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OAT, OATP, and MRP Drug Transporters and the Remote Sensing and Signaling Theory

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Abstract

The coordinated movement of organic anions (e.g., drugs, metabolites, signaling molecules, nutrients, antioxidants, gut microbiome products) between tissues and body fluids depends, in large part, on organic anion transporters (OATs) [solute carrier 22 (SLC22)], organic anion transporting polypeptides (OATPs) [solute carrier organic (SLCO)], and multidrug resistance proteins (MRPs) [ATP-binding cassette, subfamily C (ABCC)]. Depending on the range of substrates, transporters in these families can be considered multispecific, oligospecific, or (relatively) monospecific. Systems biology analyses of these transporters in the context of expression patterns reveal they are hubs in networks involved in interorgan and interorganismal communication. The remote sensing and signaling theory explains how the coordinated functions of drug transporters, drug-metabolizing enzymes, and regulatory proteins play a role in optimizing systemic and local levels of important endogenous small molecules. We focus on the role of OATs, OATPs, and MRPs in endogenous metabolism and how their substrates (e.g., bile acids, short chain fatty acids, urate, uremic toxins) mediate interorgan and interorganismal communication and help maintain and restore homeostasis in healthy and disease states.

INTRODUCTION

ADME: absorption, distribution, metabolism, excretion

DME: drug-metabolizing enzyme

OAT: organic anion transporter

OATP: organic anion transporter polypeptide

MRP: multidrug resistance protein

RSST: remote sensing and signaling theory

RSS: remote sensing and signaling

Drug transporters have been extensively studied for their role in the absorption, distribution, metabolism, and excretion (ADME) of pharmaceutical compounds (1, 2). Indeed, anionic drugs are handled by a relatively small number of (~100–200) drug transporters and drug-metabolizing enzymes (DMEs). If related transporters, enzymes, and regulatory proteins (e.g., nuclear receptors, kinases) are included, the ADME protein network may include 500–1,000 proteins, or as much as 5% of all human genes (3, 4). Even though the overwhelming focus in industry, academia, and regulatory agencies continues to be on the role of these proteins in drug ADME, it is clear that their physiological role has to do with the virtually simultaneous regulation of numerous metabolites, nutrients, antioxidants, and signaling molecules, including those derived from gut microbes (1, 5–10).

In the sections that follow, we focus on the coordinated role of organic anion transporters (OATs), organic anion transporting polypeptides (OATPs), and multidrug resistance proteins (MRPs) in the movement of anionic compounds—including drugs, toxins, endogenous metabolites, gut microbe products, nutrients, and natural products—and why this perspective is important in health and disease. We frame this discussion in the context of the remote sensing and signaling theory (RSST), which seeks to explain the biological role of "drug" and other transporters, "drug"-metabolizing enzymes, and regulatory proteins in interorgan (e.g., gut–liver–kidney–brain) and interorganismal (e.g., host–gut microbiome, mother–fetus) communication via endogenous small molecules.

OATs, OATPs, AND MRPs IN THE CONTEXTS OF DRUG ADME AND THE REMOTE SENSING AND SIGNALING THEORY

Much of our understanding of organic anion handling proteins comes from studies of small-molecule pharmaceuticals in the context of ADME. Drugs can also be viewed as probes of an evolutionarily conserved endogenous communication system that optimizes small-molecule levels in tissues and body fluids: the remote sensing and signaling (RSS) system (network). Drugs and endogenous metabolites make use of similar, but not identical, protein networks spanning organs and even organisms (3). Nevertheless, the endogenous RSS network would appear to have an objective—maintenance of small-molecule homeostasis—different from that of the drug ADME network, which is the detoxification and elimination of xenobiotics. As we discuss below, these can be viewed as overlapping networks, one for endogenous molecules and one for exogenous (often nonnatural) molecules. Alternatively, the drug ADME network can be viewed as an operational subset of the larger RSS network, the latter focused on the homeostasis of endogenous organic anions and other small molecules.

A simple way to characterize the organic anions we discuss is to describe them as small molecules with a carbon skeleton that have a net negative charge at physiological pH (~7.0) and a molecular weight roughly between 100 and 1,500 Da. Of the numerous biologically important small molecules identified to date, a large fraction are organic anions. These include drugs, endogenous metabolites, natural products, gut microbiome products, antioxidants, exogenous toxins, and nutrients. Bile acids, cyclic nucleotides, sex steroids, eicosanoids, prostaglandins, dicarboxylates, uremic toxins (e.g., indoxyl sulfate), and urate are well-characterized endogenous organic anions that serve as signaling molecules or key metabolites in physiological (and pathophysiological) processes. When their intracellular and/or extracellular levels are perturbed, homeostasis is disrupted, which can lead to disease states. For example, urate serves as an important antioxidant at baseline levels, but high serum urate can lead to gout, kidney stones, and progression of kidney disease (11). The intracellular and extracellular levels of many endogenous

organic anions must be tightly regulated to ensure proper signaling and metabolism in multiple tissues at multiple scales (interacting organisms, multiorgan systems, tissues, cells, organelles). It should also be noted that organic anions are not membrane permeable, indicating that their distribution is almost entirely mediated by transporters, further suggesting the importance of these proteins in metabolite modulation (12).

While many proteins are involved in the ADME of organic anions, a subset of transporters (OATs, OATPs, and MRPs) plays essential roles in regulating the bulk of endogenous anions at the systemic and tissue levels (13–15). Even though certain organic anions have a clear preference for one transporter over another, multispecific transporters of the OAT [solute carrier 22 (SLC22)], OATP [solute carrier organic (SLCO)], and MRP [ATP-binding cassette, subfamily C (ABCC)] families display overlapping substrate specificity, transporting numerous structurally diverse organic anions. Genetic and physiological studies support the interplay of OATs, OATPs, and MRPs in interorgan and interorganismal communication (**Figure 1**). In the kidney, OATs are the main organic anion uptake transporters and MRPs (MRP2 and MRP4) are the main efflux

SLC22: solute carrier 22

SLCO: solute carrier organic

ABCC: ATP-binding cassette

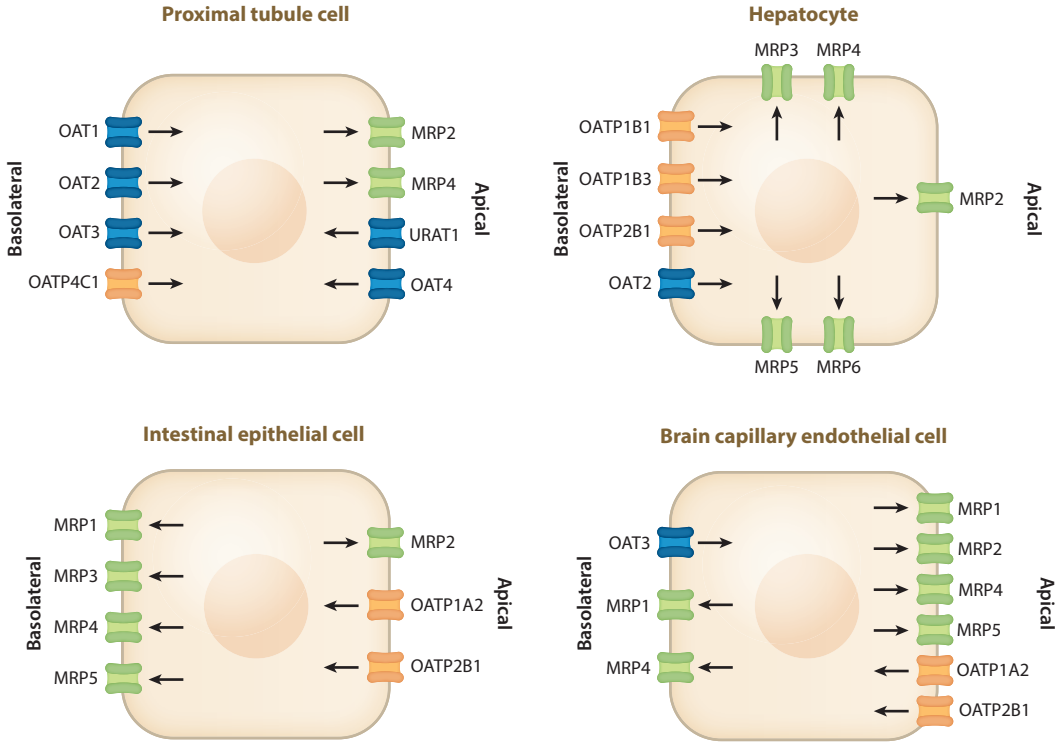


Figure 1

OATs, OATPs, and MRPs are expressed in polarized barrier epithelial tissues. Organic anion handling proteins are differentially expressed at the basolateral and apical membranes of cells in the kidney, liver, intestine, and brain. When considered in light of their uptake or efflux mechanisms, the combinatorial possibilities for interaction between these multi-, oligo-, or monospecific transporters on both surfaces and their substrates create a robust, multiorgan network for handling small molecules and affecting net flux between tissues and body fluids. We emphasize that these are not the only multi-, oligo-, and monospecific transporters expressed on these surfaces involved in handling small molecules (1, 2). The multispecific drug transporters OAT1, OAT3, OATP1B1, OATP1B3, MRP2, MRP3, and MRP4 are probably the best studied of these transporters from a functional perspective; much less is known about some of the other transporters that are shown. Abbreviations: MRP, multidrug resistance protein; OAT, organic anion transporter; OATP, organic anion transporter polypeptide.

