The organic anion transporter family: from physiology to ontogeny and the clinic

DOUGLAS H. SWEET, KEVIN T. BUSH, AND SANJAY K. NIGAM
Departments of Pediatrics and Medicine, Division of Nephrology/Hypertension, University of California, San Diego, La Jolla, California 92093

Sweet, Douglas H., Kevin T. Bush, and Sanjay K. Nigam. The organic anion transporter family: from physiology to ontogeny and the clinic. Am J Physiol Renal Physiol 281: F197–F205, 2001.—The organic anion transporter (OAT) family handles a wide variety of clinically important compounds (antibiotics, nonsteroidal anti-inflammatory drugs, etc.) and toxins. However, little is known about their appearance during development despite documented differences in the handling of anionic drugs among neonates, children, and adults. A similar spatiotemporal pattern of mRNA expression of the OATs (OAT1–4) during kidney development suggests that OAT genes may be useful in understanding the mechanisms of proximal tubule maturation. Moreover, OAT expression in unexpected extrarenal sites (e.g., spinal cord, bone, skin) has also been detected during development, possibly indicating a role for these transporters in the formation or preservation of extrarenal tissues. The cloning of these transporters also paves the way for computer-based modeling of drug-transporter interactions at the molecular level, potentially aiding in the design and assessment of new drugs. Additionally, increased understanding of single nucleotide polymorphisms in OATs and other transporters may eventually allow the use of a patient’s expression profile and polymorphisms to individualize drug therapy.

kidney; proximal tubule; tubulogenesis; renal development

AS A PHYSIOLOGICAL PROCESS, renal organic anion transport has been studied for over a century. The “classic” organic anion transport system has been shown to handle a diverse array of compounds, including pharmacologically important classes of drugs (e.g., β-lactam and sulfonamide antibiotics, loop and thiazide diuretics, nonsteroidal anti-inflammatory drugs, and antiviral agents); drugs that are toxic in overdose (e.g., barbiturates, salicylates); neurotransmitter metabolites (e.g., 5-hydroxyindoleacetic acid (from serotonin) and homovanillic acid (from dopamine)); and environmental pollutants (e.g., the anionic herbicide 2,4-dichlorophenoxyacetic acid). This system plays a critical role in protecting against the toxic effects of anionic substances, whether of endogenous or environmental origin (e.g., ochratoxin A), by removing such substances from the blood via a transport mechanism found in the basolateral membrane of renal epithelial cells (for review, see Refs. 7 and 48).

Transport of these substances across the basolateral membrane of renal epithelial cells is energetically uphill and is accomplished by a “tertiary” active process (Fig. 1). Through its action, Na\(^+-\)K\(^+-\)ATPase maintains an inwardly directed (blood-to-cell) Na\(^+\) gradient. The Na\(^+\) gradient then drives a Na\(^+\)-dicarboxylate cotransporter, sustaining an outwardly directed dicarboxylate gradient that is utilized by a dicarboxylate/organic anion (OA) exchanger to move the OA substrate into the cell (47, 57). This cascade of events indirectly links OA transport to metabolic energy and the Na\(^+\) gradient, allowing entry of a negatively charged substrate against both its chemical concentration gradient and the electrical potential of the cell. Once inside the cell, OAs are subject to intracellular binding and to sequestration within vesicular structures (22, 42). There is
evidence that microtubule-associated vesicular transport may play a role in renal transepithelial movement of OAs (39, 41). Exit into the lumen of the renal tubule across the apical membrane is less well understood. Studies utilizing renal apical membrane vesicle preparations have indicated that luminal OA secretion occurs via an OA exchanger and/or a membrane potential-sensitive facilitative diffusion carrier, depending on the species studied (38, 48, 77). However, studies in intact renal tubules (both mammalian and teleost fish) show no effect of membrane potential and only detect an organic anion exchange mechanism driving apical OA efflux (40, 72).

