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Uremic syndrome of chronic kidney disease: altered remote sensing and signaling

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Abstract

Uremic syndrome (also known as uraemic syndrome) in patients with advanced chronic kidney disease involves the accumulation in plasma of small-molecule uremic solutes and uremic toxins (also known as uraemic toxins), dysfunction of multiple organs and dysbiosis of the gut microbiota. As such, uremic syndrome can be viewed as a disease of perturbed inter-organ and inter-organism (host–microbiota) communication. Multiple biological pathways are affected, including those controlled by solute carrier (SLC) and ATP-binding cassette (ABC) transporters and drug-metabolizing enzymes, many of which are also involved in drug absorption, distribution, metabolism and elimination (ADME). The remote sensing and signaling hypothesis identifies SLC and ABC transporter-mediated communication between organs and/or between the host and gut microbiota as key to the homeostasis of metabolites, antioxidants, signaling molecules, microbiota-derived products and dietary components in body tissues and fluid compartments. Thus, this hypothesis provides a useful perspective on the pathobiology of uremic syndrome. Pathways considered central to drug ADME might be particularly important for the body's attempts to restore homeostasis, including the correction of disturbances due to kidney injury and the accumulation of uremic solutes and toxins. This Review discusses how the remote sensing and signaling hypothesis helps to provide a systems-level understanding of aspects of uremia that could lead to novel approaches to its treatment.

The term uremic syndrome refers to various signs and symptoms associated with generalized organ dysfunction occurring in patients with chronic kidney disease (CKD), which results in the accumulation in plasma of many protein-bound and water-soluble metabolites, referred to as uremic solutes. This complex systemic metabolic disorder involves metabolic derangements and aberrant signaling events that occur throughout the body, many of which

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are mediated by uremic solutes. Accordingly, this disease might best be considered from a systems biology perspective, especially given the growing amount of relevant 'omics' data as well as the availability of molecular and cellular functional information comparing diseased and healthy states. These data indicate that a multi-organ network of transporters and drug-metabolizing enzymes (DMEs) plays an important part in sensing, regulating and/or modulating the concentrations of these various small-molecule uremic solutes in tissues and body fluids¹.

In patients with advanced CKD, uremic solutes accumulate in the circulation owing to deficient renal clearance. Some of these products are considered uremic toxins and are believed to contribute to the uremic syndrome. Many uremic solutes are produced by the dysbiotic gut flora and/or the action of enzymes in organs such as the liver. These solutes are transported via solute carrier (SLC) and ATP-binding cassette (ABC) transporters into different organs, where they are thought to exert toxic effects or disrupt key signaling and metabolic pathways, before being eliminated via what remains of the injured proximal tubule²⁻⁴. Similar to drugs such as diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs), many uremic solutes are small organic molecules that circulate bound to plasma proteins, and both groups of molecules are transported into tissues and body fluid compartments by members of the SLC and ABC transporter superfamilies^{5,6}. These transporters, together with phase 1 and phase 2 DMEs, are prominent in the pharmacological literature owing to their role in drug absorption, distribution, metabolism and excretion (ADME).

A number of these transporters have been identified as particularly important in the transport of uremic solutes, including in the transport of molecules involved in the regulation of key metabolic and signaling pathways, antioxidants and mediators of cellular toxicity^{7,8} (Table 1). Such transporter-mediated movement of uremic toxins into tissues and body fluids, or from plasma into proximal tubule cells of the kidney where they can be eliminated via the urine, generally occurs via pathways not dissimilar from those involved in the distribution of drugs. Some of these small organic molecules also seem to be toxic to proximal tubule cells⁹⁻¹² and are thought to be associated with the progression of CKD. Hence, information could be transmitted between cells, organs and tissues via the movement of these small organic molecules. This remote communication involves multi-specific transporters and other ADME-related proteins that are differentially expressed in the cells that line fluid-containing body compartments, such as the intestine, kidney, liver, muscle and central nervous system (CNS)^{5,13}. Accordingly, uremic syndrome could be viewed as a systemic disease resulting in part from perturbed inter-organ and inter-organism (that is, host-microbiota) communication. The changing profile of uremic solutes in progressive CKD is both a result of dysregulated local and systemic homeostasis and a cause of it. In this Review, we frame our discussion of uremic syndrome in the context of the remote sensing and signaling hypothesis, which is more fully elucidated elsewhere^{1,5,13-15} (Fig. 1). In essence, this hypothesis emphasizes the central role of transporters and DMEs in regulating remote communication between tissues and organs via small organic molecules (Figs 1,2). As we argue, many aspects of uremic syndrome can be viewed as disordered remote sensing and signaling.

Remote sensing and signaling

The remote sensing and signaling hypothesis was formulated over a decade ago^{14,16} to explain the role of SLC and ABC transporters in the physiology of various organ systems, which had been suggested by the results of metabolomics studies and the phenotypes of mice with knockout of *Slc22a6* (which encodes SLC family 22 member 6; also known as organic anion transporter 1(OAT1)) and other transporters. Alongside unexpected developmental expression patterns¹⁷ and the discovery of unusual transporter family members (such as OAT6, which seems to be an odorant transporter in olfactory mucosa^{18,19}), one of the main findings from studies of mice lacking the ability to renally eliminate organic anions via OAT1 and/or OAT3 was the presence of many metabolic alterations, including elevated plasma levels of numerous uremic solutes, many of which were derived from the gut microbiota^{7,8}.

Many SLC and ABC transporter family members are evolutionarily highly conserved, multi-specific and have a wide range of endogenous substrates, including well-known signaling molecules, such as cAMP, prostaglandins, bile acids and short-chain fatty acids; metabolites such as α -ketoglutarate; antioxidants such as urate and ergothionine; and vitamins or cofactors such as pantothenic acid⁵. Networks of apical (efflux) and/or basolateral (influx) multi-specific SLC and ABC transporters often work to maintain metabolite homeostasis in concert with closely related (and sometimes also with unrelated) transporters of limited specificity or relative monospecificity. These homeostatic networks can be sited within a single organ or involve several organs²⁰. For example, three multi-specific transporters (OAT1, OAT3 and ABC subfamily G member 2 (ABCG2)) work closely with two limited-specificity transporters (URAT1 (also known as SLC22A12) and GLUT9 (also known as SLC2A9)) to control urate homeostasis²¹. In the absence of end-stage renal disease (ESRD), the bulk of urate handling in the kidney is carried out by these and several other transporters. Moreover, multi-specific SLC and ABC transporters in the gut, liver and kidney work in concert with monospecific and oligospecific transporters and DMEs to regulate the homeostasis of bile acids, which are involved in fat digestion and signaling via G protein-coupled receptors (GPCRs) and nuclear receptors²⁰ (reviewed elsewhere^{22–24}).

Although DMEs were not emphasized in initial descriptions of the remote sensing and signaling hypothesis, these enzymes modify various molecules, including drugs and gut-derived metabolites, thereby increasing their solubility (Box 1). As these modifications generate additional signaling molecules and putative uremic toxins, DMEs are intimately connected to remote communication pathways involving ADME-related transporters and enzymes. This connection is particularly important in uremia, because some of the most important uremic toxins (including indoxyl sulfate and *p*-cresol sulfate) are generated as a result of the actions of phase 2 DMEs on their microbiota-derived precursors (indole and *p*-cresol, respectively), resulting in both cellular toxicity and the potential for diverse types of cell signaling^{7,8}.

Thus, a multi-scale, multi-compartment network of transporters and DMEs is involved in sending and receiving information to various tissues and body fluid compartments^{1,5–8,13–15}. This information is transmitted via small organic metabolites (such as α -ketoglutarate,

polyamines, tryptophan metabolites and uric acid) and signaling molecules (such as prostaglandins, cyclic nucleotides, odorants and neurotransmitters) that are substrates of SLC and ABC transporters (Figs 1,2). These metabolites and signaling molecules, in turn, feed into well-known metabolic pathways, modulate kinase activity and/or bind to GPCRs (including metabolite GPCRs) and nuclear receptors. This organization also extends to intracellular pathways that affect transcription, signaling, protein trafficking and macromolecular interactions (including transporter–cytoskeleton interactions). Together, this network involves over 100 ADME-related proteins, which are encoded by genes that are differentially and highly expressed in epithelial cells (Fig. 2), such as those in the kidney, liver, gut and pancreas, and in non-epithelial cells, such as the endothelial cells of the blood–brain barrier and circulating cells. This network is considered to act in parallel with the neuroendocrine system, growth factors and cytokines, as well as being analogous to these classic homeostatic systems.

