The Kidney and Uremic Toxin Removal: Glomerulus or Tubule?

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Summary: Chronic kidney disease (CKD) is a condition that affects approximately 10% of the adult population in developed countries. In patients with CKD adequate renal clearance is compromised, resulting in the accumulation of a plethora of uremic solutes. These uremic retention solutes, also known as uremic toxins, are a heterogeneous group of organic compounds, many are too large to be filtered (middle molecules) or are protein-bound. Tubular secretion shifts the binding and allows for active secretion of such solutes. To mediate urinary solute excretion, renal proximal tubules are equipped with a range of transporters that cooperate in basolateral uptake and luminal excretion. These putative uremic toxins are poorly filtered across dialysis membranes because they are protein bound and current dialysis therapy does not correct the full spectrum of uremic toxicity. Residual renal function, which may represent an important contribution of solutes secreted by the proximal tubule rather than unreabsorbed filtrate, is an important predictor of survival of CKD patients. Many of the transporters that mediate the renal excretion of uremic retention solutes were first recognized as mediators of drug trafficking and drug–drug interactions, and a considerable amount of literature concerning the actions of these transporters antedates the recognition of their importance in the proximal renal tubular transport of uremic retention solutes. These transporters include members belonging to the organic cation/anion/zwitterion solute carrier family, such as the organic anion transporters (OAT)1, OAT3, and OATP4C1, and to the adenosine triphosphate binding cassette superfamily of transmembrane transporters, including the multidrug resistance proteins and breast cancer resistance protein. This article draws on this body of information to describe the renal tubular clearance mechanisms for uremic toxins, as well as the intracellular events associated with their accumulation, involving activation of the aryl hydrocarbon receptor, disturbance of mitochondrial functioning, and competition with metabolizing enzymes.
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Although hemodialysis, as initiated for the treatment of acute renal failure by Kolff and Higgins[1] in the early 1940s and as described by Atkins et al[2] in 1960 for chronic renal failure, has been highly effective in relieving the symptoms of nausea, anorexia, easy bruising, weakness, confusion, lethargy, seizures, and coma that constitute the uremic syndrome, it has become increasingly clear that patients undergoing chronic hemodialysis or peritoneal dialysis have a markedly reduced survival attributable to accelerated cardiovascular disease and to progressive renal scarring leading to anuria.[3] Pursuing the belief that uremia is caused by small, dialyzable uremic toxins for which urea and creatinine serve as surrogate markers, modifications of dialysis membranes, frequency of dialysis, and duration of dialysis treatments have been studied extensively. Despite improvements in the apparent adequacy of dialysis judged by urea or creatinine clearance kinetics, there has been little impact on the renal and cardiovascular disease that characterize chronic hemodialysis or peritoneal dialysis, which often, incorrectly, are termed renal replacement therapies.[4] Although Smith[5] devoted only one short paragraph to uremia in his seminal textbook, "The Kidney : Structure and Function in Health and Disease," he wrote, "Death, if not caused by intercurrent infection or other extrarenal disturbance, occurs from severe imbalance in the composition of body

fluids (edema, acidosis, hyponatremia, hyperkalemia, hyperphosphatemia, etc.) complicated by anemia, *circulatory disturbances*, and other factors of unknown nature." Despite the generally held belief that the great prevalence of cardiovascular disease was a reflection of comorbid risk factors (diabetes, hypertension, and hyperlipidemia), which are common in the dialysis population, analysis of several community-based longitudinal studies concluded that CKD was an independent risk factor for myocardial infarction, fatal coronary artery disease, stroke, and death.[6] Wolfe et al[7] noted better survival in patients who underwent cadaveric renal transplantation as compared with a well-matched control group of patients on the transplant waiting list. Although it might be argued that comorbid risk factors were better controlled in the transplant group, this observation has been viewed as evidence that current dialysis therapy does not correct the full spectrum of uremic toxicity.

