Kidney International, Vol. 49 (1996), pp. 1649–1654

Renal secretion of organic anions and cations

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Renal secretion of organic anions and cations. The renal proximal tubule actively transports charged, potentially toxic xenobiotics from blood to lumen. Basolateral uptake of organic anions is indirectly coupled to the sodium gradient through Na-dicarboxylate cotransport and dicarboxylate-organic anion exchange. Upon entry, a significant fraction of intracellular organic anion is sequestered within vesicles. Disruption of the cellular microtubular network can lead to both diminished vesicular movement and reduced transepithelial secretion. Luminal efflux of organic anions is energetically downhill, but carrier mediated. Both anion exchange and potential driven transport are present, but neither completely accounts for transport from cell to lumen. For organic cations, basolateral entry is downhill via potential driven facilitated diffusion. Intracellular sequestration of organic cations in vesicles is substantial, but its role in secretion is uncertain. Multiple carriers are available to drive organic cations uphill into the tubular lumen. The classical system indirectly taps the energy of the luminal Na gradient to drive organic cation efflux via Na^+-H^+ and proton-organic cation exchange. In addition, the multidrug resistance ATPase can pump organic cations into the tubular lumen. Thus, although much detailed information has been added over the last 50 years, it is not yet possible to provide a detailed, quantitative understanding of these important excretory systems.

The toxic effects of drugs and foreign chemicals are determined by the duration and level of exposure at critical sites within the body. Thus, in concert with metabolic oxidation and conjugation, renal excretion of these agents and their metabolites plays a critical role in protecting against toxicity. Two secretory transport systems mediate renal excretion of such compounds, one for organic anions and another for organic cations. Both systems are very effective. Indeed, as first documented by Smith 60 years ago using the anionic dye, phenol red [1], both are capable of completely clearing a good substrate from the renal plasma in a single pass through the kidney. Likewise, both systems are able to transport a very wide range of substrates, requiring only an appropriate charge on a hydrophobic backbone [2].

Substrates for the organic anion system include a variety of drugs (penicillins, salicylates) and xenobiotics (phenoxyacetic herbicides, benzo[α]pyrene) and their metabolites. In addition, endogenous compounds including neurotransmitter and hormone metabolites are transported. Substrates for the organic cation system are similarly diverse, including endogenous compounds (choline, histamine, serotonin), drugs (antihistaminics, anticholinergics), and xenobiotics (paraquat). As revealed by the detailed studies of Ullrich, Rumrich and Fritzsch [2], two primary rules govern interactions with these systems: (1) within a homologous series of compounds, the greater the hydrophobicity (octanol/water partition coefficient) the greater the affinity (that is, the lower the K_i); (2) inhibitory effectiveness increases with increasing percent ionization. Of course, not all compounds fit these rules precisely, but many apparent exceptions have simple explanations, such as hydrophobicity and pK_a do not necessarily vary independently or the effects of hydrophobicity may be limited by steric factors at the active site. Because these systems mediate the excretion of so many drugs, competition for excretory transport can be an important factor in drug interactions, and numerous such interactions have been described [3].

Clearly, these systems are strategically placed to play vital roles in response to toxic chemical exposure. In the sections which follow, we will review current understanding of these transport systems: (1) briefly summarizing their background, (2) examining the mechanisms mediating transport, and (3) highlighting areas of remaining uncertainty.

Organic anion transport

Background

Because a number of well transported organic anions are intensely colored—thus, easily measured in plasma and urine—study of their excretion played a prominent role in the development of renal physiology. As early as the 1870's, Heidenhain [4] examined the renal handling and tissue distribution of one such anion, indigo carmine, and correctly concluded that organic anions were secreted, that secretion was a function of the proximal tubule, and that secretion was a two step process with separate events at the peritubular and luminal faces of the tubule. These conclusions, which were hotly debated for more than half a century, were substantiated by Marshall and his collaborators in the 1920's [5]. Soon thereafter, Smith showed that the clearance of phenol red provided a measure of renal plasma flow and that its T_{max} could be used as an index for the functional excretory mass of the kidney [1]. Since Smith's time, the bulk of the effort in this field has been to provide a mechanistic basis for the extraordinary capacity of the kidney to secrete organic anions.