Furthermore, several of the metabolites and signaling molecules transported into and out of various body fluids and tissues have the ability to interact with other organisms. Remote communication consisting of unidirectional or bidirectional transport of metabolites and signaling molecules across an epithelial, endothelial or similar barrier can occur between individuals of the same species, via breast milk, amniotic fluid or urine; between the host and gut microbiota; or between different microbiota species^{1,5,7}. All these remote communication examples could be relevant to ESRD in certain contexts, although (as discussed below) most attention has been paid to bidirectional communication between the host and the gut microbiota in patients with ESRD^{25,26}. Inter-organ communication involves both well-defined physiological pathways, such as transport of bile acids and nutrients via the gut–liver–kidney axis, and those occurring in pathological states. Although DMEs and transporters have been identified and characterized in virtually every tissue of the body, inter-organ communication in the context of uremia involves the brain, muscle, pancreas, gut, liver and heart, among other tissues. The composition of metabolites, signaling molecules, antioxidants, nutrients, vitamins and cofactors in body fluids found in epithelium-lined compartments, including cerebrospinal fluid (CSF), bile, urine, plasma, amniotic fluid, breast milk and ocular fluid, is partly or largely regulated by SLC and ABC transporters. For example, the choroid plexus (which regulates the metabolite composition of CSF) is morphologically and functionally similar to the proximal tubule²⁷, and this similarity extends to the expression of OATs and organic cation transporters (OCTs)²⁸. The reader should keep in mind that, in the setting of ESRD, the composition and volume of these various body fluids can change substantially^{29,30} and that other compartments (including interstitial, peritoneal and pericardial spaces) can become important^{27,31}.

The remote sensing and signaling hypothesis emphasizes the homeostatic role of SLC and ABC multi-specific, monospecific or oligospecific transporters (particularly in settings such as renal impairment) because this system is thought to be of comparable importance to the neuroendocrine, growth factor and cytokine systems in the resetting of homeostatic mechanisms after perturbation or injury^{1,5,7}. However, the hypothesis also emphasizes the critical interconnections between transporter-based mechanisms and other homeostatic systems. For example, organic anion-transporting polypeptides (OATPs) are transporters of thyroid hormones and knocking out an OATP family member in the mouse brain capillary

endothelium leads to an underdeveloped CNS³². Similarly, expression of OAT3 in pancreatic β -cells is necessary for transport of 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), a uremic solute that is involved in the regulation of insulin secretion³³. A defect in this pathway has been linked to human gestational diabetes.

This multi-scale systems biology model comprises inter-organism communication, whole-organism homeostasis, organs, tissues, body fluids and transporter-expressing cells. This model incorporates many points of potential regulation and dysregulation, including transporter trafficking, phosphorylation, transcription and transporter–cytoskeletal associations. The model also includes multiple points for sensing of metabolites, signaling molecules, antioxidants, nutrients and other molecules, including, but not limited to, nuclear receptors and transcription factors, GPCRs, kinases and sensors involved in redox pathways. Indeed, many of the established and probable *in vivo* endogenous substrates for SLC and ABC multi-specific transporters are believed to have essential roles in activating and modulating these sensing mechanisms, which in turn can regulate the expression and/or function of DMEs as well as that of the transporters themselves⁵. As yet, not enough integrated data are available to accurately represent this model in healthy individuals, much less in patients with uremia or CKD. However, networks based on a single transporter (such as OAT1, which is one of the most important uremic toxin transporters) that include all the numerous metabolites and signaling molecules with which the transporter interacts have been developed. Building such networks is complicated, as it involves the integration of transcriptomic and metabolomic data from transporter-knockout mice, *in vitro* data and computational reconstruction of metabolic networks^{34–36}. Nevertheless, the elucidation of metabolic and signaling networks incorporating multiple transporters in health and disease should be possible in the next few years. We emphasize that this is an iterative process informed by the publication of ever-more comprehensive omics data, new functional data and improved tools for data integration and network reconstruction. Therefore, the publication of accurate networks of this kind is probably years away, particularly for complex diseases such as human CKD. This goal is likely to be more tractable in animal models of CKD.

Remote sensing and signaling in CKD

In animal models of CKD, declining renal function is associated with altered renal expression of many SLC and ABC transporters. Furthermore, changes occur in the gene expression and/or function of ADME-related proteins (namely, multi-specific transporters and DMEs) in the liver and intestine as well as other tissues³⁷. Some of these changes could be viewed as compensatory efforts to preserve homeostasis. Indeed, the changes in expression and/or function of the efflux transporter, ABCG2, in the intestine in the setting of ESRD might be an example of such a compensatory response. *Abcg2* knockout mice subjected to adenine-induced CKD not only displayed impaired survival compared with wild-type controls but also had substantially increased plasma concentrations of uremic toxins, including indoxyl sulfate (a substrate of ABCG2)³⁸. Patients with ESRD who have dysfunctional variants of ABCG2 have substantially elevated plasma levels of uric acid³⁹, also considered a uremic toxin. These data support the notion that increased expression or activity of ABCG2 (largely in the intestine) is a compensatory mechanism that decreases

plasma levels of indoxyl sulfate and urate via their excretion into the gut lumen in the setting of renal insufficiency^{38–43}. Importantly, the gut microbiota also undergoes changes in response to the increased uric acid load, including the growth of bacteria that produce uricase⁴⁴, an enzyme involved in the reduction of uric acid to allantoin. Together with the findings in mice described above, these data suggest that intestinal ABCG2 (in addition to its role in the increased excretion of uric acid and indoxyl sulfate in CKD) plays an important part in inter-organism remote sensing and signaling through its transport of uric acid and other uremic toxins.

Other multi-specific transporters also show increased expression in the gut and liver in response to impaired renal function³⁷. By contrast, many DMEs show opposing changes in expression in the gut and liver^{45–48} as well as decreased functional activity⁴⁵ in this setting. Interestingly, some of these DME changes can be reversed by renal transplantation⁴⁹. As DMEs are involved in the generation of many uremic toxins (including indoxyl sulfate), the decrease in expression and/or activity of some DMEs might be a mechanism for decreasing the organism's uremic toxin burden.

The expression of genes encoding nuclear receptors such as nuclear receptor subfamily 1 group I member 2 (PXR) and hepatocyte nuclear factor 4 α (HNF4 α) is also decreased in animal models of CKD⁴⁵. These proteins are sometimes considered master regulators of the expression of many ADME-related genes and as such are potential sensors in a remote sensing and signaling network^{5,50–54}. Decreased expression of these nuclear receptors could explain the decreases in the expression of certain DMEs but probably does not explain the observed increases in transporter expression. Other transcription factors, such as the aryl hydrocarbon receptor (AHR), probably regulate the expression of multi-specific transporters, such as P-glycoprotein (P-gp), apparently involved in resetting the system in the presence of renal impairment^{55,56}.

Analyses of omics data indicate considerable alteration in the gene expression and/or activity of transporters and other ADME-related proteins involved in remote sensing and signaling in the setting of renal insufficiency. Some of these alterations might be interpreted as an attempt to reset homeostasis by decreasing levels of uremic toxins such as indoxyl sulfate and urate⁴⁰. This interpretation, together with the many changes in expression and/or function of multi-specific transporters and DMEs across tissues, suggests that resetting of the inter-organ and inter-organism communication network occurs to preserve homeostasis in the setting of ESRD.

The example of indoxyl sulfate

A growing body of research relates to the toxic, metabolic and signaling effects of individual uremic toxins, such as albumin-bound indoxyl sulfate, which is one of the main uremic toxins implicated in uremic syndrome^{9–12,57}. Indoxyl sulfate is not optimally cleared during dialysis, and considerable translational and clinical research has focused on strategies to reduce serum levels of this molecule in patients with CKD^{57–64}.