transporters; these must work together within the same organ on the same sets of organic anion substrates to achieve net flux across the proximal tubule. Consistent with this notion, separate studies have shown that OAT1 protein expression is highly correlated with OAT3 and MRP2/MRP4 expression (16, 17). In the liver, OATPs (OATP1B1 and OATP1B3) are the main uptake transporters and MRPs are the main efflux transporters. Other tissues, such as the intestine, brain, and epithelia, also express a unique set of drug transporters on basolateral and apical surfaces, often including OATs, OATPs, and MRPs.

In a cross-tissue coexpression network of over 500 ADME and related proteins—a putative RSS network—members of the SLC22, SLCO, and ABCC families appear to be important hubs serving endogenous functions. This is notable because the networks, which have been partly validated, were generated from tissue expression patterns and protein-protein interactions (3, 18, 19). The remote sensing and signaling theory aims to explain how these and other transporters, as well as DMEs and regulatory proteins, play an active role in (re)optimizing endogenous small-molecule homeostasis in health and disease states such as organ injury (11, 20, 21). While initially conceived with the SLC22 family in mind, considerable evidence from multiple groups supports the expansion of the RSST to include other notable drug handling proteins (18, 22).

Other support for the primary endogenous function of OATs, OATPs, and MRPs comes from evolutionary studies. The ABCC family has orthologs expressed in bacteria and nearly all vertebrates, indicating an ancient origin (23). The SLCO and SLC22 families are not as deeply conserved as the ABCC family, but these families exist in species such as flies, sea urchins, and fish, even though it is often hard to identify clear orthologs for human family members (10, 24–27). Note that model organisms such as flies would seem to have their own RSS networks, the objective of which presumably remains optimizing the levels of endogenous small molecules at the systemic and local levels. In addition, the RSS network and its subnetworks have likely been heavily shaped by the need to handle xenobiotics in the context of plant–animal warfare (28). The SLC22 and SLCO transporters involved in regulating the response to oxidative stress, which are related to mammalian SLC22 transporters of antioxidants, have been localized to the fly renal system (Malpighian tubule) (10, 24, 29, 30). MRP4 has also been implicated in the fly oxidative stress response (31).

The role of OATs, OATPs, and MRPs in endogenous physiology does not imply that these and other ADME genes are not involved in handling drugs and exogenous toxins. The RSST simply argues that the remarkable ability of the body to absorb, distribute, metabolize, and excrete xenobiotics is a secondary outcome of the RSS system that coordinates interorgan and interorganismal small-molecule communication in the service of homeostasis. The RSS system must simultaneously optimize levels of numerous metabolites, signaling molecules, antioxidants, nutrients, and gut microbe products in many tissues and body fluids in the face of multiple, sometimes conflicting, objectives (e.g., multiorgan dysfunction). In that sense, it is analogous to the endocrine system and the autonomic nervous system and, indeed, works in parallel with these systems. OATs, OATPs, and MRPs are transporters of hormones (e.g., thyroid hormones and sex steroids) and neurotransmitters. Thus, the availability of key signaling molecules is regulated by the RSS system. Loss of function of a thyroid hormone-transporting OATP at the mouse blood-brain barrier leads to underdevelopment of the central nervous system (32), while a single nucleotide polymorphism (SNP) in human SLC22A24, an OAT, alters sex steroid homeostasis and is associated with acne (33).

When comparing the drug ADME network with the RSS network, note that exogenous drugs and toxins are eliminated either unchanged or after metabolism by DMEs. The goal of small-molecule drug design is generally to ensure eventual clearance from the body. Not so for endogenous metabolites, which generally are not entirely eliminated and must remain in the body at some baseline level, often within a tightly controlled range of concentrations. This difference

highlights a key RSST concept: Even as drugs and toxins hitchhike onto OATs, OATPs, MRPs, and other proteins in the RSS system, the objective of that system is to optimize endogenous small-molecule levels across multiple scales (e.g., organism, organ, organelle) (1, 34). In this view, the drug ADME network is, for the most part, a subset of the endogenous RSS network. Following this line of thinking implies that fully working out the implications of the RSST can be the basis of a new pharmacokinetic theory deeply based in biology and physiology (homeostasis) that can also predict small-molecule drug ADME, direct and indirect drug-metabolite interactions (DMIs), and drug-induced metabolic disorders (35).

DMI: drug-metabolite interaction

SLC: solute carrier

THE SLC22, SLCO, AND ABCC TRANSPORTER FAMILIES AND OTHER PROTEINS INVOLVED IN REMOTE SENSING AND SIGNALING OF ORGANIC ANIONS

SLC22 Family: OATs, OCTs, and OCTNs

The SLC22 family includes genes that code for OATs, organic cation transporters (OCTs), and organic carnitine (zwitterion) transporters (OCTNs), among other proteins (21). These proteins are expressed in nearly all tissues, especially barrier epithelia that separate blood from body fluids or other interfaces, such as the kidney, liver, intestine, retina, choroid plexus, testis, placenta, and olfactory epithelium (21, 25). All of these transporters have 12 transmembrane domains (TMDs) with one large extracellular loop and intracellular loop, and they are generally uptake transporters. Here, we focus mainly on well-studied human and/or mouse proteins involved in the classical transport of organic anions, such as OAT1, OAT3, and related OATs. They are among the proteins considered most likely to be involved in drug-drug interactions, and regulatory agencies have recommended that novel drug entities be tested for in vitro interactions with OAT1 and OAT3 (US Food and Drug Administration guidance). This testing has led to a plethora of data demonstrating transport of antivirals, antibiotics, nonsteroidal anti-inflammatory drugs, antihypertensives, diuretics, and many other clinically relevant small-molecule drugs (36–38) (**Figure 2**). Knockout mouse data also support the role of OATs in transporting drugs and toxins (39–43). In addition to drugs, there is now a large amount of data on the role of OATs in transporting small, negatively charged endogenous compounds, including metabolites, signaling molecules, nutrients, gut microbiome products, antioxidants, and uremic toxins (5–8, 44–52).

SLCO Family: OATPs

The SLCO family codes for the OATPs, which, like the SLC22 family, contain 12 TMDs and are uptake transporters (14). The human OATP family consists of 11 proteins, although the multispecific hepatic uptake transporters OATP1B1 and OATP1B3, being well-known drug transporters, receive the most research interest. Like OAT1 and OAT3, they have been recommended for in vitro testing with novel drug entities (53). These proteins tend to transport larger, more hydrophobic substrates than do the OATs and are involved in the uptake of statins and sartans, among others (54). Endogenous molecules transported by OATPs partly overlap with the OATs and include metabolites, signaling molecules (e.g., prostaglandins), nutrients, gut microbe products, and uremic toxins (32, 55–60).