General characteristics

From the very first *in vitro* experiments, it was clear that maneuvers which compromised cellular energy production, including cold, metabolic inhibitors, or anoxia, led to a marked reduction in organic anion transport [3]. The energetically uphill step in organic anion secretion must occur at the basolateral membrane where the negatively charged anion is transported against both a chemical gradient and electrical potential barrier.

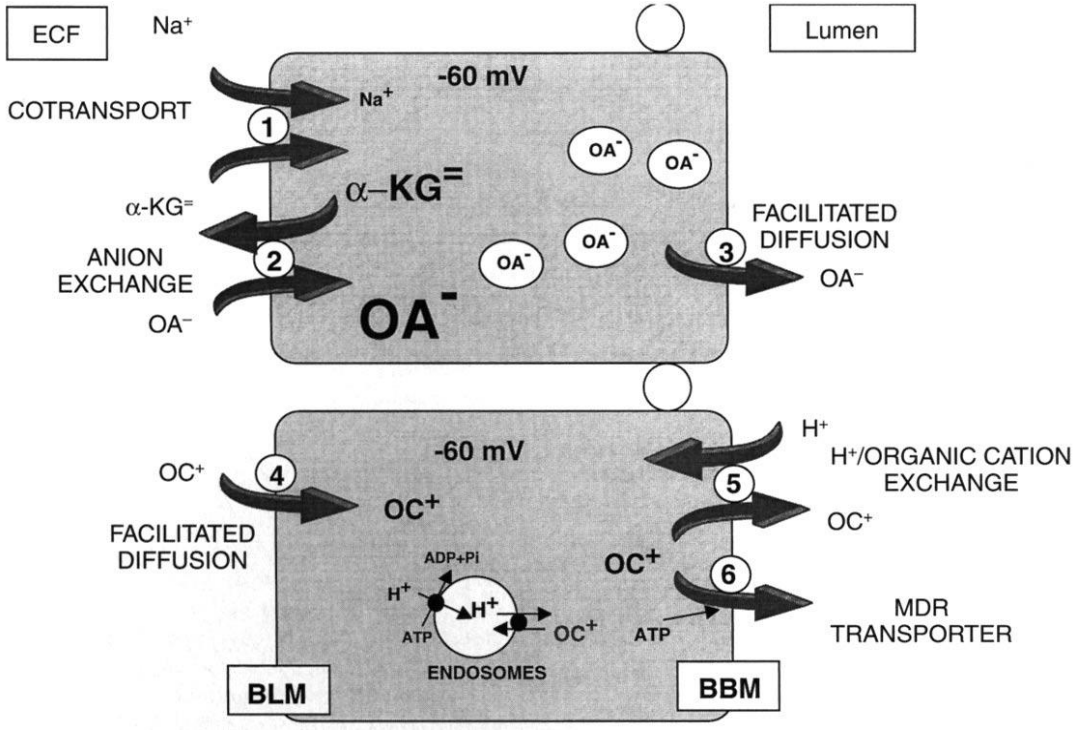

Fig. 1. *Mechanisms of organic anion (OA; top) and organic cation (OC; bottom) transport in renal proximal tubule.* For both classes of solute, lumenal concentrations exceed cellular, which exceeds that in the extracellular fluid (ECF). Organic anion entry into the cell is driven by indirect coupling to the Na gradient through Na-divalent organic anion symport (step 1) and organic anion exchange (step 2). Within the cell, organic anions are partitioned between cytoplasm and vesicles. Exit may occur through facilitated diffusion (step 3). Organic cations enter by PD-driven facilitated diffusion (step 4) and are taken up from the cytoplasm by endosomes. Organic cation exit is mediated by exchange for protons (step 5) and by the MDR transporter (step 6).

Both sodium removal and ouabain inhibition experiments indicated that this step requires the presence of an out > in Na^+ gradient [3], suggesting that the basolateral uptake step might be driven by a Na-organic anion cotransport mechanism. However, when this possibility was tested in isolated BLM vesicles by Berner and Kinne [6], direct coupling to sodium could not be demonstrated. This result led several groups to suggest that organic anion entry might be coupled to metabolism, perhaps through exchange for a metabolic intermediate [3], but how such a process might be energized remained a mystery.