THE ORGANIC ANION TRANSPORTER FAMILY

The gene now known as both novel kidney transporter (NKT) and organic anion transporter 1 (OAT1) was first isolated by the recently developed technique of codon-optimized differential display PCR (33–36). Apart from a very low level of expression in brain, NKT was found exclusively in mouse kidney. Initial sequence analysis predicted that NKT was a 546-amino acid protein having 11 or 12 putative transmembrane domains (TMD) with a large extracellular loop containing several glycosylation sites between TMD1 and TMD2 and an intracellular loop between TMD6 and TMD7 with multiple protein kinase C (PKC) phosphorylation sites (Fig. 2) (36). In the original description, it was further noted that NKT shared this topology and several transporter-specific amino acid motifs with members of a large superfamily of eukaryotic and bacterial nutrient transporters (now termed the “major facilitator superfamily”) and an even higher degree of homology with two other genes that also had been recently cloned, organic cation transporter 1 (OCT1) (13) and novel liver-specific transport protein (NLT; with undetermined function) (59). The authors further raised the possibility that these three gene products may be the first identified members of a new subgroup of transporters (now termed the “amphiphilic solute facilitator family”; Fig. 3) (36). Given these sequence homologies, the fact that in situ hybridization detected an intense signal in kidney cortex (characteristic of proximal tubule localization) and that renal OCTs and OATs were known to share considerable functional similarity and common substrates (73, 74), the authors concluded that NKT encoded a renal proximal tubule multispecific organic ion transporter (36). Subsequently, the rat homolog to NKT was independently isolated and demonstrated to function as a dicarboxylate/OA exchanger, confirming this hypothesis (64, 67). Another group also subsequently cloned the rat homolog (54, 56), although their database searches did not detect the NKT sequence (33), and it was claimed that this rat homolog represented a novel transporter. With the class of substrate established, the OAT family was identified, and NKT and its homologs are now referred to as OAT1 (10, 27, 37, 50, 51, 56, 67, 78).
It was then demonstrated that NLT (60) also transported OAs and actually represented another OAT isoform, termed OAT2 (55). A third gene of unknown specificity, “reduced in osteosclerosis transporter” (Roct), was, like NKT/OAT1, first cloned using a differential display approach (4, 5, 14). On the basis of its homology to NKT/OAT1 (47%) and NLT/OAT2 (34%), Roct was proposed to be a new OAT family member (5, 14). Indeed, although the function of Roct still remains to be demonstrated, it shares a 92 and 68% identity at the amino acid level with the subsequently cloned OAT3 isoform from rat (rOAT3) and human (hOAT3) and appears to be the murine homolog, Roct/mOAT3 (31, 50). A fourth member, hOAT4, expressed mainly in kidney and placenta, has recently been identified (9). Similar to NKT/mOAT1, all OAT family members appear to possess 12 TMDs, a large glycosylated loop between TMD1 and TMD2, and multiple PKC phosphorylation sites between TMD6 and TMD7. Both glycosylation and PKC phosphorylation seem to be of functional importance to OAT (32, 37, 58, 68, 80). (For convenience, in the ensuing discussion these transporters will be referred to as OAT1–4).

As already discussed, the driving forces of renal OA uptake at the basolateral membrane and secretion across the apical membrane may be distinctly different. The luminal-facilitated diffusion system (identified in apical membrane vesicle experiments) is markedly dependent on membrane potential (38, 77), whereas both the basolateral and luminal exchangers are not (3, 40, 47, 72). When examined, membrane depolarization had no effect on uptake of the prototypical OA substrate p-aminohippurate (PAH) mediated by rOAT1 (67), consistent with data from renal basolateral membrane vesicles (47, 57). It was also observed that the dicarboxylate α-ketoglutarate (α-KG) “cis-inhibited” rOAT1 (67). This was potentially diagnostic in that, as predicted by the model for OA transport, the basolateral dicarboxylate/OA exchanger should be inhibited by external α-KG, whereas luminal PAH carriers should not be inhibited by α-KG (for review, see Ref. 66). As such, dose dependent cis-inhibition and trans-stimulation of rOAT1-mediated PAH uptake by glutarate [also an effective counterion for this exchanger (47)] provided strong support for the functioning of rOAT1 as a dicarboxylate/OA exchanger (67). Subsequently, it was demonstrated that mOAT1 mediates PAH uptake and that this uptake is trans-stimulated by glutarate, providing physiological evidence that mOAT1 function correlates with that of the rat, flounder, and human OAT1 homologs (Sweet DH and Pritchard JB, unpublished observations; 10, 32, 67, 78). Finally, direct evidence of the basolateral subcellular localization of OAT1 was obtained in intact killifish renal proximal tubules transfected with a transporter/green fluorescent protein fusion construct and by immunohistochemistry on adult rat kidney sections (65, 71). On the basis of initial characterization studies, unlike OAT1, uptake mediated by OAT2, OAT3, and OAT4 could not be trans-stimulated, and therefore they are believed to function as facilitative transporters rather than exchangers (9, 31, 55). However, further investigation of the mechanistic properties of these transporters is needed to conclusively resolve this issue.