ABCC Family: MRPs

The ABCC genes encode the MRPs, although not all ABCC genes are considered MRPs. The MRPs differ from the aforementioned SLC transporters in that they have different structural

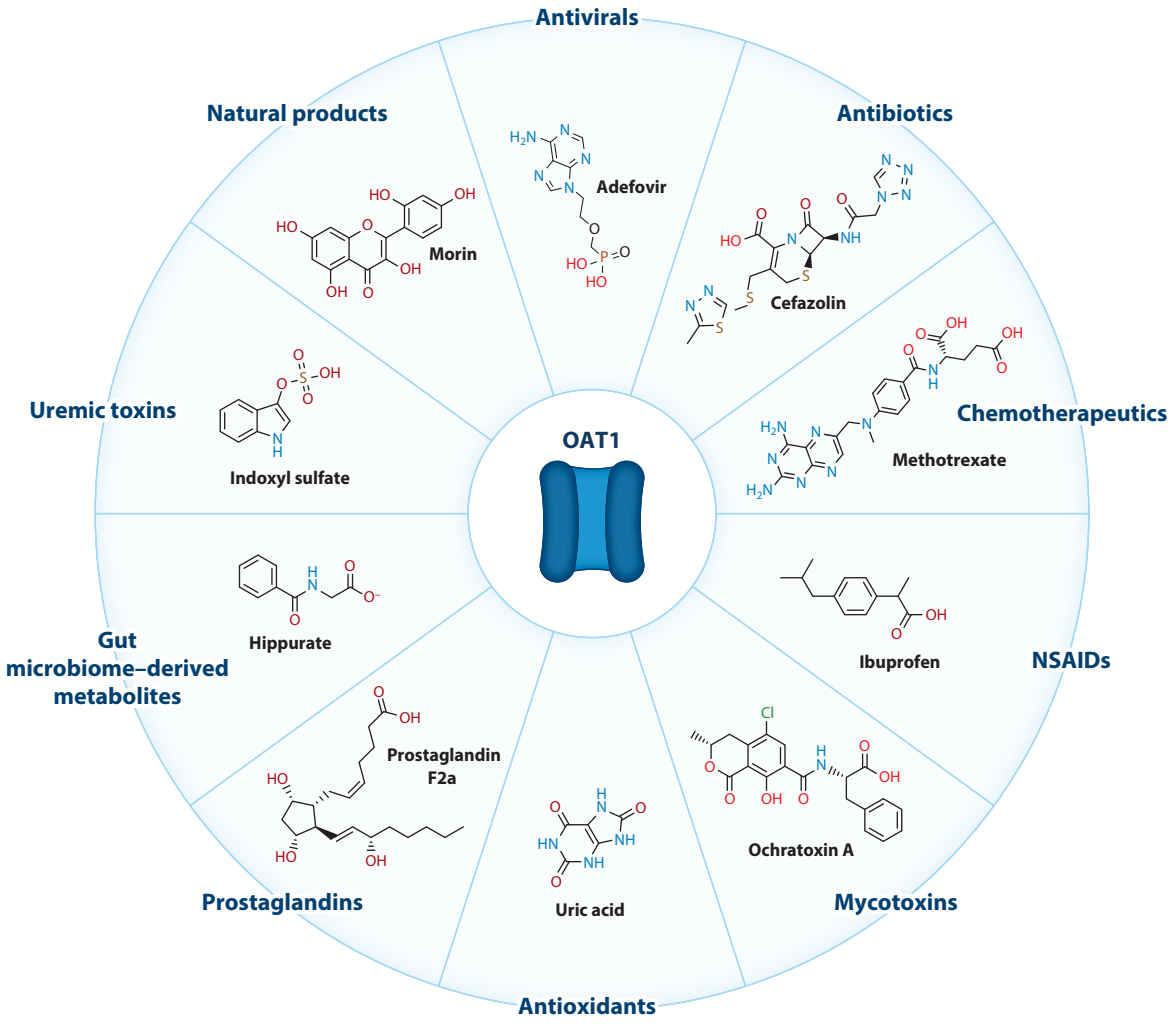


Figure 2

OAT1 is a multispecific transporter that interacts with several classes of small-molecule compounds. OAT1 interacts in vitro or in vivo with numerous drugs, endogenous metabolites, natural products, antioxidants, nutrients, gut microbiome–derived compounds, and toxins. Other transporters in the OAT (OAT3), OATP (OATP1B1/OATP1B3), and MRP (MRP2/MRP4) families handle similar classes of small molecules. Abbreviations: MRP, multidrug resistance protein; NSAID, nonsteroidal anti-inflammatory drug; OAT, organic anion transporters; OATP, organic anion transporter polypeptide.

features and are efflux transporters that use ATP hydrolysis to supply the energy for their function (61). As a group, these transporters are widely expressed in tissues, including liver, kidney, brain, intestine, and placenta, and they efflux compounds into body fluids (e.g., bile, urine, cerebrospinal fluid). The MRPs are heavily studied because of their perceived role in drug resistance via the rapid efflux of drugs and drug conjugates, which typically have sulfate, glucuronide, or glutathione modifications (15, 62, 63). However, this perceived role seems to be changing in light of the now considerable data on the roles of MRPs in transporting endogenous organic anions, many of which overlap with those transported by OATs and OATPs (15, 61, 62, 64).

Other Important Proteins: BCRP, BSEP, OSTs, DMEs, and Nuclear Receptors

While this review focuses on OATs, OATPs, and MRPs involved in organic anion transport, they are not the only proteins participating in this process. The parts list involved in local and systemic regulation of organic anions—and particularly interorgan and interorganismal communication described in the RSST—is considerably larger. Several other drug transporters, including breast cancer resistance protein (BCRP) (ABCG2) and P-glycoprotein (ABCB1), are involved in the movement of organic anions, most notably drugs and toxins (65, 66). From the perspective of endogenous physiology, also note that bile acids have several associated transporters (67). Na^+-taurocholate cotransporting polypeptide (NTCP) (SLC10A1), bile salt export pump (BSEP) (ABCB11), organic solute transporters (OSTs) (SLC51A/SLC51B), and other proteins are important in the regulation of bile acids in the liver (68–70).

DMEs, particularly Phase II sulfotransferases, glucuronosyltransferases, and glutathione transferases, are essential to the broader physiological function of OATs, OATPs, and MRPs (e.g., gut–liver–kidney axis), as they convert active compounds to organic anions by conjugating a polar group, thus generating substrates for the OATs, OATPs, and MRPs (71). Evidence supports the interplay between enzymes and transporters, whether drugs or metabolites, particularly in the liver (72). Given growing evidence of renal Phase II drug metabolism, we expect this to be the case in the kidney as well (73).

Nuclear receptors respond to small-molecule ligands (including some organic anions) and regulate the expression of the genes that handle these small molecules across several tissues (74). They are among the most well-established sensors in the RSS system (network): Farnesoid X receptor (FXR) responds to bile acids, aryl hydrocarbon receptor (AHR) binds to tryptophan metabolites, peroxisome proliferator-activated receptor (PPAR) and hepatocyte nuclear factor 4 alpha (HNF4α) are activated by fatty acids, and the estrogen receptor and androgen receptor (ER/AR) have sex steroids as ligands (75–77). Furthermore, many nuclear receptors remain orphans, meaning that their endogenous ligands have yet to be discovered (78). These and other orphan or understudied proteins could prove important to the RSST, and their evolutionary conservation suggests an important role (79). There is also growing evidence for the importance of various kinases, including serine-threonine kinases and tyrosine kinases, in remote metabolite sensing and in the direct and indirect regulation of drug and other transporters (80, 81).

NTCP: Na^+-taurocholate cotransporting polypeptide

BSEP: bile salt export pump

OST: organic solute transporter

FXR: farnesoid X receptor

AHR: aryl hydrocarbon receptor

Regulation via Transcription, Posttranscriptional Modification, Translation, and Posttranslational Modification

Crucial to the coordinated expression and function of OATs, OATPs, and MRPs in the optimization of many endogenous small molecules as described in the RSST is the ability to effectively respond to stimuli by changes in expression and activity. This is particularly important in the setting of perturbed homeostasis such as in organ injury, metabolic disorders, and severe kidney disease, all of which can lead to accumulation of deleterious organic anions. Mechanisms for sensing and responding to such changes include transcriptional regulation, which includes activation of nuclear receptors as well as other transcriptional factors. This process is generally considered slow (hours to days) relative to other mechanisms (82).

RNA-binding and RNA-cleaving proteins can lead to several unique transcripts, which are then translated, in what may be a preferential process for certain transcripts. There are reported examples of transporter isoforms that affect organic anion handling. SLC2A9 transports urate on the basolateral membrane; however, an isoform of SLC2A9 is expressed on the apical membrane, which can potentially change the net flux of urate (83). The factors that determine isoform expression and function and how these relate to function are likely relevant to interorgan and

interorganismal small-molecule communication and optimization as described in the RSST, but they have yet to be fully elucidated.

URAT1: urate transporter 1

The RSST is proposed to function as a complex adaptive system that can quickly respond to stimuli (13, 18, 19). While many studies have focused on transcriptional regulation, in consideration of the speed at which these processes might have to occur, it is unlikely that this is the sole mechanism for rapid adaptations. Posttranslational modifications (PTMs) are likely to play a major role in the initial response to homeostatic perturbations, as they can occur at the scale of minutes to hours. Recent reviews have highlighted advances in the biology of PTMs that affect OAT and OATP function (9, 84–86). Among the key results are that kinases, which are activated by endogenous organic anions (cyclic nucleotides), indirectly affect the expression and/or function of OATs at the plasma membrane (87). Seeing that cyclic nucleotides are also substrates of OATs as well as MRPs, we can begin to appreciate the complex web of interactions that lead to transporter-mediated homeostatic mechanisms (88–90).

