of their metabolism, mechanism of action, or mode of excretion.

The expanding group of proven and putative uremic toxins has recently been highlighted by the European Uremic Toxin Work Group (http://EUTox.info) and the count has reached over 110 moieties.[1] This highly diverse group of substances ranges from inorganic solutes to organic substances including acids, guanidine, peptides, indoles, nucleotides, peptides, and others.[2] The chemical properties of these moieties are as expansive as their identities, with a broad range of molecular weight (outside the 10- to 30-kD middle molecule class), hydrophobicity, protein binding, a host of post-translational modifications, and a myriad of target organs and mechanisms to impart damage. Many of these molecules are normal constituents of the *milieu intérieur* when their levels are maintained within discreet ranges. Clearly no single biologic system will possess the broad span to handle the excretion of this vast group of molecules. Excretion of these molecules in health includes some contribution from hepatic conjugation, but they largely rely on glomerular filtration or tubular secretion by a host of transporter proteins.

In general, one can devise two broad categories of countermeasures to combat pernicious uremic toxins. First is attempting to directly block their actions (*e.g.*, angiotensin receptor blockade) or neutralize downstream effects on target organs (*e.g.*, alkali replacement), and a second is their enhanced removal either by improvement of dialytic clearance (*e.g.*, large-pore dialysis membranes), inhibition of production (*e.g.*, calcimimetics for parathyroid hormone), or enhancement of endogenous clearance perhaps by pharmacologic means. All of these approaches have been attempted for various uremic toxins over the years. In this issue of *JASN*, the paper by Toyohara and coworkers[3] demonstrates success of one of the methods—enhancement of endogenous clearance—which has been attempted the least.

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The mammalian renal proximal tubule, which is likely the most archaic part of the vertebrate nephron, is endowed with a multitude of solute transporters devoted to reabsorption, but also to secretion of unwanted substances. These transporters are usually committed to anionic, cationic, or neutral small organic molecules, but any given transporter typically can accept a vast array of substrates at least when tested in a heterologous system.[4] Enomoto and Niwa[5] previously presented us with an elegant summary of the potential roles of organic anion and cation transports in uremic toxin clearance and the reader is referred to this article for details.

The *SLCO* family of genes also encodes many transporters that accept an extremely broad range of substrates. Following up on a finding made by the same group that *SLCO4C1* expression is reduced in a 5/6 nephrectomy model of chronic kidney disease (CKD),[6] Toyohara and coworkers[3] conduct an interesting and informative set of experiments in this issue of *JASN* by overexpressing *SLCO4C1* in mice as a transgene to test whether these animals fare better when confronted with renal failure. Genetic overexpression of the organic anion transporter *SLCO4C1* in mice reduces levels of specific uremic toxins in the plasma such as asymmetric dimethylarginine (ADMA), guanidine succinate, and *trans*-aconitate, which is an inhibitor of the tricarboxylic acid cycle. The reduction of these toxins associates with changes in phenotype such as amelioration of hypertension and histologic indices of renal inflammation. Of note is that elevation of *trans*-aconitate in CKD and its hypertensive and pro-oxidative stress effects is novel. Because the probability of genetic manipulation of humans with CKD is not within a realistic realm in the near future, the authors next searched for agonists that activate the promoter of *SLC04C1 in vitro* and found the statin class of drugs are effective. The findings were next tested *in vivo* where the authors found that statins induced native *SLCO4C1* mRNA transcripts, increased ADMA and *trans*-aconitate clearance, and improved markers of left ventricular hypertrophy. Interestingly, there were no detectable effects in blood pressure at the dose of statin administered, suggesting that the reduction of left ventricular hypertrophy may not be secondary to blood pressure changes, which brings forth once again the entity of uremic cardiomyopathy that is unrelated to hypertensive or coronary heart disease.[7] Finally, the authors provide a very comprehensible metabolomic analysis of the CKD model and effect of transgenic expression of *SLCO4C1* that is a valuable database for all investigators in this field.

This is one of the more convincing studies that show overexpression or induction of a transporter can alleviate some aspects of uremia. However, some caution is order in terms of the interpretation and generalization of the study. There were no data present to indicate ADMA, guanidine succinate, or *trans*-aconitate are direct substrates of the SLCO1C4 transporter, so their increased clearance could be due to indirect effects of statins or downstream effects from SLCO1C4 activity. The improvement in clearance is compatible with the uremic toxin model, but the changes in whole animal phenotype were modest. This latter point is because amelioration of a few uremic toxins among hundreds will likely have beneficial but incomplete effects. Moreover, genetic polymorphisms in *SLCO4C1* may exist that affect an individual's ability to handle selected uremic toxins. This caveat is compatible with the human literature of conflicting results of statin therapy on progression of CKD, cardiovascular complications, and mortality (reviewed in reference 8).

Nevertheless, this paper should not be viewed as a test of whether statins can be used to treat certain aspects of CKD—they might with proper validation—or be diminished by previous negative or equivocal clinical trials with statins. Rather, one should embrace a broader view to further explore the role of transporters and their activators in the handling of substances that become toxins in CKD with the prospect of therapeutically manipulating these transporters to enhance their activity in progressive renal disease.

DISCLOSURES

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See related article, "SLCO4C1 Transporter Eliminates Uremic Toxins and Attenuates Hypertension and Renal Inflammation," on pages 2546–2555.