Indirect sodium coupling

These suggestions led Shimada, Moewes and Burckhardt [7] and Pritchard [8] to propose that organic anions were taken up across the basolateral membrane in exchange for an anion that was maintained at a high in > out concentration gradient through Na cotransport. Based on its abundance *in vivo* and the impact of changes in α-ketoglutarate (αKG) concentration and gradient on organic anion transport in the intact tissue, αKG appears to be the physiological counterion for organic anion secretion [9]. As depicted in Figure 1, this is a tertiary active process, coupled to metabolic energy through two intervening steps. ATP is hydrolyzed to drive the Na pump, creating the out > in Na gradient, Na entry down this gradient drives the uptake of α-ketoglutarate, creating an in > out αKG gradient, and the organic anion is taken up in exchange for αKG. Thus, the αKG is recycled and the overall process yields net uptake of Na and organic anion. As reviewed recently [3], subsequent intact tissue studies in slices and isolated tubules not only confirmed the indirect coupling model, but also demonstrated that increased BLM uptake led to increased transepithelial flux, that is, secretion. Inhibitors of either organic anion/αKG exchange, such as probenecid, or of Na/αKG cotransport, such as lithium or fumarate, inhibited the coupled system. Interestingly, unlike the organic anion site on the exchanger which accepts such a broad range of substrates, the dicarboxylate site is very specific. Only glutarate, suberate, or adipate can substitute for αKG.

Intracellular events

Secreted anions are not uniformly distributed within the tubular cells. It has been known for many years that they are subject to extensive intracellular binding [3]. Recent imaging studies using fluorescein, a fluorescent organic anion, have shown that intracellular organic anions may also be sequestered within vesicular structures (Fig. 2) and that sequestration takes place via a mediated process which was inhibited when *p*-aminohippurate (PAH) or probenecid were microinjected into the cells [10]. The physiological roles of binding and sequestration, if any, remain to be established. However, two likely possibilities are under study. First, both processes decrease free cytoplasmic concentrations of intracellular organic anions during secretion, perhaps reducing the likelihood of toxicity. Second, intracellular trafficking of vesicular structures, known to occur in many cell types including kidney, could play a role in transcellular organic anion movement.