Indoxyl sulfate is part of an inter-organism (microbiota- host) and inter-organ (gut, liver, kidney and brain) communication network regulated by transporters and DMEs (Fig. 3). Indole is produced by the gut microbiota as a result of the metabolism of tryptophan. Once absorbed across the intestinal wall into the blood, indole is taken up by hepatocytes, where it is metabolized first to indoxyl by hepatic DMEs (namely, CYP2E1) and then to indoxyl sulfate by sulfotransferases⁶⁵. Indoxyl sulfate is then secreted back into the blood by hepatocyte transporters, whereupon it interacts with various tissues, organs and body fluids, largely via SLC and ABC transporters. In vitro data indicate that indoxyl sulfate can participate in or at least affect numerous intracellular signaling pathways, including those involving transcription factors (such as AHR) and various kinases^{66–74}. Indoxyl sulfate is ultimately cleared from the blood via OAT1 and OAT3 transporters expressed on the basolateral membrane of kidney proximal tubule cells^{7,8}. This uremic solute is then secreted into the tubular lumen via apical efflux transporters (although precisely which transporters are involved remains unclear at present) and eliminated from the body in urine. However, high levels of indoxyl sulfate seem to exert toxicity in proximal tubule cells as well as cells of the vasculature and CNS⁵⁷. Movement of indoxyl sulfate into these cells is probably mediated by OAT3 and other transporters⁷⁵. Moreover, AHR (to which indoxyl sulfate binds^{67,76}) regulates the expression of members of the cytochrome P450 family, other DMEs and transporters^{77,78}. At concentrations observed in the serum of patients with uremia, indoxyl sulfate activates expression of *CYP1A1*, *CYP1A2* and *CYP1B1* genes, as well as expression of *UGT1A1* and *UGT1A6* (encoding the phase 2 DMEs UDP-glucuronosyltransferase 1–1 and UDP-glucuronosyltransferase 1–6, respectively) in primary human hepatocytes^{69,76}. This uremic toxin also regulates the expression of hepatic P-gp via binding to AHR in rodent and cell culture models of CKD⁵⁵. The observation that patients with CKD who have high plasma levels of indoxyl sulfate also show increased hepatic metabolism of cyclosporin, a P-gp substrate, suggests that this increased expression is likely to be clinically relevant⁵⁵.

These data are consistent with the notion that remote communication between the failing kidney and the liver occurs via one or more uremic toxins, which act through nuclear receptor signaling. In addition to activation of AHR, indoxyl sulfate can also activate nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) signaling pathways in macrophages, as demonstrated by increased phosphorylation of p38 MAPKs, c-Jun N-terminal kinases (JNKs) and the NF- κ B p65 subunit^{70,79}. However, the relevance of many of these intriguing findings remains to be determined in human CKD. Indoxyl sulfate is but one example of a well-studied uremic solute or toxin involved in inter-organ and/or inter-organism communication. Later in this article, we discuss other examples.

ADME networks in resetting homeostasis

Under physiological circumstances, numerous multi-specific, oligospecific and monospecific transporters, DMEs and their substrates function as a regulated local and systemic small-molecule remote communication network that is closely linked to the neuroendocrine, autonomic, growth factor and cytokine systems traditionally associated with homeostasis (Figs 1,2,4). As with other homeostatic systems, the ADME-related remote sensing and signaling network adapts to help the organism recover from or compensate for

disturbances^{1,5,13–15} (Fig. 4). For example, in a rodent model of obesity-associated renal disease, diminished function of OAT3 was caused by its reduced expression at the plasma membrane, possibly owing to increased internalization of OAT3⁸⁰. Feeding a probiotic to these rodents prevented renal damage and resulted in increased activity of OAT3 at the plasma membrane. This observation was interpreted by the authors as an instance of remote sensing and signaling between the intestine, gut microflora and kidney⁸⁰.

Therefore, regulation of the expression of SLC and ABC transporters (as well as DMEs) results in a highly adaptable system^{5,15,81–83} capable of responding to acute or chronic perturbations of homeostasis, such as occur in CKD and acute AKI (Fig. 4). For example, the internalization, degradation, membrane trafficking and cytoskeletal association of transporters are affected by post-translational modifications, any of which could modify their function and cell surface expression in response to changing levels of substrate, such as are seen in CKD^{81,83}. In addition, covalent modifications might also affect protein–protein interactions involving the transporters. For example, OAT1 seems to exist as a functional homo-oligomer, and the association of OAT1 into homo-oligomers might be dynamic^{83,84}. The expression of OAT4 and other transporters also seems to be regulated by PDZ domain-containing proteins^{85–91}.

As discussed above, the functioning of this remote communication network is likely to be altered in patients with CKD and early uremia. Indeed, many of the components of this network (including multi-specific transporters, transporters of limited specificity and DMEs) show altered expression in the kidney, gut, liver and other tissues in the presence of renal dysfunction.

Gut dysbiosis and remote communication

Many uremic toxins are derived from the gut microflora^{66,92–94}, and numerous reviews have highlighted the role of the gut microbiota as a source of uremic toxins in patients with CKD^{25,65,94,95}. Here, however, we focus on the gut dysbiosis associated with CKD as an indicator of disordered host–microbiota communication. It is becoming increasingly clear that the relationship between the gut microbiota and the host is very complicated, particularly in the setting of CKD. For example, gut dysbiosis is a typical feature of CKD and is characterized by increases in bacterial species involved in the production of several gut-derived uremic toxins⁶⁵, many of which can alter the function and expression of transporters and DMEs and potentially contribute to the progression of CKD⁶⁵. These bacteria are believed to communicate not only with the host but also among themselves⁹⁶, in part through transporters that are evolutionarily related to the ABC and SLC transporters involved in inter-organ communication within the host. Therefore, bidirectional communication seems to operate between the gut microbiota and the host, mediated by small-molecule metabolites derived from the gut microbiota. These metabolites alter the expression and function of transporters and DMEs in the kidney, liver and other tissues, leading to the accumulation of uremic toxins in the blood. In addition, changes in the host ADME-protein-related signaling and communication network in the progressively failing kidney will, in turn, probably lead to further alterations in the gut microbiota. The mechanisms of gut dysbiosis are not well understood, and it is possible that the types and

amounts of uremic toxins arising from the gut microbiota could differ depending on the cause and stage of CKD.

Intriguingly, many microbiota-derived uremic solutes have well-characterized roles in normal and aberrant signaling pathways (kynurenine)⁹⁷, carbohydrate metabolism (CMPF)⁹⁸, redox state (urate)⁹⁹ and cell proliferation (polyamines)¹⁰⁰ and are also considered to be uremic toxins, suggesting that they have a dual toxic and regulatory or metabolic function. This duality might hold important clues for understanding the pathophysiology of CKD at a systems level and for understanding the complex metabolic aberrations that characterize the uremic syndrome in patients with different types and stages of kidney disease. The efficacy of interventions aimed at influencing the gut microbiota might differ according to the type and stage of renal disease.

OAT1 and OAT3 knockout metabolomics

The prototypic OAT, OAT1 (originally identified by us in mice as NKT¹⁰¹), is the main probenecid-sensitive transporter of *para*-aminohippurate in the kidney^{102,103}. The OAT1 pathway has been extremely well studied from the viewpoint of renal physiology, toxicology and pharmacokinetics^{13,15} because it is the route through which many toxins, protein-bound antibiotics, NSAIDs, diuretics and antiviral agents are eliminated^{102,104–108}. For example, mercury, a highly toxic environmental pollutant, is conjugated to glutathione or cystathione and then eliminated from the circulation via OAT1 (reFs^{109–111}). OAT1 also seems to be a major transporter of indoxyl sulfate^{7,8,112}.

Much of our understanding of the role of OAT1 and OAT3 is based on data from *Slc22a6*-knockout and *Slc22a8*-knockout mouse models^{5,13,15}. Metabolomic data and other studies in these mice indicate that OAT1 directly and indirectly influences a wide range of metabolic pathways via transport of many metabolites (such as α -ketoglutarate, urate and pantothenic acid) and signaling molecules, including prostaglandins, cyclic nucleotides, fatty acids and odorants^{7,34,35}.