COMBINATORIAL POSSIBILITIES OF MULTI-, OLIGO-, AND MONOSPECIFIC TRANSPORTERS ON APICAL AND BASOLATERAL SURFACES

Thus far, we have focused mainly on multispecific members of the SLC22, SLCO, and ABCC families. However, these drug transporter families also have what might be called oligospecific (e.g., certain zwitterion transporters) and relatively monospecific [e.g., SLC22A12 or urate transporter 1 (URAT1), a urate transporter] substrate specificities. Because SLC22, SLCO, and ABCC transporters are expressed on apical and basolateral surfaces of epithelial barrier cells in the kidney, liver, and intestine, as well as on opposite surfaces of the brain capillary endothelium constituting the blood-brain barrier, various combinations of multi-, oligo-, and monospecific transporters on both sides of these cells can regulate flux across epithelial and endothelial barriers (13) (**Figure 1**). By modulating the numerous combinations of transporters on apical and basolateral surfaces of many epithelial and endothelial barriers throughout the body, the transcriptional mechanisms and posttranscriptional mechanisms described above can thus regulate net flux of organic anions across these barriers between tissues and body fluid compartments and thereby (re)optimize systemic levels of metabolites, signaling molecules, nutrients, antioxidants, and gut microbe products at multiple scales (91, 92).

IN VIVO EVIDENCE FOR THE ROLE OF OATs, OATPs, AND MRPs IN THE HANDLING OF METABOLITES, SIGNALING MOLECULES, GUT MICROBIOME PRODUCTS, ANTIOXIDANTS, AND NUTRIENTS

In Vivo Knockout Mouse Data

While in vitro assays allow for convenient investigation into transporter function, they are often devoid of physiological context and require in vivo validation. Genetically engineered knockout mice, on the other hand, provide an in vivo context for transporter function (5–8, 18, 39, 42, 46–51, 93–95). With the advances in the generation and analysis of multi-omics data, intermediate phenotypes (e.g., serum/urine metabolomics, tissue transcriptomics, fecal metagenomics) can be determined. These studies have shown that hundreds of endogenous metabolites (e.g., eicosanoids, bilirubin, bile acids, conjugated sex steroids, thyroxine) are likely regulated by OATs, OATPs, and MRPs (32, 96–105). Particularly in the case of the *Oat1* and *Oat3* knockout mice, multi-omics data (e.g., transcriptomics, metabolomics) have been useful for performing systems biology metabolic reconstructions that provide a different, and arguably deeper, understanding of the impact of the gene deletion on metabolism compared with conventional pathway analysis (6–8, 45–47).

Genome Wide Association Studies

Genome wide association studies can be used to predict the role of transporters in physiology and pharmacology in humans by linking phenotypes to SNPs in genes. Numerous studies from both the pharmaceutical and the physiological perspectives have associated drug handling genes with the levels of small-molecule compounds. Some of the organic anion handling proteins appear to be more susceptible to SNPs that lead to phenotypes. For example, the *SLCO1B1* and *SLCO1B3* genes are linked to dozens of unique traits, including altered drug clearance and endogenous metabolite concentration (106). A recent study argued that mutations are not random, and essential genes are less likely to develop SNPs (107).

Human Disease

Studies of SNPs, human mutations, and patients with complex metabolic disease have revealed dysregulation of organic anions and indicated that OATs, OATPs, and MRPs play critical roles in disease. ABCC2 (MRP2) has a strong association with Dubin-Johnson syndrome, a condition characterized by jaundice and abnormal levels of bilirubin, a substrate of ABCC2 (108). SLC22A12, an OAT, is linked to uric acid disorders, including gout, which is in line with its known function as a uric acid reuptake transporter in the apical membrane of the kidney proximal tubule (109). SLCO1B1 and SLCO1B3, which are in tandem on chromosome 12, are associated with Rotor syndrome, which is characterized by hyperbilirubinemia and is consistent with the role of liver OATP1B1 and OATP1B3 in transporting bilirubin and its conjugates (110). It is also possible that these OATs, OATPs, and MRPs play important roles in the progression of complex diseases that are not characterized by perturbed handling of a single metabolite.

THE REMOTE SENSING AND SIGNALING THEORY IN THE CONTEXT OF MULTIORGAN ENDOGENOUS PHYSIOLOGICAL PATHWAYS

The RSST posits that the actively coordinated function of 500 to 1,000 proteins, including ~100–200 multispecific and oligospecific drug ADME proteins, is essential to optimizing the levels of hundreds to thousands of metabolites virtually simultaneously across multiple tissues, body fluids, and even organisms (e.g., host–gut microbiome, mother–fetus, mother–nursing infant). A key concept is how multi-, oligo-, and (relatively) monospecific transporters and enzymes work combinatorially along different, and sometimes intersecting, axes (e.g., gut microbiome–gut–liver–kidney, gut–brain) to regulate interorgan and interorganismal communication via small molecules with high informational content; as we have seen, many of these small molecules with high informational content—key metabolites, signaling molecules, antioxidants, essential nutrients—are organic anions transported by OATs, OATPs, and MRPs (**Figure 3**). Another key concept to appreciate is the operation of the RSS system at multiple scales: organisms, organ systems, organs and tissues, cells, and organelles. Finally, we emphasize that the ADME network for the handling of drugs and exogenous (often industrial) toxins can be viewed as either an overlapping network or, possibly, a subset of the broader RSS network. But we emphasize again that the ADME network is generally viewed in the context of the metabolism/detoxification of drugs and their elimination, whereas the RSS network appears involved mainly in the optimization of levels of endogenous small molecules in tissues and body fluids (homeostasis) as well as remote communication between organisms. Here, we illustrate different aspects of the RSST with well-known examples that show interorgan and interorganismal communication via organic anions with high informational content.