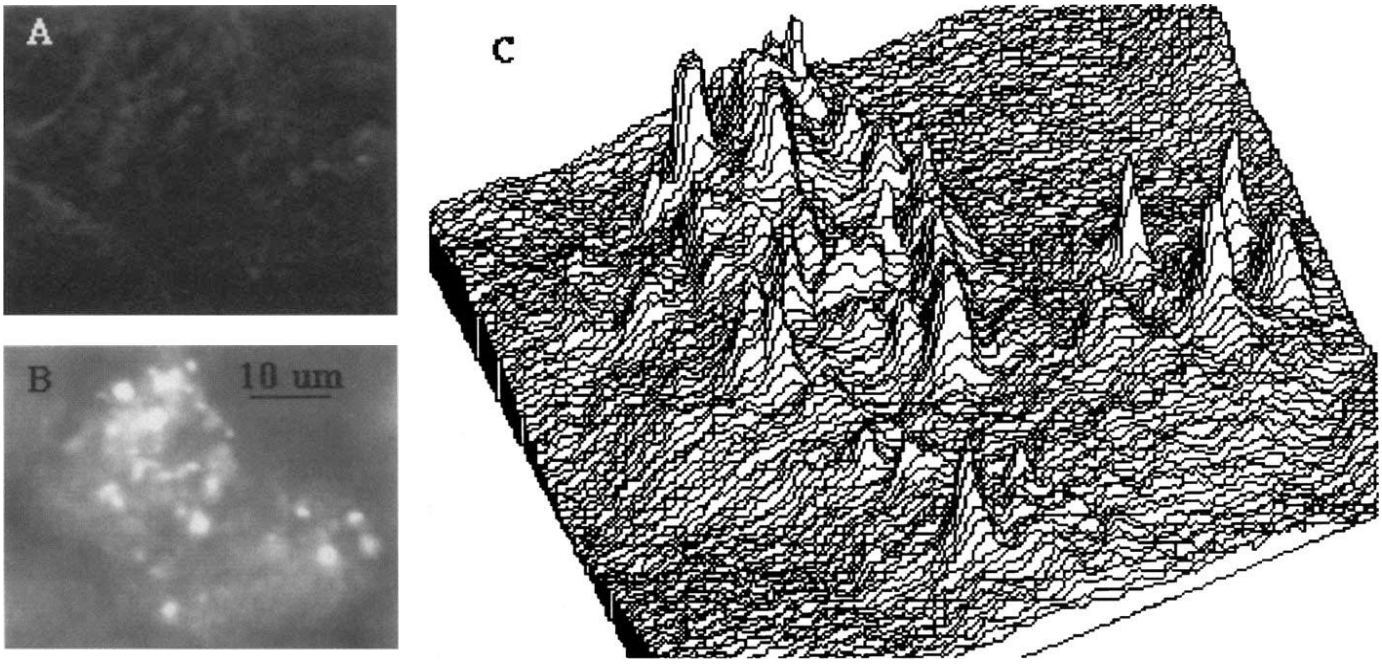

Fig. 2. *Fluorescein (FL) compartmentation in cells of crab urinary bladder.* Like vertebrate renal proximal tubule, this flat-sheet epithelium secretes organic anions and organic cations. Shown are transmitted light (**A**) and epifluorescence micrographs (**B**) of bladder tissue removed from an animal that was secreting FL *in vivo*. In both cells, dye is distributed over two compartments, one diffuse and the other punctate. (**C**) Three-dimensional plot of fluorescence intensity (z-axis) versus location in the image (xy plane). From Miller et al [11]; used with permission from the *American Journal of Physiology*.

Fluorescein loaded vesicles were shown to move in a basolateral to apical direction, and this movement was reversibly blocked by nocodazole, a microtubule depolymerizing drug [11]. Nocodazole also reduced fluorescein secretion in the intact renal tubule [12], suggesting that vesicular uptake and movement may play a direct role in transcellular movement and/or luminal exit of secreted organic anions.

Luminal mechanism

Two potential pathways for exit of secreted organic anions have been observed in luminal, or brush border, membrane (BBM) vesicles. In 1980 Blomstedt and Aronson [13] described a luminal organic anion exchanger which is shared by PAH, lactate, and urate, as well as several inorganic anions (Cl^-, HCO_3 , OH^-). However, this transporter has been found only in urate reabsorbers (dog, rat) and is absent in urate secreters (rabbit, pig) [3]. Since both groups secrete organic anions, this exchanger does not appear to be an obligatory component of secretion. Furthermore, the presence of luminal Na/H antiport, which makes the cell interior more alkaline than tubular fluid, favors reabsorptive (lumen-to-cell) flux. Thus, it appears that the BBM exchanger may be more important in urate reabsorption than in organic anion secretion. Recent studies in both urate secreters (pig) and reabsorbers (rat) have documented the presence of a probenecid sensitive, potential driven carrier in the luminal membrane [3, 14]. Given the steep electrochemical gradient favoring efflux of anions across this membrane, such an electrogenic carrier should be sufficient to account for luminal flux of secreted organic anions (Fig. 1). However, when this conclusion was tested directly by depolarizing intact teleost tubules in elevated external K^+, organic anion transport was unchanged, even though transport of an organic cation decreased in response to decreased electrical driving force (Fig. 3). Thus, although two mediated routes for organic anion efflux have been identified in BBM versicles, significant gaps in our current understanding of this process remain.

Organic cation transport

General characteristics

All animals studied, from crustaceans and fish to mammals, have been shown to secrete organic cations [3]. During secretion, these solutes must cross two hydrophobic membrane barriers and the intervening aqueous cytoplasm. Data from renal clearance studies, isolated perfused tubules, and monolayers of proximal tubule cells indicate that specific, membrane-bound carrier proteins mediate the transport of organic cations across both the basolateral and luminal membranes of the tubular epithelial cell. In addition, these studies show that the movement of organic cations from interstitial fluid to tubular lumen cannot be explained by passive driving forces, such as simple diffusion, fluid reabsorption from the lumen, and electrogenic transport driven by the transepithelial potential difference (PD), which is small in this "leaky" epithelium. Rather, transepithelial transport of organic cations is energetically uphill and is disrupted by inhibitors of metabolism and cellular pH and ion regulation.