Although plasma levels of indoxyl sulfate display a major increase in *Slc22a6*-knockout mice^{7,8}, OAT1 also transports other uremic solutes, including *p*-cresol sulfate, kynurenine and hippurate^{7,8}. These molecules (and many others, including kynurenate, indolelactate and xanthurenate) are also transported by the closely related transporter OAT3, which is also found on the basolateral surface of the proximal tubule^{8,20}. OAT1 and OAT3 have partly overlapping specificities for metabolites, signaling molecules and gut microbiota products, including uremic toxins^{8,15,108,113}. Many other uremic solutes thought to be of relevance to CKD or uremia are transported from blood to urine by OAT1 and OAT3, including CMPF, 1-methylguanosine and urate^{7,8}. Indeed, a substantial fraction of all uremic solutes identified thus far interact with OAT1 and/or OAT3 (Table 2), as well as with other SLC family 22 members^{92,93,114}. Single-nucleotide polymorphisms (SNPs) in *SLC22A6* are associated with human CKD and have been suggested to affect the ability of the kidney to handle uremic toxins¹¹⁵

Other uremic solute transporters

OCT2 (encoded by *SLC22A2*) transports cationic uremic solutes, including polyamines (putrescine, spermine and spermidine) and creatinine¹¹⁶, although some of these cationic or zwitterionic molecules can also, to a limited degree, be transported by OATs^{34,117}.

Another member of SLC family 22, OAT2 (encoded by *SLC22A7*), is expressed on erythrocytes^{118,119}. OAT2 seems to be responsible for transporting indoxyl sulfate into erythrocytes, where it induces cell death owing to the production of reactive oxygen species (ROS) via the NADPH oxidase-dependent pathway^{113,119}.

OATP4C1, a member of the OATP family (encoded by *SLCO4C1*), transports a somewhat different set of uremic solutes¹²⁰. Transgenic mice that overexpress human *SLCO4C1* display decreased plasma levels of some uremic toxins, including asymmetric dimethylarginine, guanidine succinate and *trans*-aconitate, compared with wild-type controls¹²⁰.

Transport of the cationic uremic toxin trimethylamine-*N*-oxide (TMAO), which is strongly associated with cardiovascular morbidity^{121,122}, is likely to be mediated by OCT2 and several ABC transporters¹²³. TMAO accumulates in the plasma of *Slc22a8* knockout mice, although whether TMAO is actually transported by OAT3 is not clear⁸. The apical (luminal) efflux of cationic uremic solutes probably involves the SLC47 family of transporters, including multi-drug and toxin extrusion protein 1 (MATE1) and the 2K splice variant of MATE2 (MATE2K)^{124–126}. In general, however, the apical efflux transporters for uremic solutes are not well studied.

Pharmacokinetic implications

Patients with CKD show diminished transport of drugs that are normally excreted in bile as well as increased levels of uremic toxins. These observations suggest that these toxins compete with the drugs for transport via OATP1B1 and OATP1B3, which are expressed in the sinusoidal membrane of hepatocytes as well as other non-renal tissues¹²⁷. In support of this notion, the uremic toxins kynurenate and indoxyl sulfate inhibit OATP1B1-mediated and OATP1B3-mediated transport of methotrexate in a dose-dependent manner¹²⁷.

Several uremic toxins (including CMPF, hippuric acid, indole-3-acetate and indoxyl sulfate) inhibit OATP1B1-mediated uptake of an active metabolite of irinotecan in cells engineered to stably express this transporter¹²⁸. These findings might partially explain why the half-life of this drug metabolite, which is normally excreted in bile, is increased in patients with ESRD¹²⁸. Together, these data provide evidence for potential drug–metabolite interactions at the level of the transporters in non-renal tissues, a phenomenon that seems to be exacerbated in uremia. Indeed, the data also support the notion that non-OAT transporters (such as OATPs) are important for the movement of uremic toxins into non-renal tissue.

Under physiological circumstances, the expression of phase 1 and phase 2 DMEs and transporters is regulated, at least in part, by the gut microbiota^{129–133}. Therefore, not surprisingly, many gut-derived uremic toxins have adverse effects on the expression and

function of phase 1 and phase 2 DMEs and transporters⁶⁵. Patients with CKD are routinely treated with many drugs^{134,135} (an average of 12 different medications¹³⁵) that require DMEs and transporters for ADME. Uremic-toxin-mediated alterations in the function or expression of DMEs and transporters have the potential to drastically affect biotransformation, leading to increased drug half-lives and plasma levels.

Moreover, to the extent that uremia is partly a remote sensing and signaling disorder involving multi-specific SLC and ABC drug transporters, it follows that drug–metabolite interactions resulting from competition for transporters, such as those described above, can exert widespread and unpredictable effects on metabolism and signaling in patients with kidney disease^{6,15}. As CKD progresses and uremic toxins continue to accumulate, drug–metabolite interactions involving transporters and/or DMEs can become more prevalent and more deleterious, potentially contributing to new and/or increased drug toxicities⁶⁵. For example, competition between paracetamol and *p*-cresol for liver sulfotransferases not only leads to increased glucuronidation of paracetamol, instead of its sulfation, but also leads to the production of toxic metabolites of this analgesic owing to shunting of paracetamol to a different metabolic enzyme^{65,136}. In addition, sulfated conjugates of morinidazole are dramatically increased in the plasma of patients with CKD, leading to increased drug exposure, perhaps because this drug competes with uremic toxins for OAT3-mediated uptake in the proximal tubule¹³⁷. Similarly, administration of NSAIDs that inhibit OAT1-mediated and OAT3-mediated transport (namely, ketoprofen and diclofenac)^{138,139} markedly decreases the renal clearance of indoxyl sulfate. The resulting increase in systemic exposure to this uremic toxin¹⁴⁰ could have important clinical ramifications.

Furthermore, the OAT1 and OAT3 metabolic networks extrapolated from omics data obtained in healthy individuals suggest that OAT-transported drugs affect a broad range of metabolic pathways beyond those involved in transporter-level drug–metabolite competition^{34–36}. Although similar metabolic networks have not yet been constructed to reflect the changes resulting from uremia, a similarly wide range of pathways is likely to be affected by OAT-transported drugs⁵. A detailed catalogue of all potential drug–metabolite interactions occurring as a result of competition between drugs and uremic solutes at the transporter level is greatly needed to provide a sound basis for drug dosing in the setting of renal disease⁶.

The reader should also keep in mind that transporters are important therapeutic targets and that almost one-third of the top 200 most frequently prescribed drugs depend upon active secretion in the proximal tubule of the kidney for elimination¹⁴¹. Thus, although drug–drug interactions occur even in patients without renal impairment, they are likely to be even more important in patients with CKD owing to the presence of high levels of uremic solutes. Many uremic solutes also compete with administered drugs and with each other for transporters and DMEs⁶⁵. Hence, drug–drug interactions, drug–uremic solute interactions and uremic solute–uremic solute interactions are likely to be very complicated⁶.

Remote signaling by uremic solutes

Several uremic solutes that are toxic to cells and tissues at high concentrations also directly affect or participate in signaling pathways at low concentrations, some of which are discussed below. However, we emphasize that much of the data come from experiments performed using solute concentrations that differ from those occurring at the relevant tissue site in uremia. Much more data need to be obtained on local levels of uremic toxins, as well as the cellular expression and function of their putative targets, to assess which particular pathways are likely to be affected in patients with renal disease. Nevertheless, the available reports give an indication of potential mechanisms by which uremic toxins can modulate a wide range of metabolic pathways and signaling events.

Kynurenic acid is a ligand of both AHR and GPCR 35 (GPR35)^{142–144} and is important in CNS signaling both under physiological conditions and in disorders such as depression, schizophrenia and Alzheimer disease^{144–146}. Kynurenic acid is synthesized via the kynurenine pathway (through which >95% of dietary tryptophan is metabolized¹⁴⁷) from kynurenine, an intermediate of tryptophan metabolism, by the gut microflora. In the CNS, kynurenic acid is thought to act as an antagonist of *N*-methyl-d-aspartate, kainite and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors¹⁴⁸, as well as the α 7-nicotinic receptor¹⁴⁶.

Outside the CNS, kynurenic acid affects a number of metabolic and immune system pathways. For example, this uremic toxin modulates immune cell function^{149,150} and attenuates the increases in expression and production of tumour necrosis factor induced by treatment with lipopolysaccharide¹⁴⁵. Kynurenic acid-mediated GPR35 signaling also regulates energy metabolism by stimulating lipid metabolism, thermogenesis and the expression of anti-inflammatory genes in adipose tissue¹⁵¹. Kynurenic acid also suppresses weight gain and improves glucose tolerance in animals fed a high-fat diet¹⁵¹. Some of these findings might be relevant to the uremic syndrome.