Although the substrate specificities of the OATs overlap, some noticeable differences have been identified (for review, see Ref. 7). For example, PAH is a good substrate for both OAT1 and OAT3 [Michaelis-Menten constant (Km) = ~10–100 μM], but transport by OAT2 and OAT4 is weak (9, 10, 31, 32, 55, 67, 78). Both OAT1 and OAT2 have been demonstrated to transport salic-
ylate, whereas OAT3 does not, and estrone sulfate uptake by OAT4 was relatively unaffected by a 10,000-fold excess of salicylate (1, 9, 31, 55). Finally, estrone sulfate is a high-affinity substrate for OAT3 and OAT4 ($K_m = \sim 1–3 \, \mu M$) but is not transported by OAT2 (9, 31, 55). Thus despite their polyspecific nature, eventually compounds may be discovered that provide a measure of the individual contributions of each OAT isoform to the overall OA transport capacity of the renal proximal tubule.

**EXPRESSION PATTERNS IN THE EMBRYO, NEWBORN, AND ADULT**

**Adult**

Initially, OAT1 expression was detected in mouse kidney and brain and in human kidney by Northern blot analysis using a mOAT1 probe (Table 1) (36). In situ hybridization on sections of adult mouse kidney for mOAT1 showed that the most intense signal was present in kidney cortex, following a pattern characteristic of proximal tubule localization (36). Subsequently, rOAT1 was detected in kidney and specifically in the choroid plexus by Northern blot and RT-PCR (Sweet DH, unpublished observations; 49, 67). Similarly, hOAT1 expression was observed in kidney and brain via Northern and RT-PCR (10). rOAT2 was found to be highly expressed in liver and at a lower level in kidney (59). Northern analysis showed rOAT3 also was most highly expressed in liver, to a lesser extent in kidney and brain, and with a faint signal in the eye, whereas hOAT3 was strongly detected in the kidney and showed a weak signal in brain after prolonged exposure (31, 50). In situ hybridization detected mOAT3 in developing bone and kidney (5). hOAT4 was seen to be predominantly expressed in the kidney; however, a smaller transcript was readily detected in placenta (9). This is unique to hOAT4, as no other OAT isoform has been observed in placenta, and the authors reported the size difference was due to a shorter 5′-untranslated region in the placental transcript (9). Thus in the adult animal, OATs are consistently found in barrier epithelia, where, at a minimum, they function in the elimination of toxic OAs, whether of endogenous or exogenous origin.

**Developmental**

The ontogeny of renal OA transport maturity has been studied indirectly through physiology. Over fifty years ago, it was noted that newborn infants excreted penicillin at a rate lower than that predicted by body weight alone (2). Studies demonstrated that the primary pharmacokinetic difference was the reduced ability of the newborn kidney to eliminate the drug, most likely due to the “immaturity” of the kidney (23). Indeed, studies of PAH secretion demonstrated a common theme whereby OA secretion is low at birth [in humans, dogs, rats, rabbits, and sheep (8, 25, 26, 46)], increases over the first few weeks of neonatal life, and then declines to adult levels (24, 30, 52). This increase in OA secretion was disproportionate to the increase in renal mass and was thought to reflect the specific maturation of the organic anion transport system (23). Moreover, studies also have shown that OA transport activity varies considerably not only with development but also with exposure to substrate or certain hormones. For example, prior in vivo exposure to a variety of OAs led to increased OA uptake into renal cortical slices, and this induction of OA uptake was prevented by inhibition of protein synthesis by cycloheximide treatment (15, 16, 18, 20, 23). Therefore, substrate exposure induces either synthesis of the OAT, or another transporter or enzyme, required for OA uptake (e.g., Na$^+$-K$^+$-ATPase, Na$^+$-dicarboxylate cotransporter, and/or mitochondrial enzymes) or synthesis of proteins required for the recruitment of transporters that were not previously available for transport at the basolateral surface (conceivably through sorting from an intracellular pool). OA transport also has been shown to be under endocrine regulation. PAH transport can be stimulated by treatment with dexamethasone or thyroid hormones, particularly in young rats (6, 17). Indeed, this may be one potential mechanism by which OA transport is activated during neonatal development. However, susceptibility to induction seems to be restricted to particular periods in the newborn and varies with species, with rabbits exhibiting induction at 1–2 wk but not at 4 wk of age (19), whereas rats exhibit induction at 8 wk but not at 2 wk or before (61). Thus the assumption that clearance of a drug or toxin will remain constant over the course of development is erroneous, and yet precise information concerning the