In 1979, initial studies of N^1-methylnicotinamide (NMN) uptake in luminal and basolateral membrane vesicles from dog kidney led Kinsella et al [15] to propose a two step model in which organic cation secretion was mediated by distinctly different carriers at each face of the proximal tubule cells. At the basolateral membrane, organic cations entered by facilitated diffusion,

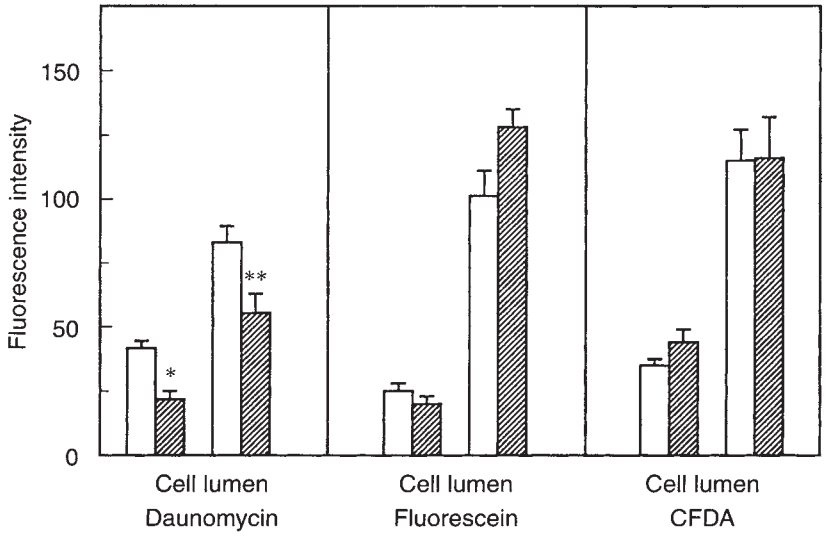

Fig. 3. *Effects of membrane depolarization on steady state distribution of fluorescent solutes in killifish renal proximal tubules.* Raising medium K from 2.5 (□) to 25 (▨) mM depolarized by about 30 mV [18]. High K significantly reduced accumulation of an organic base, daunomycin. Transport of daunomycin was measured in the presence of cyslosporin A to block secretion through the MDR transporter. High K had no effects on the accumulation of the organic anions, fluorescein and carboxyfluorescein, which was generated intracellularly from carboxyfluorescein diacetate (CFDA; Miller, unpublished data). $^{*}P < 0.05$; $^{**}P < 0.01$.

driven by the inside negative transmembrane electrical potential. Luminal exit was mediated by exchange for other organic cations or protons (antiport). Additional vesicle studies in several species soon established that all required elements were present in the correct locations [3]. However, this model must be modified to include two new elements: (1) sequestration of organic cations by intracellular elements, and (2) participation of an ATP-driven luminal transporter.

Basolateral entry

Studies with BLM vesicles from dog, rat, and rabbit renal cortex have shown that organic cation uptake is a carrier mediated, but passive phenomenon, dependent on transmembrane electrical potential difference [3]. In rabbit renal BLM, a second process was also found, organic cation exchange. However, it appears that potential driven organic cation uptake and organic cation exchange represent two modes of a single BLM carrier rather than two carriers with differing energetics [16, 17]. Thus, the vesicle data are consistent with cellular accumulation of organic cations being driven primarily by facilitated diffusion (Fig. 1). In intact renal cells, one should be able to detect electrogenic, facilitated entry of organic cations through its dependence on basolateral membrane PD and by organic cation induced membrane depolarization. Smith, Pritchard and Miller [18] measured both basolateral membrane potential and tetraethylammonium (TEA) uptake in flounder and killifish tubular masses and found that maneuvers which depolarized the basolateral membrane (high K^+, Ba^{++}) inhibited TEA uptake and maneuvers that hyperpolarized (low K^+) stimulated uptake. Furthermore, addition of TEA or darstine to the medium reversibly depolarized the basolateral membrane potential [18], consistent with electrogenic uptake of both cations. Likewise, increasing potassium in the external medium reduces TEA, NMN, and cimetidine uptake by isolated mammalian proximal tubules, renal cortical slices, and renal tubules studied *in situ*, as do reducing medium sodium or bicarbonate, which also depolarize [3].