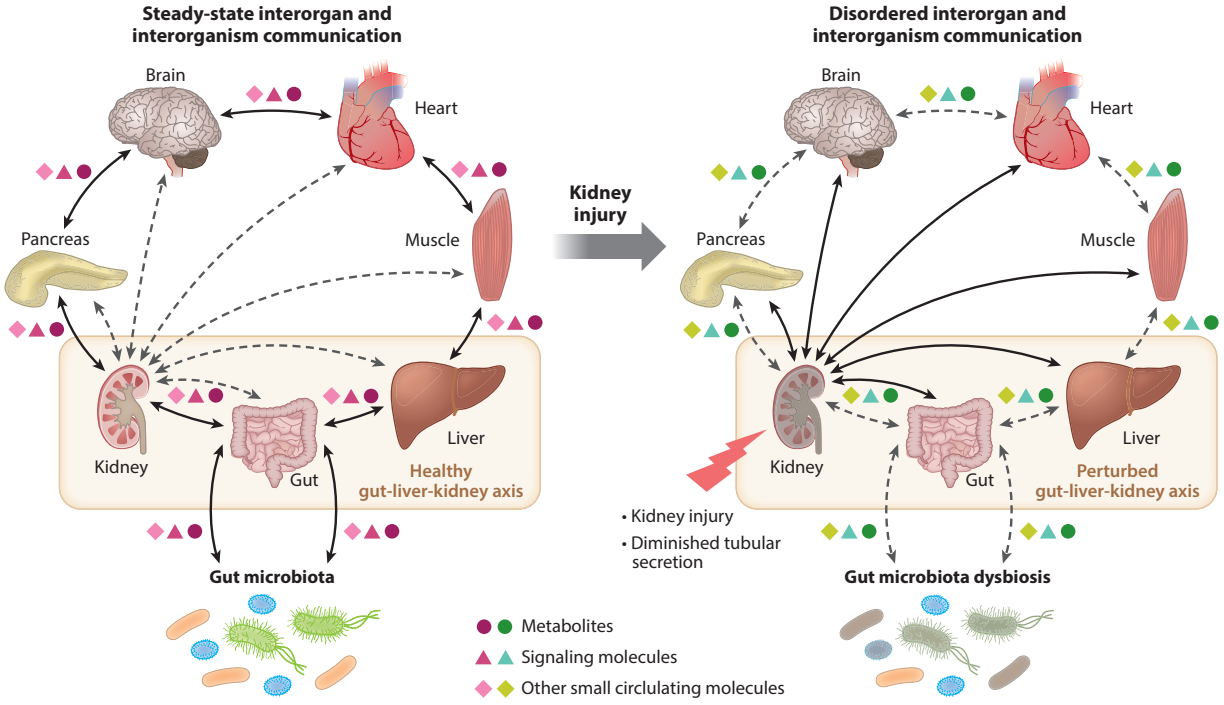


Figure 3

The RSST focuses on the optimization in tissues and body fluids of metabolites, signaling molecules, nutrients, antioxidants, gut microbe products, and other small circulating molecules via OATs, OATPs, MRPs, and other multi-, oligo-, and monospecific transporters and DMEs. These transporters and DMEs are expressed in many tissues, creating the opportunity for interorgan communication involving the aforementioned endogenous small molecules. As shown here, kidney injury leads to decreased function and disordered remote communication. Some of the transported endogenous small molecules activate nuclear receptors, kinases, and other regulatory proteins and thereby alter the expression and/or function of SLC and ABC transporters and DMEs across multiple scales (organelles, cells, tissues, organs). This results in local and global physiological changes as well as alterations of the gut microbiome (i.e., the loss or gain of bacterial strains). The combinations of multi-, oligo-, and monospecificity of transporters and enzymes, as well as their varied tissue expression patterns and posttranslational modifications, aid in the effort to restore homeostasis—in large part by reoptimizing levels of endogenous small molecules in the face of organ dysfunction. Figure adapted with permission from Reference 133. Abbreviations: ABC, ATP-binding cassette; DME, drug-metabolizing enzyme; MRP, multidrug resistance protein; OAT, organic anion transporter; OATP, organic anion transporter polypeptide; RSST, remote sensing and signaling theory; SLC, solute carrier.

Bile Acids

Bile acids are derived from cholesterol in the liver and enter the enterohepatic circulation, where they aid in the emulsification of fats. Bile acids also regulate multiple aspects of signaling through their binding to the nuclear receptor FXR and to G protein–coupled receptors (GPCRs) (e.g., TGR5) (111, 112). Most bile acids activate FXR, which regulates the expression of drug transporters, DMEs, and other genes involved in the RSS system. Bile acids are endogenous anions that are strong ligands for a critical nuclear receptor (master sensor) and can, in part, regulate their own metabolism and transport by altering gene expression patterns in multiple FXR-expressing tissues, including the liver and kidney (113).

Bile acids are generated by cytochrome P450 enzymes acting upon cholesterol. Following the generation of cholic acid or chenodeoxycholic acid, host enzymes in the liver conjugate the bile acids with taurine or glycine. Bile acids have several associated transporters, indicating there are

several redundant and potentially compensatory mechanisms to keep their levels tightly regulated. OATP1B1 and OATP1B3 are the primary uptake transporters in the liver, while MRP2 and MRP4 are the main hepatic efflux transporters. In the intestine, OATPs and MRPs are expressed to help modulate the movement of bile acids into and out of the blood. When bile acids exit enterohepatic circulation, they can become available to other organs, including the kidney. The kidney expresses OAT3, which uptakes certain bile acids, potentially to activate FXR and trigger signaling cascades within the proximal tubule. FXR activation increases the expression of key transporters and enzymes in various tissues, and many of these transporters and enzymes interact directly with bile acids, creating feedback loops that optimize bile acid levels in cells, tissues, and body fluids. Thus, many multispecific transporters (OATs, OATPs, and MRPs) work together with oligospecific and relatively monospecific transporters [OSTs, NTCP, apical sodium-dependent bile acid transporter (ASBT), BSEP] and enzymes to move signaling molecules (bile acids) that activate a remote sensor (FXR) that results in feedback affecting the expression and function of the same transporters and enzymes across tissues, thereby continually optimizing the levels of these signaling molecules.

In addition to the clear interorgan communication via bile acids, there is also an interorganismal aspect mediated by the transport of these small organic anions. The gut microbiome acts directly upon host-generated bile acids through bacterial enzymes that produce deoxycholic acid and lithocholic acid, both of which cannot be produced by the host alone. These secondary bile acids are transported into and out of remote tissues by similar sets of multi-, oligo-, and monospecific transporters, including the OATs, OATPs, and MRPs.

Urate

Urate is briefly mentioned above as an example of the RSST in the setting of organ injury. Urate is one of the downstream products of purine metabolism, and it has been suggested that urate may account for 50% of the human body's antioxidant activity (114). Because of this crucial role, and because high levels of urate can lead to diseases (e.g., gout, kidney stones, hypertension, progression of kidney disease), it is essential that urate be tightly regulated. Commensurately, urate has multiple transporters, mostly in the kidney, that combine to ensure that it remains at the proper concentration (115). Much of urate is filtered by the glomerulus but is highly reabsorbed by apical uptake transporters in the proximal tubule.

In the proximal tubule of the kidney, multi-, oligo-, and relatively monospecific transporters (e.g., OAT1, OAT2, OAT3, SLC2A9, URAT1, OAT4, SLC17A1, SLC17A3, ABCC2, ABCC4, ABCG2) all contribute to urate regulation (11, 49). OAT1 and OAT3 are uptake transporters on the basolateral membrane, SLC2A9 is an efflux transporter on the basolateral membrane that also has an isoform expressed on the apical membrane. OAT2 is another uptake transporter that also transports urate in the kidney and potentially other tissues (116). The apical side of the proximal tubule expresses URAT1 and OAT4, both of which are uptake transporters that rescue urinary urate (117). ABCC2, ABCC4, and ABCG2 are efflux transporters expressed on the apical side of the proximal tubule and also in the intestine (118). Other urate transporters are SLC17A1, which is expressed in the kidney, and SLC17A3, which is expressed in the liver and intestine (119, 120). Importantly, the combinatorial possibilities with all these apical and basolateral transporters in polarized epithelial cells of the kidney, intestine, and liver create a robust system for urate handling.

In health, most urate handling occurs in the kidney, where the major transporters have very high expression, but when renal function is compromised, the expression or activity of ABCG2 in the intestine is increased to promote fecal excretion of urate, demonstrating compensatory

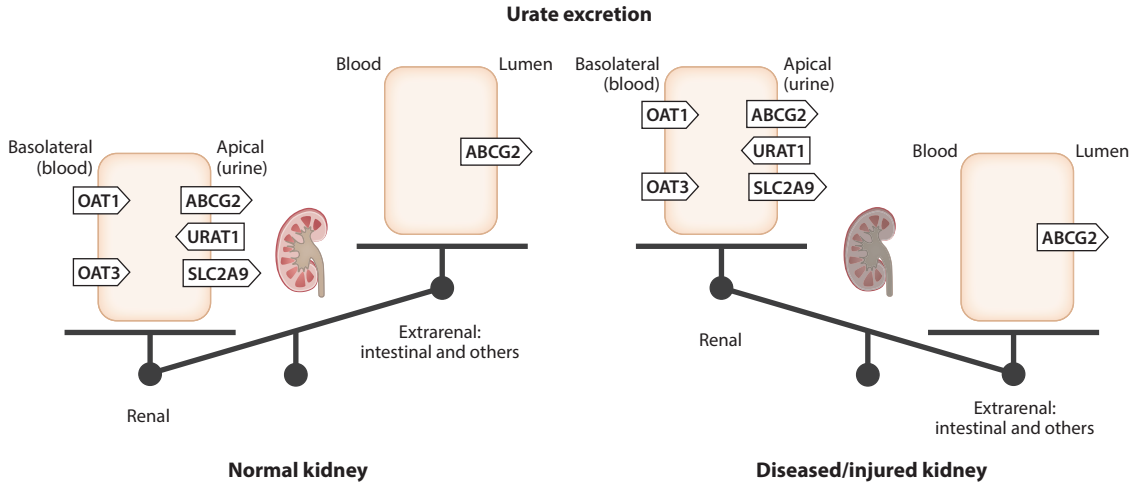


Figure 4

Urate handling in CKD is an example of interorgan compensation by the remote sensing and signaling system (network) to regulate an important endogenous small-molecule antioxidant. In healthy conditions, the systemic levels of urate are largely regulated (about 70% of excretion) by multi-, oligo-, and monospecific uptake and efflux transporters expressed on the basolateral and apical membranes of the kidney proximal tubule, with the remaining 30% of urate excreted by the intestine into the feces. However, when renal function is compromised, as in CKD, the intestinal functional activity/expression of ABCG2 is increased to compensate for the high levels of urate in the setting of a failing kidney. Human, rodent, and in vitro data support the view that transporter-mediated remote small-molecule interorgan communication is an essential part of the compensatory mechanism. Abbreviations: ABC, ATP-binding cassette; CKD, chronic kidney disease; OAT, organic anion transporter; SLC, solute carrier; URAT, urate transporter. Figure adapted with permission from Reference 115.

remote interorgan communication (121) (**Figure 4**). While the mechanism by which ABCG2 is upregulated is not clear, cell culture studies suggest that urate itself or other uremic toxins that accumulate in renal disease trigger this response through transcriptional regulation (122).