<table>
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<th>Transporter</th>
<th>Appearance in Murine Kidney</th>
<th>Extrarenal Murine Embryonic Expression</th>
<th>Adult Expression</th>
<th>Ref. No(s).</th>
<th>(Adult)</th>
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<tbody>
<tr>
<td>OAT1 (NKT)</td>
<td>e14–e15 Brain, choroid plexus, spinal cord, dura mater</td>
<td>Kidney, brain, choroid plexus</td>
<td>11, 36, 38, 48, 66</td>
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<tr>
<td>OAT2 (NLT)</td>
<td>e14–e15 Liver, lung, bone, intestine, skin</td>
<td>Kidney, liver</td>
<td>58</td>
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<td></td>
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<tr>
<td>OAT3 (Roct)</td>
<td>e15–e16 Liver, brain, spinal cord</td>
<td>Kidney, liver, bone, brain, eye</td>
<td>6, 33, 49</td>
<td></td>
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<tr>
<td>OAT4</td>
<td>Unknown Unknown</td>
<td>Kidney, placenta</td>
<td>10</td>
<td></td>
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<tr>
<td>OCT1</td>
<td>e15–e16 Liver, atrium, ascending aorta</td>
<td>Kidney, liver, brain, heart, spleen, intestine, placenta, skeletal muscle</td>
<td>14</td>
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OAT, organic anion transporter; NKT, novel kidney transport; NLT, novel liver-specific transport; Roct, reduced in osteosclerosis transporter; OCT, organic cation transporter; e, embryonic day.
mechanisms involved in the ontogeny and expression of these transporters is lacking. Clearly, an appreciation of the ontogeny of OA secretion is central to understanding how anionic drugs are handled by children compared with adults. Nevertheless, until recently virtually nothing was known about the in utero development of the OA transport system. 

In the original description of the NKT/OAT1 gene product, expression was examined during murine development by Northern blot, where no signal was observed until embryonic day 18 (e18), and continued to increase through birth (36). In a more recent study by the same group, very low levels of renal expression of mOAT1 could be detected by Northern analysis as early as e14 or e15 (Table 1), with increasing expression levels through adulthood (45). In situ hybridization analysis confirmed detectable renal mOAT1 transcript expression starting at e14 and also demonstrated a continued rise through embryogenesis, with the highest detectable level present in the adult kidney (there was no detectable expression in metanephric kidneys at e12 or e13) (45). A recent study conducted in rats reproduced the observation in mouse that OAT1 mRNA expression increased through birth, with the highest levels detectable at 1 day postpartum, followed by a decrease to adult levels (44). This appeared to coincide with the capacity of rat cortical slices to transport PAH (44).

Examination of other OAT family members revealed a similar pattern of renal mRNA expression (Table 1). For example, Northern blot and in situ hybridization analysis showed detectable levels of mOAT2 message expression at e14, with the highest level of expression in the adult (45). Levels of mOAT2 transcript in fetal and adult murine kidneys were lower than those seen in the liver (45). This developmental pattern of expression was consistent with previous findings for rOAT2 in the liver (59). Expression of mOAT3 mRNA was detected by in situ hybridization in the developing kidney at e15–e16 of embryogenesis and displayed a distinctive labeling in the renal cortex (45). Similar to the expression pattern seen by Northern blot with mOAT1 and mOAT2, renal mOAT3 transcript levels continued to increase during development in utero and into adulthood (45).

Interestingly, this same pattern of expression was found for OCT1 (Table 1), a member of the OCT family with which OAT1 shares a high degree of homology (36). OCT1 transcripts appeared in the embryonic mouse kidney between e15 and e16 and increased during development (45). All of these transporters are almost exclusively expressed in the proximal tubule of the kidney at about the same time of development. Thus not only do these genes represent potentially useful and important markers of proximal tubule maturation, but this remarkably similar pattern of spatiotemporal expression of related genes also raises the possibility of a common regulatory pathway governing developmental expression, not just for OATs but for OCTs and for OATs.