These observations have led to a re-examination of the question of the nature of uremic toxins.[8] The European Uremic Toxin Workgroup listed more than 150 substances found at higher concentrations in the plasma of patients with uremia as compared with normal individuals[8,9] (http://www.uremic-toxins.org/). Many represent poorly dialyzable protein-bound solutes whose excretion requires active tubular secretion. Before the advent of stopped flow measurements and glomerular micropuncture, renal physiology focused predominately on renal tubular transport, tubular reabsorption, and secretion. Smith's[10] suggestion that toxins might be secreted rather than filtered arose from his observation that prochordates living in osmotic equilibrium with their salt water habitat did not have glomeruli and disposed of wastes via tubules that drained into the coelomic cavity. He pointed out that although glomeruli evolved when life moved into fresh water in the Cambrian era 500 million years ago, aglomerular species of fish have persisted throughout evolution up to the present.[10] Micropuncture studies in glomerular teleosts have shown that the importance of tubular secretion is not limited to aglomerular fish.[11]

The renal proximal tubules are equipped with a range of transporters, consisting of multiple carriers with overlapping substrate specificities that cooperate in basolateral uptake and luminal excretion. These transporters often are involved in clinically significant interactions, leading to unexpected changes in plasma metabolite levels and/or nephrotoxicity.[12] We can distinguish the organic anion and the organic cation systems, each comprising transporters belonging to the organic cation/anion/zwitterion solute carrier family (*SLC*; eg, organic cation transporter 2 [OCT2; *SLC22A2*], organic anion transporter 1 and 3 [OAT1/3; *SLC22A6* and *SLC22A8*], organic anion transporting polypeptide 4C1 [OATP4C1; *SLCO4C1*], the multidrug and toxin extrusion proteins [MATEs; *SLC47A1/2*]), the adenosine triphosphate (ATP)-binding cassette transporter family (P-glycoprotein [P-gp, also termed Multi Drug Resistance gene 1; *ABCB1*], multidrug resistance-associated protein 2 and 4 [MRP2/4; *ABCC2/4*], and the breast cancer resistance protein [BCRP; *ABCG2*]), as shown in Figure 1.[13–16] The importance of these systems in uremic toxin removal is still partially unknown.

OATS AS DETERMINANTS IN TUBULAR SECRETION OF UREMIC TOXINS

Active transport of organic anions (both secretory and reabsorptive) is an essential renal function. It was shown as early as the 1960s that serum isolated from uremic rats or patients inhibited uptake of the prototypical organic anion substrate, *p*-aminohippurate (PAH), in rat renal cortical slices.[17,18] More recently, in vitro studies found that the uremic toxins hippuric acid and indoxyl sulfate effectively inhibited uptake of PAH in isolated rabbit renal tubules and that indoxyl sulfate administered in vivo significantly reduced the renal clearance of PAH in rats.[19,20] These data strongly implicate involvement of the classic organic anion transport system in the renal elimination of uremic

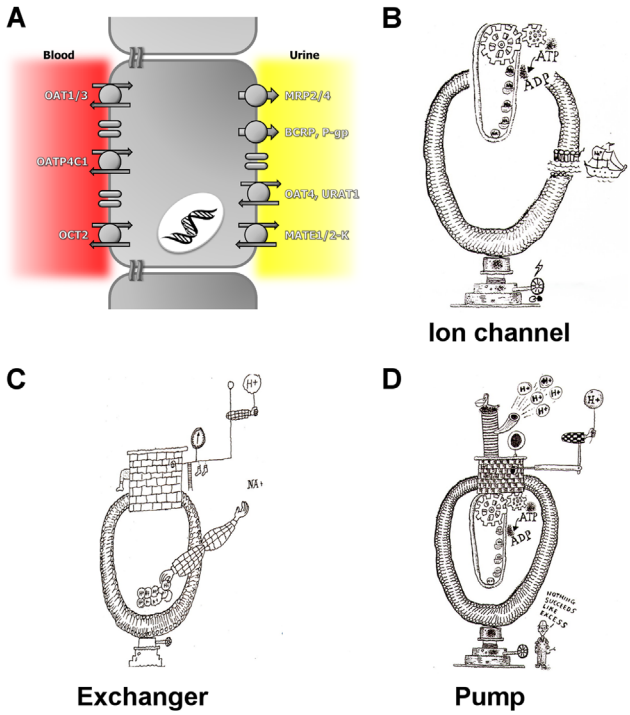

Figure 1. Renal tubular transport systems. Transporters present in the renal proximal tubule and potentially relevant for (A) tubular uremic toxin handling and (B-D) their physical metaphors. Membrane transport can be facilitated (B; not discussed in this article), through channels (C) through exchange proteins such as the facilitated diffusion carrier OCT2, the OATs, or OATP4C1, or (D) through ATP-dependent pumps such as P-gp, MRP2, MRP4, and BCRP.