Interorganismal Communication

The relevant RSST examples have focused mainly on interorgan communication along axes that express genes/proteins with overlapping substrate specificity. In addition to interorgan communication, there is interorganismal communication, such as between the gut microbes and the host. Interorganismal communication can also occur between the same species, as between the mother and the fetus. This communication is heavily influenced by the transporters expressed at the placenta, which mediates the exchange of nutrients. The placenta expresses several OATs, OATPs, and MRPs, including MRP1–MRP4, SLCO2A1, SLCO22B1, SLCO4A1, SLCO1B1, SLCO3A1, SLC22A6, and SLC22A11, among other transporters (123). Although just beginning to be understood, this is likely another example of numerous multi-, oligo-, and (relatively) monospecific transporters coordinating the tight regulation of the levels of dozens of metabolites to both nourish and protect the fetus.

The host–gut microbiome is another example of interorganismal communication, but it is between different species, as there are thousands of unique bacterial species that exist in communication with the host. The host and gut microbiome have coevolved over time and participate in a symbiotic and dynamic relationship. The microbiome expresses enzymes that are not expressed by the host and generates key signaling molecules that have targets that affect the physiology of the host (124). The list of gut-derived metabolites includes tryptophan derivatives,

tyrosine derivatives, secondary bile acids, short chain fatty acids, and choline derivatives, among others (125–127). Many of these compounds are organic anions and interact with OATs, OATPs, and MRPs in vitro and in vivo.

CKD: chronic kidney disease

From the perspective of OATs, OATPs, and MRPs, gut-derived uremic toxins have garnered research interest because of their accumulation in renal disease. Indoxyl sulfate is a uremic toxin generated from tryptophan that is associated with negative outcomes in late-stage chronic kidney disease (CKD) (128). Indoxyl sulfate is highly bound to albumin and other serum proteins; thus, its regulation is heavily dependent on OAT1 and OAT3 in the proximal tubule (8). One interesting aspect of indoxyl sulfate is that it is not just a toxin, as there is a basal level that exists in all humans, suggesting it may play an endogenous role that is physiologically necessary (129). Thus far, one likely target has been clearly established: AHR, which is best known for its regulation of drug and toxin handling genes in the liver (130). However, recent experiments have provided a clear example

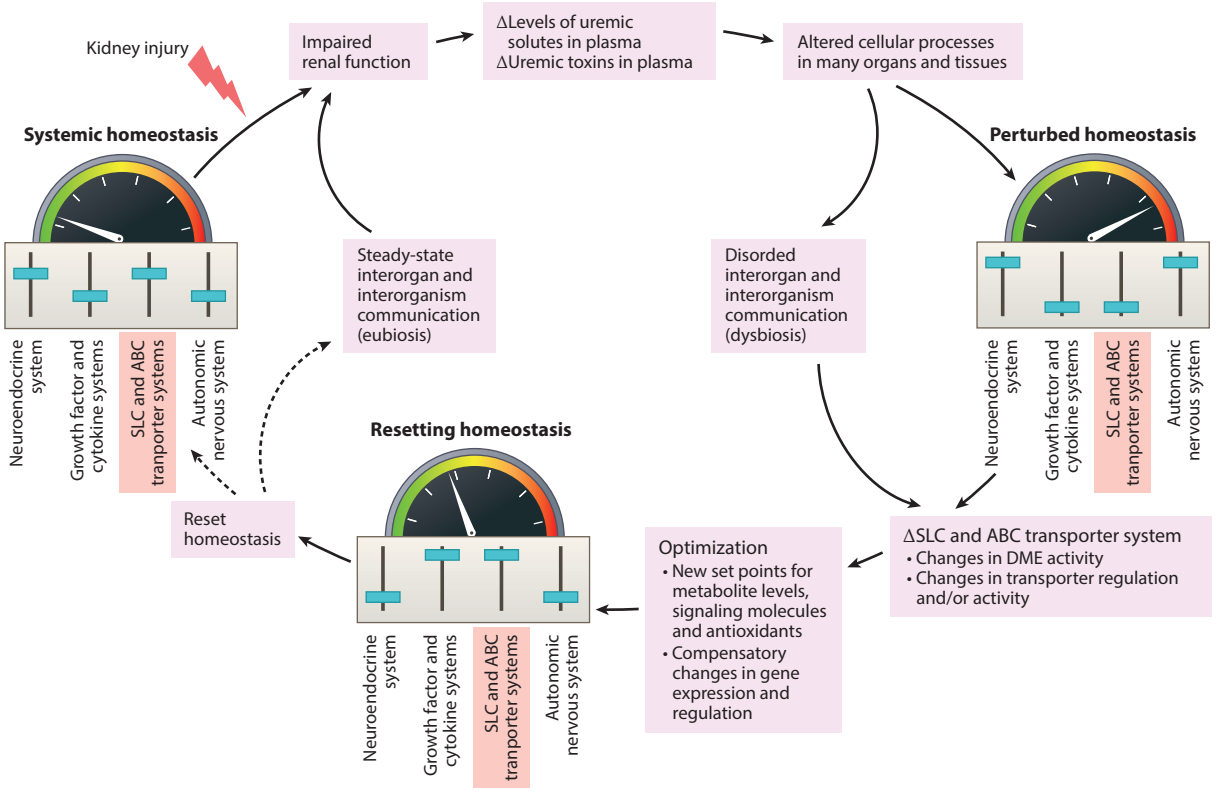


Figure 5

The Remote Sensing and Signaling system works alongside other homeostatic systems, such as the autonomic nervous, neuroendocrine, immune, and growth factor and cytokine systems. Through the transport of relevant small molecules, such as hormones (e.g., thyroxine, sex steroids) and neurotransmitters, the RSS system feeds into the dynamic interplay between well-established homeostatic mechanisms. In this example, kidney injury leads to an increase in circulating uremic toxins. The system senses these abnormal levels as well as other signals from the injured kidney and responds by altering the activity of key transporters, enzymes, and regulatory proteins to return to a new state of homeostasis, and other systems respond accordingly. (Note height of blue indicator bars in the panels labeled Systemic homeostasis, Perturbed homeostasis, and Resetting homeostasis.) Abbreviations: ABC, ATP-binding cassette; DME, drug-metabolizing enzymes; RSS, remote sensing and signaling; SLC, solute carrier. Figure adapted with permission from Reference 133 (CC BY 4.0).

of its role in renal RSS. Indoxyl sulfate was transported into cells via OAT1 and activated AHR, which then upregulated OAT1 activity, presumably to enhance uptake of more indoxyl sulfate and other endogenous organic anions (131). This result raises the possibility that indoxyl sulfate can mediate its own excretion.

CONCLUSION AND REFLECTIONS ON THE REMOTE SENSING AND SIGNALING THEORY

The aforementioned examples cover many aspects of the RSST. The theory necessitates an upending of the traditional role of drug transporters and DMEs. Indeed, the RSST can serve as the underlying biological basis for a radical revision of pharmacokinetics based on the endogenous function of ADME proteins (35). Perhaps the most important aspect of the RSST is understanding what endogenous functions—probably multitudes of sometimes conflicting objectives—are being served by a complex adaptive system that may involve up to 5% of all human genes and that works in collaboration with other homeostatic systems (**Figure 5**). Given the evolutionary conservation of the key gene families, and even perhaps much of the network topology itself, the system seems highly unlikely to have evolved to deal with human-made pharmaceuticals, especially those not derived from natural products. Broadly speaking, the RSS system regulates the levels of hundreds to thousands of molecules across many tissues, body fluids, and scales (**Figures 6–8**). The tightness of the homeostatic regulation presumably depends on the ranges tolerated by organelles, cells, tissues, organs, and the whole system—as well as delays in response to changes in the metabolic and signaling states. In the RSS network, several subnetworks, at least operationally, bear on aspects of exogenous small-molecule handling, for example, toxins and pharmaceutical ADME. In this review, we have focused on the interplay of an important subset of proteins in the RSS