Another uremic toxin, CMPF (which is transported into pancreatic islet cells by OAT3) is involved in insulin secretion, and this mechanism seems to become aberrant in the setting of gestational diabetes³³. Administration of CMPF to mice fed a high-fat diet not only prevented insulin resistance but also inhibited the activity of acetyl-CoA carboxylase and induced long-term reductions in the expression of several genes (namely, *Acaca*, *Acacb*, *Srebp1* and *Cyp7a1*) involved in the regulation of lipogenesis and glucose metabolism¹⁵². These gene expression changes were correlated with increased levels of fibroblast growth factor 21 and alterations in the expression of components of the mechanistic target of rapamycin (mTOR) pathway¹⁵².

Similar to indoxyl sulfate, *p*-cresol sulfate can affect many intracellular kinase pathways, including those involving cAMP and MAPKs, after being transported into cells^{153,154}. For example, osteoblasts exposed to *p*-cresol sulfate showed evidence of intracellular oxidative stress, including an increase in ROS that could be inhibited by probenecid (presumably reflecting the involvement of an OAT) and activation of the JNK or p38 MAPK pathways leading to apoptotic cell death¹⁵³. Likewise, treatment of human renal proximal tubular

epithelial cells with indoxyl sulfate not only induced ROS production but also activated the MAPK, NF- κ B p65 and RAC α serine/threonine-protein kinase (AKT) signaling pathways¹⁵⁵.

Polyamines that accumulate in patients with CKD, such as spermidine, spermine and putrescine, are implicated in many cellular pathways including apoptosis; cell division, differentiation and proliferation; and signal transduction^{156,157}. For example, activation of eukaryotic translation initiation factor 5A1 (eIF5A1) requires the unusual post-translational modification of a lysine residue at position 50 to hypusine, an essential mechanism for control of cell proliferation that is dependent upon spermidine¹⁵⁸. Binding of polyamines such as spermine to inwardly rectifying K⁺ (Kir) channels also modulates cell proliferation¹⁵⁹.

Uremic solutes potentially affect a wide array of other signaling pathways. For example, redox potential is altered by urate, as are signaling events^{160–162}. In vascular smooth muscle cells, urate activates p38 MAPKs, ERK1 and ERK2 (also known as MAPK3 and MAPK1, respectively), as well as the transcription factors NF- κ B and activator protein 1 (AP-1), leading to increased cellular proliferation and a pro-inflammatory phenotype¹⁶³. Pathways involving nitric oxide are affected by asymmetric and symmetric dimethylarginines as well as some guanidine compounds^{164–166}. For example, asymmetric dimethylarginine is an inhibitor of nitric oxide synthase and directly competes with arginine for the binding site of this enzyme, leading to a reduction in nitric oxide formation. Symmetric dimethylarginine perturbs nitric oxide concentration by inhibiting arginine entry into cells via amino acid transporters¹⁶⁷.

Another uremic toxin, 4-ethylphenyl sulfate (a benzoate-derived compound), is one of several gut-derived uremic toxins that show substantially increased levels in plasma, liver, heart and kidneys in a rat model of CKD¹⁶⁸. Interestingly, this compound accumulates in plasma in a mouse model of autism (which could be reversed by inoculation with the gut bacterium *Bacteroides fragilis*)¹⁶⁹; moreover, administration of 4-ethylphenyl sulfate induces anxiety-like behaviour in wild-type mice¹⁶⁹. This uremic toxin is a component of the urine of male rats, and both 4-ethylphenyl sulfate and its unconjugated form, 4-ethylphenol, are thought to participate in pheromonal communication¹⁷⁰. Taken together, these data suggest that this uremic toxin is involved in inter-organism and inter-organ remote sensing and signaling.

Clinical implications

The remote sensing and signaling hypothesis addresses the roles of drug transporters and DMEs in inter-organ and inter-organism communication via small organic molecules in health and disease. These small organic molecules include metabolites, signaling molecules, gut microbiota products, antioxidants, vitamins and dietary components^{1,5,13–15}. Within the conceptual framework of the remote sensing and signaling hypothesis, uremia can be considered a disorder of inter-organism and inter-organ communication mediated by multi-specific SLC and ABC transporters that are involved in normal metabolism and signaling as well as in the restoration of homeostasis.

Ultimately, this conceptual framework might lead to the development of a formal biological understanding of uremia at a systems biology level and new approaches to the treatment of uremia. For example, inter-organism communication might be modulated by treatment with prebiotics and probiotics, which affect the gut microbiota¹⁷¹ and would presumably reduce levels of gut-microbiota-derived uremic toxins. Another approach is to perturb inter-organism communication by oral administration of agents that absorb uremic toxins, such as AST-120¹⁷². Moreover, given that uremia can be considered a disorder of specific metabolic and signaling pathways, these pathways (as is the case for other complex metabolic diseases) might be amenable not only to nutritional therapy but also to specific targeting by drugs that are already approved for use in other settings. Alone or in combination, these strategies could, perhaps quite rapidly, be translated into novel approaches in the clinic.

Another potential approach involves modulating the expression or function of transporters located in the proximal tubule, perhaps through drugs that affect key transcriptional regulators of these transporters, with the goal of enhancing the renal excretion of uremic toxins. In this regard, it is worth noting that OATs, OCTs and other transporters seem to be regulated by nuclear receptors and transcription factors, including the hepatocyte nuclear factors HNF1 α and HNF4 α ^{51,52}. Strategies that lower the levels of uremic toxins in various tissues and body fluid compartments by targeting influx (SLC) or efflux (mostly ABC) transporters are expected to alter local or systemic toxin levels and might help to ameliorate uremic syndrome. Some anionic uremic solutes (such as hippurate and benzoate) contribute to chronic metabolic acidosis in patients with CKD, and diminishing blood levels of these compounds could attenuate this symptom.

Several published studies indicate that disproportionately high tubular secretion, including of OAT-transported uremic toxins, probably occurs in patients with impaired renal function^{3,173–176}. The disproportionately active residual function of the proximal tubule indicates its probable importance in regulating uremic toxin levels and thereby uremia-induced metabolism. Therefore, residual function (and particularly OAT activity) in the proximal tubule might be especially important in patients with declining kidney function in CKD — not only for eliminating uremic toxins and drugs but also for regulating systemic metabolism, possibly via remote communication between the proximal tubule and other organs and/or the gut microbiota. We speculate that there could be a period early in the development of uremic syndrome when local and systemic aberrations are subtle and affect a limited number of disparate metabolic and signaling pathways. This situation might be analogous to metabolic syndrome, which is a potentially reversible precursor to the development of type 2 diabetes mellitus. Perhaps early uremic syndrome might be similarly amenable to drug-based or dietary interventions that selectively target specific metabolic and signaling pathways. However, as uremia progresses, similar or different but overlapping sets of molecules might cause overt cellular toxicity and further progression of CKD and pleiotropically affect many aspects of metabolism and signaling. In this situation, approaches that target multiple pathways might be necessary.

Among patients with similar levels of renal dysfunction, who will get uremic syndrome and which tissues will primarily be affected is difficult to predict. This difficulty might, in substantial part, be a function of the specific SLC influx and ABC efflux transporters

expressed in susceptible tissue, their levels of expression at the cell surface and the functional capacity of these transporters. Thus, we might expect that SNPs or combinations of SNPs that determine either the level of expression (non-coding SNPs) or the function (coding SNPs) of a transporter might adversely affect the handling of uremic toxins^{177,178}. Patients with ESRD on dialysis bearing SNPs in *ABCG2* (Q126X, rs72552713; and Q141K, rs22331142) that impair the function of the corresponding protein, a renal and intestinal transporter, not only had significantly higher serum levels of urate than patients with normal versions of the protein but also required earlier initiation of dialysis³⁹. A single SNP in OAT1 has also been associated with CKD¹¹⁵. As net levels of uremic toxins depend on influx as well as efflux, the function of both influx and efflux transporters needs to be considered¹⁷⁸.

The links between these drug transporters and phase 1 and phase 2 DMEs provide another opportunity to alter the levels of toxic uremic solutes, many of which are substrates for DMEs. The function and/or expression of phase 1 or phase 2 DMEs could potentially be modulated by enzyme activators and/or inhibitors or nuclear receptor agonists that regulate DME expression and thereby affect local or systemic levels of toxic uremic solutes. Given the plethora of DMEs, which are likely to act on dozens of clinically important uremic solutes, many potential targets can be explored.