Intracellular sequestration

Basolateral PD in proximal tubule cells averages −60 to −80 mV. Therefore, if facilitated diffusion were the only mechanism contributing to cellular accumulation, one would not expect tissue-to-medium concentration ratios (T/M) greater than about 10 to 15 for monovalent organic cations. Clearly, facilitated diffusion by itself cannot account for the high cellular accumulation of TEA found in proximal tubules from rabbit and snake, where T/M values can exceed 100 [19, 20]. Since no additional concentrative uptake mechanism has yet been identified, several workers have suggested that organic cations may be sequestered intracellularly and, therefore, the average cellular concentration may overestimate the actual concentration of "free" substrate within the cytoplasm [3].

Certainly, intracellular binding to cytosolic proteins may contribute to total uptake. Binding is indicated by the frequent observation that metabolic poisons do not completely eliminate concentrative uptake of organic cations [3]. A second type of sequestration, accumulation of organic cations within acidic intracellular organelles, such as endosomes, lysosomes, and golgi vesicles, is also likely (Fig. 1). In studies of endosomal membrane vesicles from rat renal cortex [21], TEA uptake was markedly stimulated by millimolar concentrations of ATP (Fig. 4). ATP-dependent TEA uptake was saturable and was inhibited by several organic cations, including darstine, quinine, and NMN. TEA uptake was also dependent on low intravesicular pH, maintained by the H^+-ATPase on the endosomal membrane. Since TEA is a quaternary amine, pH trapping could not account for the ATP-dependent accumulation seen in renal endosomal vesicles, indicating proton-organic cation exchange. Consistent with this interpretation, the ATP requirement could be bypassed by imposing a pH gradient across the endosome membrane (inside acidic). Furthermore, TEA and other organic cations accelerated the dissipation of an ATP-generated pH gradient across the endosome membrane [21].

If the capacity of intracellular sites to sequester organic cations were high enough, TEA activity in the cytoplasm of rabbit and snake proximal tubule cells might be reduced to a value at or below its Nernst potential, eliminating the need to postulate an additional active uptake step at the basolateral membrane. In addition, it is possible that endosomal sequestration and vectorial vesicular trafficking play a role in organic cation secretion. In

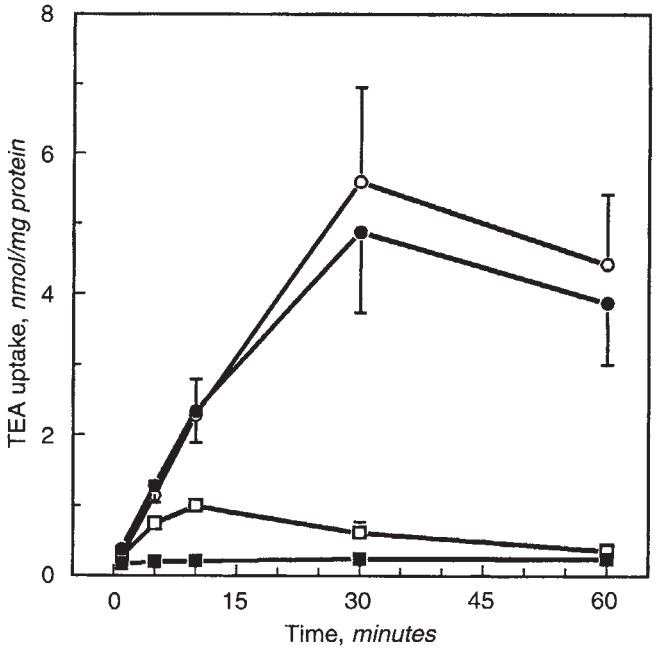

Fig. 4. *ATP stimulates TEA accumulation by endosomes prepared from rat renal cortex.* Symbols are: (■) 0 [ATP] mM; (□) 0.2 [ATP] mM; (●) 2 [ATP] mM; (○) 5 [ATP] mM. Data are from Pritchard et al [21]; used with permission of the *American Journal of Physiology*.

many cells, including renal epithelial cells, there is a continual flux of membrane-bound organelles from one region to another. If organic cation-loaded vesicles subsequently fused with the luminal membrane, organic cations would be released into the tubular lumen. However, the entire process has yet to be demonstrated in intact renal cells.