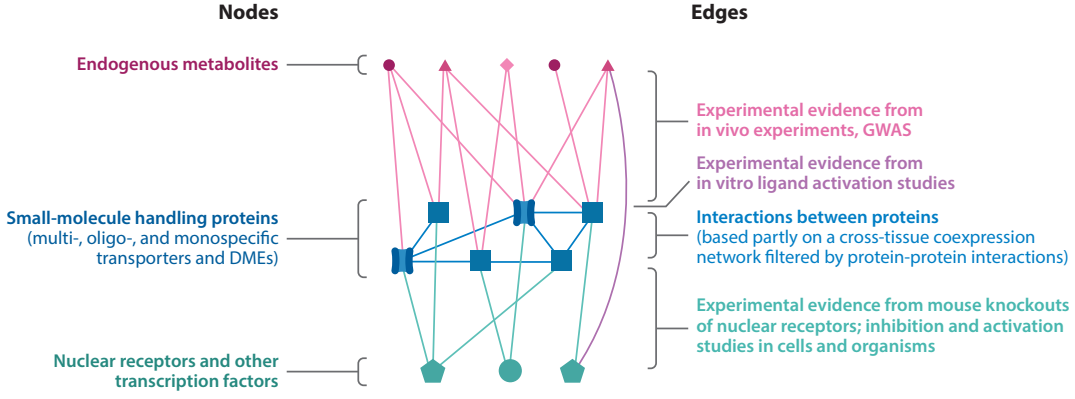


Figure 6

The Remote Sensing and Signaling Network can be represented by overlaying interactions at multiple scales: High-informational-content small molecules (*magenta shapes*) interact with multi-, oligo-, and monospecific transporters and DMEs (*blue shapes*) through direct means such as transport or metabolism. These small molecule–protein interactions (in vitro, in vivo, GWAS) are represented by pink lines in the schematic. In addition to transporters, enzymes, and related proteins, small molecules can also serve as ligands for nuclear receptors and other transcriptional regulators (*teal shapes*). These interactions are represented by the purple line in the schematic. The proteins themselves interact with one another on the basis of similar expression and/or shared functions (*blue lines*). The expression of these proteins is often regulated by ligand-activated nuclear receptors and other transcriptional regulators (*teal lines*). Many such ligands for nuclear receptors are transported by multi-, oligo-, and monospecific transporters into and out of cells and/or metabolized by DMEs. This creates many potential points of regulation as well as feedforward and feedback loops in the Remote Sensing and Signaling Network. Abbreviations: DME, drug-metabolizing enzyme; GWAS, genome-wide association study.

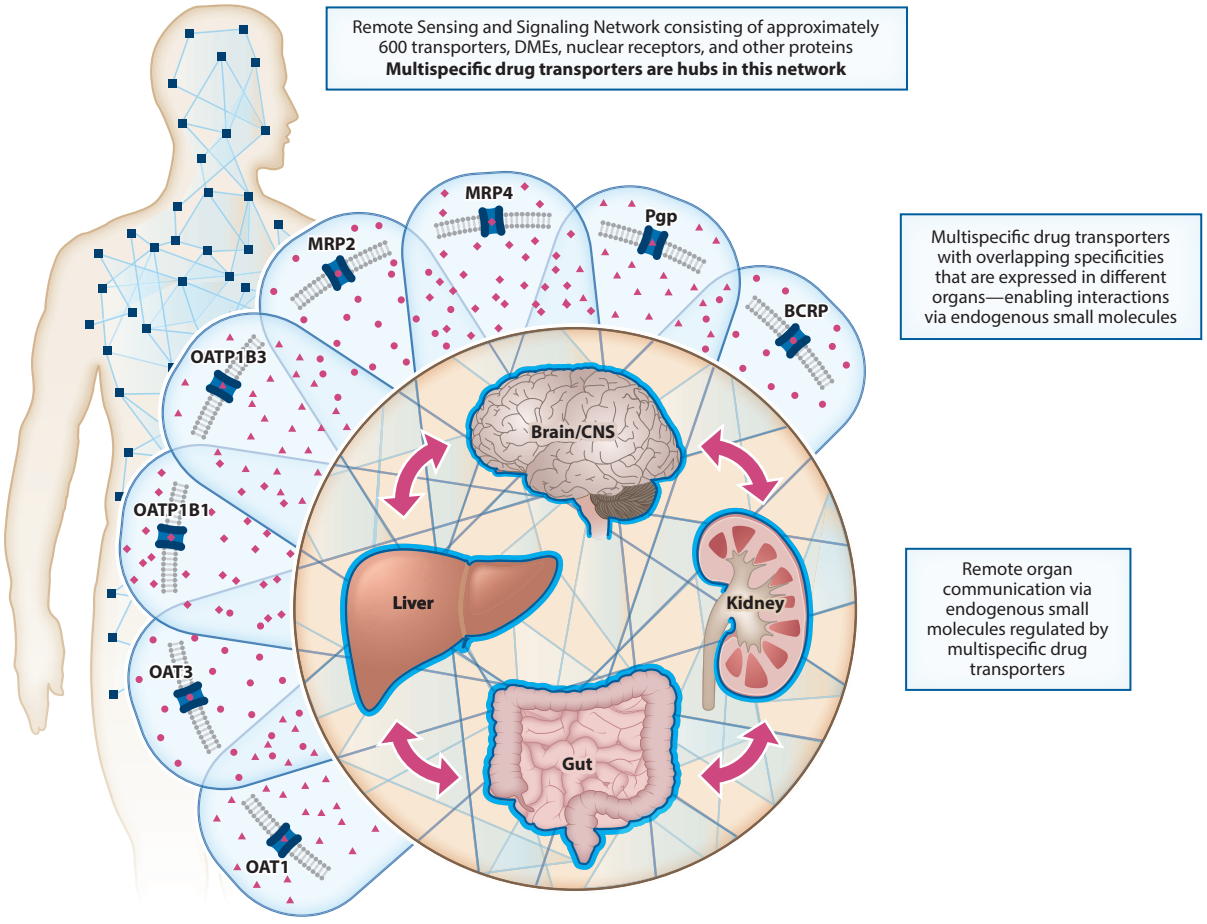
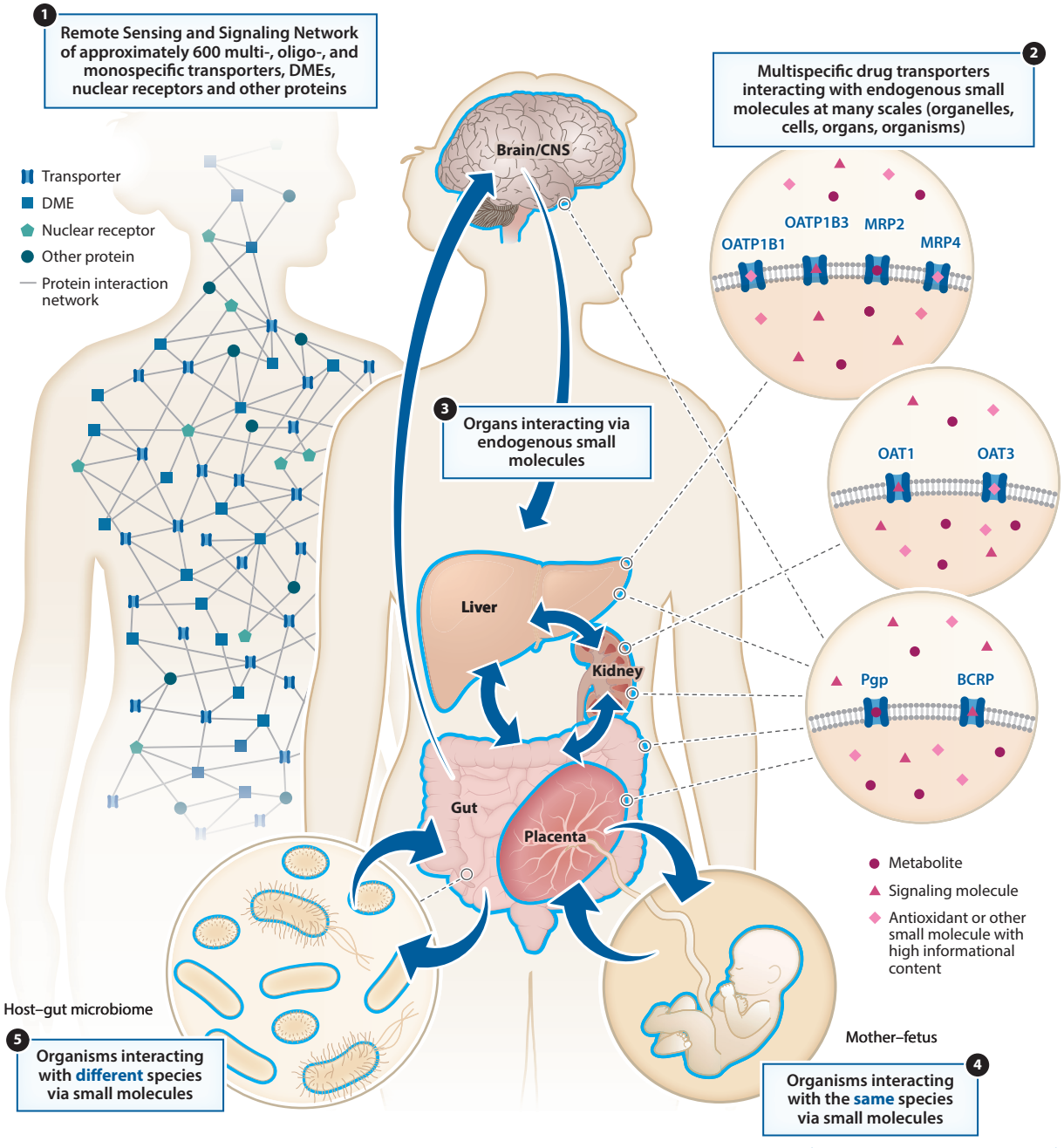