These transporters were demonstrated to be abundantly expressed during murine development in many extrarenal tissues as well (45). For example, transcripts were found for mOAT1 in choroid plexus, dura mater, and spinal cord. The mOAT1 transcript levels in the brain were significantly greater during fetal and early postnatal development, with strong mOAT1 labeling in brain seen as early as e12 and in spinal cord through e14, but disappearing by e16 (45). mOAT2 message was observed to be expressed at e14 in fetal liver, lung, intestine, skin, and bone and was still detectable in liver, stomach, skin, and hindbrain at postpartum day 5 (45). For mOAT3, transcripts were found in fetal liver and brain at e12 (45). mOAT3 expression in the liver peaked by e14 and decreased after e16 with a dramatic downregulation toward adulthood, temporally coinciding with the onset of hematopoiesis (45). Strong mOAT3 labeling was observed throughout the entire nervous system by e14, peaked by e16, and was seen only at very low levels in the adult brain (45). Unexpectedly, mOCT1 expression was detected not only in the liver but also in the atrium and ascending aorta beginning at e14 (45). This expression was specific to these regions of the cardiovascular system and was transient, with levels of expression falling sharply after e16 and disappearing altogether by birth (45). Interestingly, a gene with homology to OCT1, termed “organic cation transporter-like,” has been circumstantially implicated in processes related to imaginal disc formation during Drosophila melanogaster development (70). Thus expression of OATs and OCTs during embryogenesis in these and other extrarenal sites may indicate that these transporters play a fundamental role in the formation and/or maintenance of nonrenal tissues, including, potentially, the transport of endogenous organic molecules with morphogenetic activity or substances necessary for normal development (e.g., folate in the developing central nervous system). It is conceivable that the multispecificity of an OAT (or OCT) allows the same or a related transporter to be used by different developing tissues to take up key organic ions that are necessary for organogenesis, and, after the morphogenetic event is over, expression is downregulated.

FUTURE PERSPECTIVES

Regulation of Expression During Proximal Tubulogenesis

Despite the fact that the kidney is the major site of renal drug handling, aside from morphology little is known about the development and maturation of the proximal tubule. The proximal tubule develops after epithelialization of the metanephric mesenchyme, which has been induced by the ureteric bud (for review, see Refs. 53 and 62). In the mouse, the induction occurs at e11, and early tubular structures of the proximal nephron begin to form around e13–e14. Evaluation of the developmental expression of OAT1, OAT2, and OAT3 demonstrated a more or less coordinated appearance of the mRNAs for each of these proteins during
development of the renal proximal tubule (e14–e15 in mice) (45). This finding raises the possibility that these proteins share a common signal for expression and/or a common regulatory pathway for transcription. Comprehensive analysis of OAT gene promoter regions, complemented by phylogenetic footprinting and motif analysis, will aid in the identification of specific transcription factors involved in OAT gene regulation. Understanding their (and other transporters’) polarized expression in relation to the formation of intercellular junctions may also shed light on mechanisms of proximal tubulogenesis and of epithelial cell polarization during development. Because these transporters are vital to the elimination of a wide variety of xenobiotics, elucidation of the specific mechanisms for the regulation of renal OAT expression may provide insight into the mechanisms controlling development and maturation of drug handling capacity in the kidney. This information may also begin to explain clinical differences in renal drug handling by premature infants, neonates, children, and adults.

Another unexplored aspect of OAT regulation concerns the body’s response to disease states. For example, it is conceivable that during renal failure, OAT expression may become altered in the liver to increase the capacity of the liver to handle toxic substances or vice versa in the kidney during liver injury. Similarly, if one OAT isoform is not appropriately expressed, the other OATs may be upregulated in an attempt to compensate for the loss. This points to a fundamental question, which is, Why are so many OAT isoforms expressed in kidney and why do their substrate specificities overlap so much? It may be that OATs perform such an essential function to the organism’s survival (perhaps of the fetus as well as the adult) that, in the event of the loss of individual transporters or decreased transport function, there is a backup system made up of several transporters partly overlapping in specificity, so that the loss of one transporter is compensated for by others. There may be an advantage, in that by expressing several OATs the kidney can respond to conditions of increased substrate load with a larger increase in transport capacity by upregulating more than one gene. Eventually, however, it would be expected that the transporter with greater capacity for handling the OA at hand would be more markedly upregulated. This could lead to a kind of “affinity maturation” of OA transport capacity (obviously, the same hypothesis can also be advanced for multiple OCTs and other transporter systems). Clearly there are many unanswered questions about how this system responds to changes in the environment and in the organism that need to be addressed.