Luminal organic cation/proton exchange

A large body of data for isolated BBM vesicles from dog, rat, rabbit, human, and snake kidney, as well as for proximal tubule cell lines show that luminal organic cation transport is mediated by an electroneutral, organic cation/proton antiporter which can use potential energy stored in a pH gradient to drive uphill movement of a variety of cationic substrates (Fig. 1) [3]. Although BBM vesicles show impressive stimulation of organic cation transport with investigator-imposed gradients of 1 to 2 pH units (H^+ activity gradients of 10 to 100), the actual pH gradient across the luminal membrane of the intact tubule is substantially smaller, 0.5 pH units. This gradient corresponds to a hydrogen ion activity gradient of only 3.2 and may not be sufficient to account for luminal organic cation movement against substantial concentration and electrical gradients. Instead, the luminal antiporter provides an electroneutral path for organic cation efflux, a path which bypasses the electrical potential barrier at the luminal membrane. The price paid for this benefit would be increased Na^+/H^+ exchange to restore the luminal pH gradient, and ultimately, increased ATP hydrolysis to maintain the out > in Na^+ gradient.

Multidrug resistance transporter

One important mechanism by which some tumor cells develop resistance to chemotherapeutic agents is to express a plasma membrane-bound ATPase that pumps drugs out of the cell. This multidrug transporter (called MDR, p-glycoprotein, or gp-170) exhibits a broad substrate specificity, handling calcium channel blockers, anthracyclines, Vinca alkaloids, calmodulin antagonists, steroids, cyclosporins, and miscellaneous hydrophobic organic cations [22]. Normal tissues also express MDR and proximal tubule, in particular, contains high levels. In proximal tubule, MDR is localized to the luminal membrane, where it could pump xenobiotics into the lumen (Fig. 1) [23, 24]. In this regard, recent imaging studies have demonstrated active secretion of a fluorescent cyclosporine A (CsA) derivative and of the fluorescent anthracycline, daunomycin, into the lumen of intact teleost (killifish) renal proximal tubules [25, 26]. In both cases, transport from cell to tubular lumen was reduced by several p-glycoprotein substrates, including CSA and verapamil, and by vanadate, a potent inhibitor of the MDR transporter. In the case of the weak organic base, daunomycin, transport was mediated by both the MDR transporter and the classical organic cation transport system, with partitioning between the two being pH-dependent.

Perspectives

This review provides numerous instances where understanding of the individual cellular processes mediating renal secretion has increased thanks to technical advances in the study of transport mechanisms. For example, just a decade ago, we were unaware of basolateral indirect sodium-coupled uptake of organic anions, vesicle-mediated transport of both organic anions and cations, and MDR transporter-mediated organic cation secretion into the lumen. Nevertheless, as pointed out above, much remains to be worked out.

Two areas which were not discussed above are particularly interesting and potentially important. First, little is known about the regulation of organic anion and cation transport in the kidney or in extrarenal epithelia. Recent reports from one laboratory implicate the protein kinase C system in control of PAH and TEA uptake by rabbit proximal tubules [27, 28]. Although receptors for several hormones acting through that signalling system, such as PTH and endothelin, have been localized to proximal tubule, at present it is not clear which physiological stimuli might affect secretion. Second, molecular biological techniques are just beginning to bear fruit. In the past year one of the transport proteins involved, a PD-dependent carrier for organic cations (OCT1), was cloned and sequenced [29]. However, none of the transporters for monovalent organic anions have been cloned. Once the individual transporters are cloned and sequenced, the primary structure of the proteins may be deduced and probes prepared for study of transporter production and control. Thus, molecular biology can pay large dividends in areas where we currently have little information, such as structure-function relationships for the transporters and their physiological and/or pharmacological regulation.

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