Figure 7

The Remote Sensing and Signaling Network consists of approximately 600 interacting proteins that mediate organ cross talk and regulate the levels of endogenous small molecules in different cells, organs, and body fluid compartments. This can be understood as a protein interaction network consisting of approximately 600 multi-, oligo- and monospecific transporters, DMEs, nuclear receptors, and other proteins. This Remote Sensing and Signaling Network regulates interorgan communication via small molecules with high informational content such as metabolites, signaling molecules, antioxidants, and nutrients. Many of these small molecules are organic anions. Multispecific drug transporters expressed in the gut, liver, kidney, brain, and other organs—including OATs, OATPs, MRPs, BCRP (ABCG2), and Pgp (ABCB1)—play key roles in the regulation of hundreds to thousands of these endogenous small molecules. There is considerable overlap in the metabolic space regulated by these multispecific transporters, creating considerable robustness to perturbation of homeostasis (see **Figures 3** and **4**). This figure emphasizes how multispecific drug transporters, which are hubs in the larger protein interaction network, play a disproportionate role in the regulation of organ cross talk via their effects on small-molecule homeostasis. Not shown here is the role of these transporters in remote communication between organisms, an essential aspect of the remote sensing and signaling theory that is depicted in **Figure 8**. Abbreviations: ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; CNS, central nervous system; DME, drug-metabolizing enzyme; MRP, multidrug resistance protein; OAT, organic anion transporter; OATP, organic anion transporter polypeptide; Pgp, P-glycoprotein; SLC, solute carrier.

network that overlaps with ADME proteins: OATs, OATPs, MRPs, and regulatory proteins involved in handling organic anions. As we have detailed, organic anions, both endogenous and exogenous, have a profound role in physiology and pharmacology/toxicology. Organic anions must be tightly modulated not only by transporters but also by sets of proteins that are able to perform

a wide array of sensing and regulatory functions in a speedy and adaptive manner. The implications of the RSST for understanding DMIs and diseases such as the uremia of CKD have been covered elsewhere (22, 132–135). The theory, deeply based in biology and physiology, provides a new perspective on pharmacokinetics, DMI, and complex metabolic disease.



(*Caption appears on following page*)

Figure 8 (*Figure appears on preceding page*)

The Remote Sensing and Signaling Network can be represented by overlaying interactions at multiple scales: (①) protein interaction network (*blue* and *teal icons*), (②) multispecific drug and other transporters interacting with endogenous small molecules (*magenta* and *pink icons*), (③) organs interacting via endogenous small molecules (*blue arrows*), and organisms interacting with the same (④) or different (⑤) species (*blue arrows*). OATs, OATPs, MRPs, and other multi-, oligo-, or monospecific transporters, such as Pgp (MDR) and BCRP (ABCG2), transport a wide array of endogenous small-molecule substrates. Some of the main drug transporters have overlapping substrate specificity (see **Figure 7**), potentially adding robustness to the regulation of systemic and local levels of organic anions. Remote organs communicate via transporters and enzymes (including DMEs) that regulate the movement and optimization of these high-informational-content metabolites. Each organ expresses a distinct set of transporters and enzymes that preferentially facilitate the movement of specific endogenous small molecules (signals) that interact with regulatory proteins (sensors) and enable numerous feedback loops. Together, this helps optimize levels of endogenous small molecules across multiple scales (e.g., organelles, cells, organs, multiorgan systems, multiple organisms). The Remote Sensing and Signaling Network enables two types of interorganismal communication via these transporters and DMEs. Within the same species, as in the mother–fetus connection, the placenta expresses many multi-, oligo-, and monospecific transporters that aid in the nutrition of the fetus by transporting metabolites and signaling molecules. Host–gut microbiome interactions are also mediated by transporters and enzymes in different organs (e.g., gut–liver–kidney–brain) as indicated, for example, by the effects of numerous small molecules arising in the gut microbiome (tryptophan-derived metabolites, secondary bile acids, fatty acids, and other signaling molecules) upon nuclear receptors, GPCRs, and kinases in remote organs. Not shown is how the Remote Sensing and Signaling Network works alongside other homeostatic systems, such as the autonomic nervous, neuroendocrine, immune, and growth factor and cytokine systems (**Figure 5**). Abbreviations: ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; CNS, central nervous system; DME, drug-metabolizing enzymes; GPCR, G protein–coupled receptor; MRP, multidrug resistance protein; OAT, organic anion transporter; OATP, organic anion transporter polypeptide; Pgp, P-glycoprotein; SLC, solute carrier.

SUMMARY POINTS

1. Organic anion transporters (OATs), organic anion transporter polypeptides (OATPs), multidrug resistance proteins (MRPs) and other transporters, drug-metabolizing enzymes (DMEs), and regulatory proteins are the key actors in the remote sensing and signaling (RSS) system necessary for maintaining and restoring endogenous small-molecule homeostasis. This system functions at multiple scales (multiorganism, organism, organ, organelle).
2. OATs, OATPs, and MRPs regulate the levels of anionic endogenous metabolites, signaling molecules, vitamins, antioxidants, and gut microbiome–derived molecules.
3. OATs, OATPs, MRPs, and other transporters in the RSS system are highly expressed in epithelial tissues (e.g., kidney, liver, intestine), where they localize to apical or basolateral membranes and thereby affect net flux of small molecules between blood, barrier tissue, and body fluids.
4. The tissue expression, apical/basolateral localization, direction of transport, and substrate specificity of OATs, OATPs, and MRPs lead to combinatorial possibilities that allow the RSS system to function as a robust and flexible system capable of facilitating optimization of metabolite levels.
5. OATs, OATPs, MRPs, and other proteins mentioned above regulate interorgan small-molecule remote communication (e.g., gut–liver–kidney) and interorganismal small-molecule remote communication (e.g., host–gut microbiome, mother–fetus) via high-informational-content small molecules. These include signaling molecules that activate nuclear receptors, G protein–coupled receptors, and kinases; antioxidants that regulate the redox state; and endogenous metabolites that feed into key biochemical pathways.

6. The RSS system can be represented as a network consisting of ~500 to 1,000 proteins, including, but not limited to, drug transporters, DMEs, and regulatory proteins (e.g., nuclear receptors). However, drug absorption, distribution, metabolism, and excretion (ADME) proteins are only a subset of this RSS network; along with the other proteins in the network, they primarily serve roles in endogenous metabolism.
7. OATs, OATPs, and MRPs are evolutionarily conserved, suggesting key endogenous roles.
8. The RSS system works in parallel with other homeostatic systems (e.g., autonomic nervous, growth factor, neuroendocrine), resulting in cross talk between these systems mediated by organic anions (e.g., thyroid hormone, sex steroids, neurotransmitters).

FUTURE ISSUES

1. Can the remote sensing and signaling theory (RSST) serve as a biological basis for a new kind of pharmacokinetics?
2. Does the RSST explain drug-metabolite interactions at the level of transporters and enzymes as well as downstream metabolic effects?
3. Since OATs, OATPs, and MRPs transport uremic toxins accumulating in chronic kidney disease (CKD), can the RSST provide a systems biology representation for understanding the metabolic consequences of the uremic syndrome of CKD and other complex metabolic diseases? Can such systems biology representations be used to devise novel therapeutic approaches?
4. What is the relationship of the RSS system (network) to the network of proteins well known to play key roles in the ADME of xenobiotics?

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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