Pharmacogenetics and Pharmacogenomics

In the last decade a great number of renal transport proteins have been cloned, and their role in the handling of a wide variety of drugs has been firmly established (7, 66). Now, the cloned transporters can be expressed in cell culture systems, under highly controlled conditions, allowing direct examination of the pharmacological transport efficacies of individual transporter gene products. The role that a specific transporter plays in the effectiveness of a clinical treatment regimen or in the adverse clinical effects (e.g., nephrotoxicity/cytotoxicity) of a particular drug can be examined in isolation. For example, the antiviral adefovir, a high-affinity hOAT1 substrate (10), is effective in the treatment of human immunodeficiency virus (HIV)-infected patients; however, some individuals develop nephrotoxicity after prolonged therapy (28). Experiments using stably transfected cells confirmed the role of hOAT1 in adefovir-induced cytotoxicity (21). It has been further demonstrated that clinically relevant concentrations of certain nonsteroidal anti-inflammatory drugs significantly inhibited hOAT1-mediated adefovir transport without altering the anti-HIV activity of adefovir, possibly providing a new strategy for reducing adefovir-associated nephrotoxicity (43). Such high-throughput, cell-based assays provide a powerful tool for the pharmacokinetic evaluation of drug-drug interactions, the assessment of pharmacokinetic effects of changes in a drug’s molecular structure, and identification of potential toxicity before a compound goes to clinical trial. Indeed, with the knowledge of the sequence of the transporters, active substrate binding domains can be identified and drug-transporter interactions can be modeled on a computer at the molecular level. With the use of these models, it may also be possible to design drugs that are more likely to be eliminated by the kidney, liver, or choroid plexus (or some combination of these). This will provide new and powerful insight, at the gene level, into the design of new therapeutics and/or protective agents and allow more effective prediction of potential clinical outcomes. Analysis of expression patterns of OATs and other drug transporters in patients may one day become routine.

The link between clinical poor-metabolizer phenotypes and single nucleotide polymorphisms (SNPs) in various P-450 enzymes has been established for some time (11, 12, 29, 63), and associations between an individual’s therapeutic response and genetic polymorphisms in drug targets (e.g., enzymes and receptors) have also been documented (75, 79). More than likely, a similar situation exists for the OATs; presumably, certain SNPs prevalent in the population lead to variability in drug handling. Indeed, thus far three different single nucleotide mutations (a substitution, a deletion, and an insertion) have been identified in the human carnitine transporter hOCTN2, leading to systemic carnitine deficiency (69, 76). Presently, these so-called “monogenetic” traits, where mutations or polymorphism in a single gene leads to an observable effect, are readily identified. However, given the biochemical complexity of the human body, it is likely that the bulk of clinically important phenotypes is actually the culmination of polygenic traits with varying degrees of impact on the overall phenotype. Consider that, for a drug taken orally, uptake (including absorption across the gut, entry into the circulation, and
perhaps penetration of target cells), modification (activation or deactivation of the parent compound), interaction with drug targets, intracellular binding and/or sequestration, and elimination (secretion into bile or urine), potentially in combination with substrate interaction/competition at any or all of these steps, ultimately determine an individual’s response to therapeutic treatment or xenobiotic exposure. The emerging field of pharmacogenomics is beginning to provide a more comprehensive overview of the genetic profile of the proteins responsible for each of these steps and is subsequently changing the areas of drug discovery and therapy. In combination with data from powerful diagnostic tools such as microarrays, DNA and protein chips, PCR-based assays, and high-throughput screening, drugs may soon be designed to treat specific populations exhibiting certain combinations of traits. Given that as many as half a dozen OAT family members may be expressed in the kidney, it is likely that SNPs in multiple family members specify, singly or in combinatorial fashion, phenotypes ranging from more “resistant” to a particular therapy or exposure to one that is more “sensitive” to a similar drug dose or toxic exposure. These predictive considerations obviously apply to other transporter families as well. Treatment regimens may be tailored to consist of particular drug combinations chosen to specifically manipulate the identified genetic profile the individual has inherited so as to provide the desired therapeutic outcome. Pharmacogenomics will conceivably have an ever-increasing impact on the ability to personalize an individual’s medical treatment, thereby reducing the risk of toxicity while maximizing the therapeutic effect.

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