Finally, it is obvious from the complexity of the metabolic networks constructed around OAT1 and other transporters^{34,35} that uremic toxins might not simply compete directly for transport with drugs and physiologically beneficial metabolites. Rather, the competition between drugs, key endogenous metabolites and uremic toxins could lead to unexpected and complex cascade effects. These will be important to define in future studies on the role of OATs and other uremic toxin transporters in regulating metabolic networks in both healthy states and in CKD.

Conclusions

A characteristic feature of kidney failure and the uremic syndrome is the accumulation of protein-bound and free small molecules in plasma. Many are endogenous compounds derived from cellular metabolism but others are derived from the gut microbiota, which also undergoes dramatic changes in response to the host's loss of kidney function. Dysbiosis of the gut microbiota leads to increased production of existing as well as new uremic solutes and toxins. ADME of many of these compounds is mediated by a complex network of SLC and ABC transporters and DMEs. Consequently, dynamic changes occur in transporter-mediated and DME-mediated small-molecule remote communication between the gut microbiota and the failing kidney (and possibly other organs). In other words, the reduced elimination and plasma accumulation of these small molecules, driven by the progressively failing kidney, as well as their continued generation by the gut microbiota, reset the 'normal' levels of these substrates for the network of SLC and ABC transporters and DMEs involved in their ADME. This resetting of the system (which probably involves organs other than the failing kidney) occurs in addition to the resetting of homeostasis associated with the loss of other renal functions. These other renal functions might or might not directly involve

transporters or DMEs but could still be indirectly related to ADME via growth factor, cytokine and neuroendocrine pathways.

Moreover, many gut-microbiota-derived uremic solutes also function as signaling molecules. These signaling molecules regulate or modulate the expression of genes encoding ADME-related proteins via their effects on nuclear receptors, GPCRs, kinases and redox status. Accordingly, these small molecules transmit critical situational (homeostatic) information back and forth between cells (including between organelles), tissues and organs (that is, the intestine, liver, kidney and brain) and between organisms (namely, the host and gut microbiota). Thus, from the perspective of the remote sensing and signaling hypothesis, the failing kidney and worsening uremic syndrome profoundly influence both inter-organism and inter-organ small-molecule remote communication. The many changes in expression and/or function of multi-specific transporters and DMEs across tissues in the setting of CKD suggest that alterations in this inter-organ and inter-organism communication network represent an attempt to preserve homeostasis in this pathophysiological setting. As this network of genes and proteins is also involved in drug ADME, perturbations of remote sensing and signaling are likely to be further exacerbated by the many pharmacological agents administered to patients with CKD owing to increased competition between these drugs and uremic solutes for transporters that are part of the ADME network. Understanding the uremic syndrome from the systems biology perspective of the remote sensing and signaling hypothesis could have important clinical ramifications. For example, implicit in this framework is the idea that early in the development of kidney failure and uremic syndrome, the number of ADME pathways affected by alterations in remote communication and sensing might be limited and therefore could be specifically targeted to forestall full-blown uremia.

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Key points

- The uremic syndrome (also known as uraemic syndrome) associated with chronic kidney disease (CKD) is characterized by complex local and systemic derangements in metabolism and signaling.
- CKD involves aberrant inter-organ (gut–liver–kidney–brain) and inter-organism (host–gut microbiota) remote communication via small molecules, including uremic solutes, metabolites and signaling molecules.
- Aspects of uremic syndrome can be considered disordered remote sensing and signaling mediated by a multi-organ network of solute carrier (SLC) and ATP-binding cassette (ABC) transporters and drug-metabolizing enzymes (DMEs).
- The remote sensing and signaling hypothesis provides a systems biology framework for understanding the role of these transporters and DMEs in small-molecule-mediated inter-organ and inter-organism communication.
- Transported uremic solutes (including gut-microbiota-derived indoxyl sulfate) can affect multiple signaling pathways.
- Viewing CKD and uremic syndrome through the lens of the remote sensing and signaling hypothesis provides fresh perspectives on the metabolic derangements of CKD that might lead to novel therapies.

Box 1 |**Xenobiotic absorption, distribution, metabolism and elimination**

After intestinal absorption, xenobiotic metabolism modifies the chemical structure of potentially hazardous compounds, including exogenous drugs and toxins and endogenous metabolites and signalling molecules. This biotransformation increases the water solubility of lipophilic compounds, which facilitates their excretion from the body. Hepatocytes are the primary site of xenobiotic metabolism, but it also occurs in cells of the gastrointestinal tract, lungs, kidneys and skin^{179,180}.

Phase 1 xenobiotic metabolism involves the introduction or unmasking of a functional group through the action of various drug-metabolizing enzymes (DMEs), including oxidases, reductases, hydrolases and hydroxylases. The most important enzyme family involved in biotransformation is the cytochrome P450 superfamily^{179,180}. Xenobiotics can also undergo phase 2 metabolism, in which conjugation reactions attach species such as acetyl groups, methyl groups, glutathione, sulfate, glucuronic acid and glycine^{179,180}. The resulting compounds are generally very polar and can be rapidly eliminated from the body.

Some solute carrier (SLC) and ATP-binding cassette (ABC) transporters in tissues such as the gut, liver and kidney are key to the absorption, distribution, metabolism and elimination (ADME) not only of xenobiotics but also of metabolites, signalling molecules, nutrients and antioxidants. Sometimes, transporter-mediated ADME is referred to as phase 3 xenobiotic metabolism^{179,181–183}. For example, in the liver, transporter-mediated uptake clears xenobiotics from blood into hepatocytes^{182,183}. The biotransformed metabolites of these xenobiotics are directly secreted into bile by ABC transporters expressed on the canalicular membrane and excreted via the gut (although some metabolites are resorbed back into the blood from the intestine)¹⁸⁰. In addition, some biotransformed metabolites are transported from hepatocytes into the blood by ABC transporters expressed on the basolateral cell membrane. Once in the systemic circulation, these metabolites — some of which are active and/or toxic (for example, indoxyl sulfate) — can access other organs and body fluids via other SLC and ABC transporters. Ultimately, they are cleared from the blood and eliminated in the urine via the SLC transporters organic anion transporter 1 (OAT1), OAT3 and organic cation transporter 2 (OCT2) and the ABC transporters P-glycoprotein, multidrug resistance-associated protein 2 (MRP2; also known as canalicular multispecific organic anion transporter 1) and MRP4 on renal proximal tubule cells.

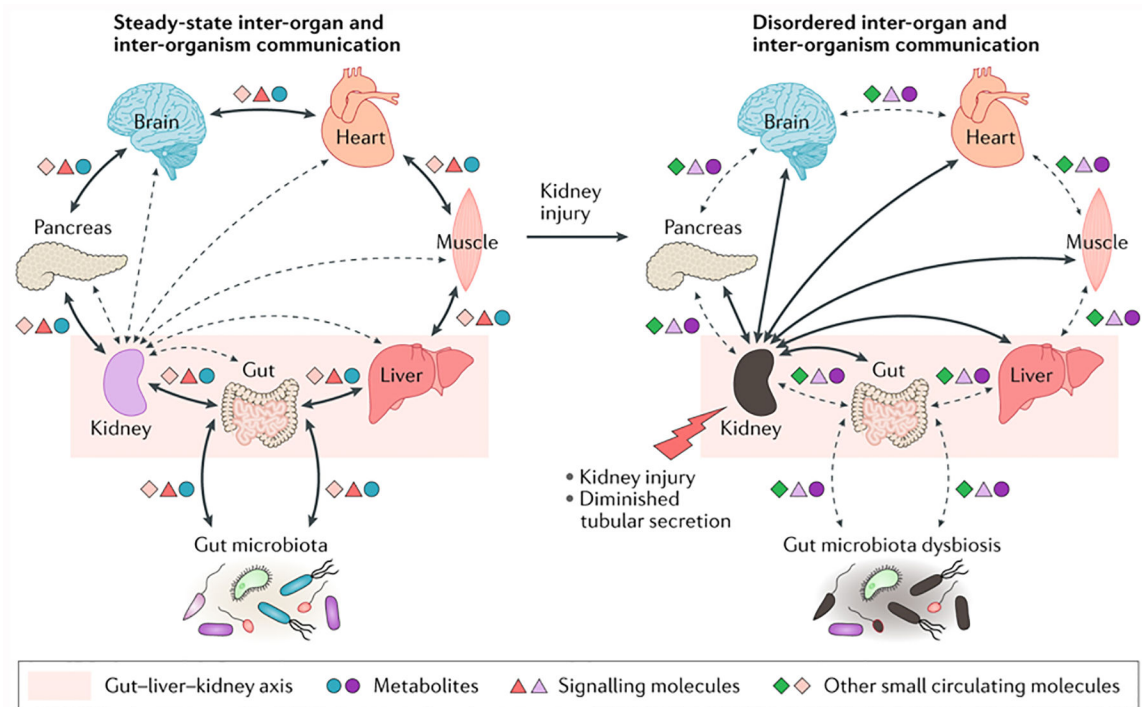


Figure 1. Aberrant inter-organ and inter-organism communication contributes to uremic syndrome.

According to the remote sensing and signaling hypothesis, illustrated here from the perspective of the kidney, steady-state communication between the kidney and other organs and body fluids involves the movement of metabolites, signaling molecules and other small circulating molecules via solute carrier (SLC) and ATP-binding cassette (ABC) transporters. These transporters are expressed in many tissues, including the kidney, liver, pancreas, brain, intestine and muscle. Therefore, injury to the kidney leads to diminished tubular secretion and results in disordered remote communication. Some of these molecules can regulate the expression (via nuclear receptor activation) and/or function of SLC and ABC transporters or phase 1 and phase 2 drug-metabolizing enzymes (DMEs) in distinct cells, tissues and organs, thereby effecting local and global physiological alterations, accompanied by dysbiosis of gut microbiota (including the loss or gain of some bacterial strains). The multi-specificity of some ABC and SLC transporters, together with their different and modifiable tissue expression and/or trafficking, might help to restore homeostasis after organ dysfunction and injury. The differences in color of the symbols representing metabolites, signaling molecules and other small circulating molecules that interact with transporters represent alterations in the concentration and/or identity of these compounds under physiological versus pathological conditions.

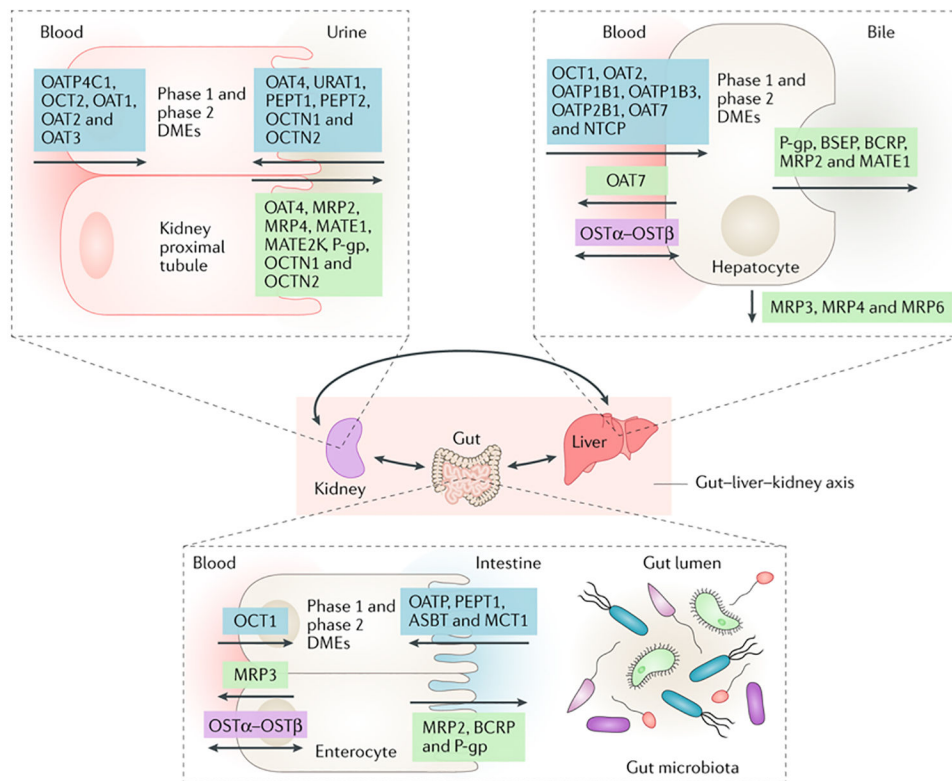


Figure 2. The gut–liver–kidney axis.

Within the remote sensing and signaling communication network, the gut–liver–kidney axis drives the absorption, distribution, metabolism and excretion of small molecules, including endogenous metabolites, signaling molecules, products of the gut microbiota, nuclear receptors and antioxidants. Products derived from gut microbiota that cross the intestinal barrier are removed from the blood by solute carrier (SLC) and ATP-binding cassette (ABC) transporters on hepatocytes, where they (and other small molecules) are metabolized by phase 1 and phase 2 drug-metabolizing enzymes (DMEs). Ultimately, many of these products are cleared from the body via the kidney in the urine through the action of SLC and ABC transporters on the proximal tubule cells. Some transporters in different tissues are thought to function in both directions. MATE1, multi-drug and toxin extrusion protein 1; MATE2K, 2K splice variant of MATE2; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein.

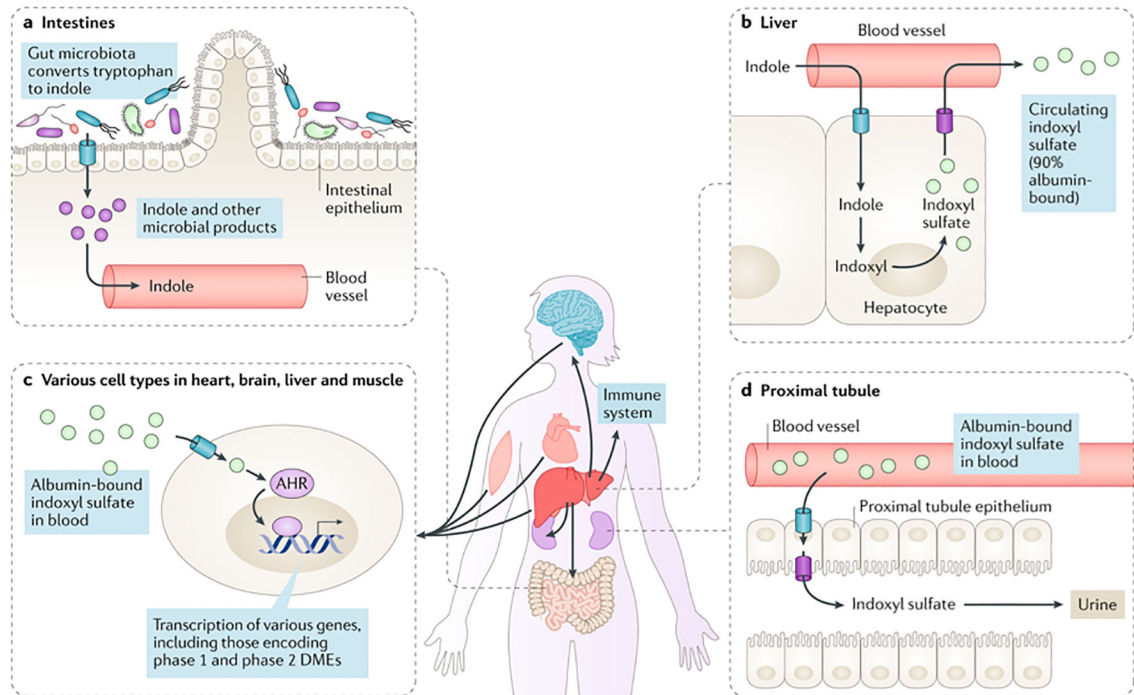


Figure 3. The role of indoxyl sulfate in inter-organism and inter-organ remote communication.
a) Indole is created in the lumen of the gut, via the metabolism of tryptophan by the gut microbiota, and absorbed across the gut wall into the blood. **b)** Circulating indole is taken up by hepatocytes, where it is metabolized first to indoxyl and then to indoxyl sulfate. Indoxyl sulfate is transported back into the circulation where the majority of it circulates bound to albumin and where it is distributed to and interacts with other organs, such as the brain, immune system and muscle, and with the gut microbiota. **c)** Indoxyl sulfate gains access to tissues and cells, where it signals through the aryl hydrocarbon receptor (AHR), leading to alterations in the expression of a number of genes in these tissues. **d)** Indoxyl sulfate is ultimately excreted by the kidney via solute carrier (SLC) and ATP-binding cassette (ABC) transporters located in the basolateral (such as organic anion transporter 1 (OAT1) and OAT3) and apical (such as multidrug resistance-associated protein 4 (MRP4)) membranes of proximal tubule cells (influx and efflux transporters are indicated by blue and purple barrels, respectively).

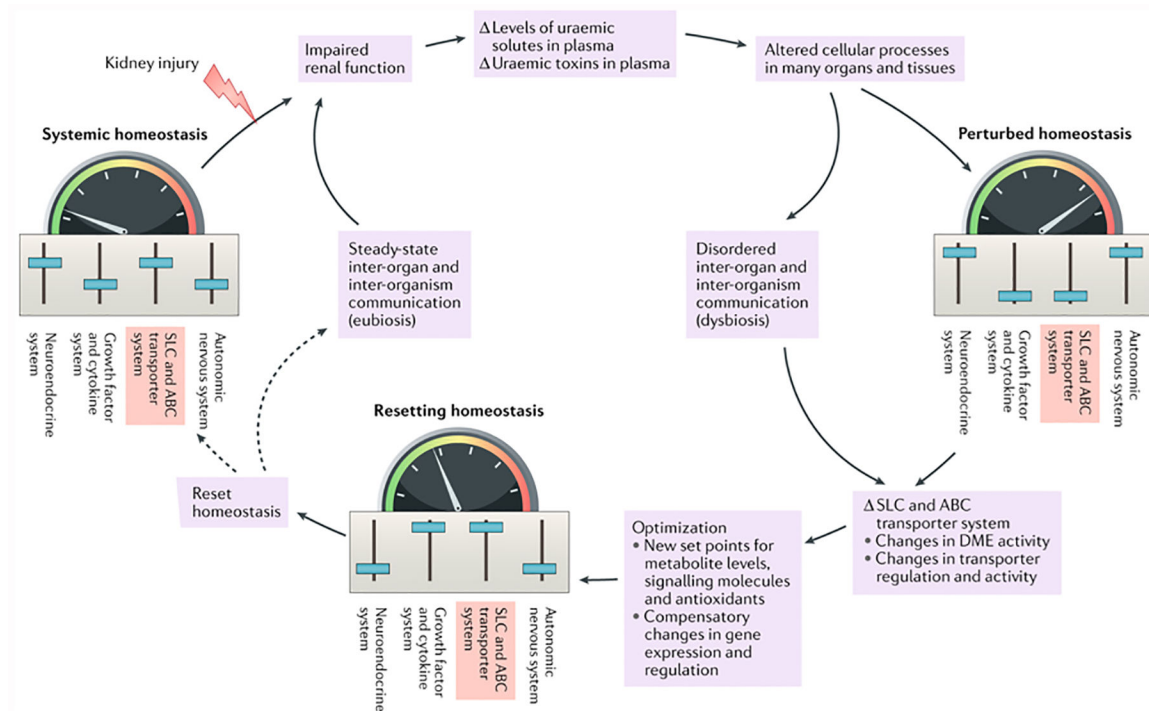


Figure 4. A remote sensing and signalling system maintains homeostasis in the steady state and resets homeostasis following perturbations due to kidney dysfunction and microbiota dysbiosis. Small molecules with informational content are important in transmitting signals to remote tissues and/or organs in the maintenance of homeostasis. In essence, the small-molecule substrates of multi-specific solute carrier (SLC) and ATP-binding cassette (ABC) transporters act in concert with other transporters of limited specificity, as well as with phase 1 and phase 2 drug-metabolizing enzymes (DMEs), as part of a highly flexible inter-organ and inter-organism communication network. Under physiological conditions, this network works in concert with other systems to maintain steady-state homeostasis. Injury to the kidney resulting in diminished kidney function and reduced tubular secretion can lead to the accumulation of uremic solutes and uremic toxins in plasma. The increased levels of these small molecules can lead to alterations in cell functions and processes in multiple tissues and organs, resulting in perturbed homeostasis. The components of this network optimize metabolic pathways, signaling pathways, the control of redox status and other mechanisms necessary for homeostasis in different tissues and body fluid compartments, as well as in different organisms. This system is intertwined with and works in parallel with other homeostatic mediators, such as growth factors, cytokines and the neuroendocrine and vasoregulatory systems. The flexibility of the system enables homeostasis to be restored or reset at a new (presumably compensatory) set point despite the presence or progression of renal disease. Sliders in each picture represent the set points of each of the homeostatic systems, which are altered following organ injury and adjusted during the resetting of homeostasis. The colored scale and arrow represent the homeostatic setting in the various stages.

Table 1 |

Transporters in the kidney of importance for uremic toxins

Transporter name		ligand polarity	Tissue expression	examples of drugs interacting with transporter	examples of uremic toxins interacting with transporter
protein	gene				
Basolateral (influx) transporters					
OAT1	SLC22A6	Anion	Kidney and choroid plexus	Probenecid, adefovir and indometacin	Anthranilic acid, indoxyl sulfate and p-cresol sulfate
OAT3	SLC22A8	Anion	Kidney, choroid plexus and blood-brain barrier	Probenecid, methotrexate and cimetidine	Indoxyl sulfate, p-cresol sulfate and CMPF
OATP1B1	SLCO1B1	Anion	Liver	Methotrexate and lopinavir	Kynurenic acid, indole-3-acetic acid and indoxyl sulfate
OATP1B3	SLCO1B3	Anion	Liver	Methotrexate and telmisartan	Kynurenic acid, indole-3-acetic acid and indoxyl sulfate
OATP4C1	SLCO4C1	Anion	Kidney	Ritonavir, crizotinib and saquinavir	Symmetric dimethylarginine, guanidine succinate and trans-aconitate
OCT1	SLC22A1	Cation	Kidney and liver	Metformin, ganciclovir and acyclovir	TMAO and methylguanidine
OCT2	SLC22A2	Cation	Kidney	Metformin, cimetidine and lamivudine	TMAO, putrescine and methylguanidine
Apical (efflux) transporters					
MRP2	ABCC2	Anion	Kidney, intestine and liver	Probenecid, methotrexate and amoxicillin	Anthranilic acid, indoxyl sulfate and p-cresol sulfate
MRP4	ABCC4	Anion	Kidney, liver and blood-brain barrier	Methotrexate, cefotaxime and furosemide	Anthranilic acid, indoxyl sulfate and p-cresol sulfate
MATE1	SLC47A1	Cation	Kidney and liver	Metformin, cimetidine and topotecan	TMAO and creatinine
MATE2K	SLC47A2	Cation	Kidney	Metformin, cimetidine and topotecan	TMAO and creatinine
BCRP	ABCG2	Anion	Kidney, intestine, liver and blood-brain barrier	Methotrexate, gefitinib and imatinib	Uric acid, indoxyl sulfate, hippuric acid and kynurenic acid

CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid; MATE1, multi-drug and toxin extrusion protein 1; MATE2K, 2K splice variant of MATE2; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; TMAO, trimethylamine-*N*-oxide.

Table 2 |

Some uremic toxins that interact with OAT1 and/or OAT3

Metabolite	In vivo metabolomics ^a		In vitro Interaction	
	OAT1	OAT3	OAT1	OAT3
CMPF	NS	✓	✓	✓
Creatinine	✓	✓	✓	✓
Cysteine	✓	NS	✓	✓
Hypoxanthine	NS	NS	✓	✓
Indoleacetate	NS	✓	✓	✓
Indoxyl sulfate	✓	✓	✓	✓
Kynurenate	✓	NS	✓	✓
Kynurenine	✓	✓	✓	ND
N2,N2-dimethyl-guanosine	✓	NS	ND	ND
N6-methyladenosine	✓	NS	ND	ND
Orotate	✓	NS	ND	ND
p-Cresol sulfate	NS	✓	✓	✓
Putrescine	NS	✓	ND	ND
S-adenosylhomocysteine	✓	NS	ND	ND
Trimethylamine-N-oxide	NS	✓	ND	ND
Uric acid	✓	✓	✓	✓

CMPF; 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid; ND, not done; NS, no significant change; OAT, organic anion transporter.

^aPlasma and urine levels of each metabolite were compared in *Slc22a6*-knockout and *Slc22a8*-knockout mice, both versus wild-type mice. Data compiled from several studies, including refs^{7,102,184,185}.