Modeling transport in the kidney: investigating function and dysfunction

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The role of the kidney is to maintain fluid and electrolyte homeostasis and to excrete metabolic waste products. The kidney adjusts the composition of urine so that the osmolality of blood, and thus that of surrounding tissues, stays within a narrow interval, around 300 mosmol/kg H₂O in mammals. The kidney also plays an essential role in regulating the balance of sodium, potassium, and protons (1, 19, 94). Remarkably, after many decades of careful theoretical and experimental research, key physiological aspects of renal function are still poorly understood, from the microscopic to the macroscopic scale. Perhaps the central question at the macroscale is how highly concentrated urine is formed in the inner medulla. At the cellular scale, several fundamental transport mechanisms are recognized to play an important role in the pathogenesis of diseases such as proteinuria and hypertension, but they have yet to be fully elucidated.

In the search for answers to these questions, mathematical models play a role complementary to experimental investigations. Mathematical models are used to formulate and test hypotheses related to renal function, to incorporate microscale findings (i.e., at the molecular or cellular levels) into more integrated systems (such as the tubule or the whole nephron) so as to understand how the activity of these complex systems is regulated, and to predict the effects of drugs or genetic mutations.

In this review, I describe recent advances in renal transport modeling, over the past two to three years, and emphasize the physiological and pathophysiological relevance of these theoretical studies. Whereas more in-depth descriptions of the history, major assumptions, and basic equations of renal transport models can be found elsewhere (41, 76, 90, 99), I aim to identify areas where collaborations between experimentalists and modelers hold promise for accelerating progress toward a better understanding of unresolved issues.

How Can the Kidney Produce Highly Concentrated Urine?

Macroscopic mathematical models of water, NaCl, and urea transport in populations of nephrons have served to test, confirm, or refute a number of hypotheses related to the urine concentrating mechanism (UCM). In the outer medulla (OM), generation of the corticomedullary osmolality gradient has long been ascribed to the multiplication of a single effect. According to this paradigm, the active transport of NaCl out of thick ascending limbs generates a small transverse osmolality difference at each level of the OM (i.e., the single effect), which is then converted into a large axial osmolality gradient by the countercurrent flows in tubules and vessels. Mathematical models have confirmed that active NaCl reabsorption from thick ascending limbs can generate an OM osmolality gradient that is comparable to experimental measurements, as reviewed in Ref. 76.
Nevertheless, Layton et al. (37) recently suggested that the standard description of countercurrent multiplication in the OM be revised in light of several observations. In the OM of mammalian species such as rats and mice, the structural organization of tubules and vessels is highly specific. The loops of Henle and the collecting ducts (CDs) are arranged in a roughly concentric manner around tightly packed vascular bundles (32, 33). In addition, immunohistochemistry studies have shown that significant portions of short descending limbs do not express aquaporin-1 (AQP-1) water channels in rats, mice, and humans (57, 93, 106); thus water reabsorption from these segments is likely to be small. Both sets of findings suggest that radial osmolality differences between tubules and vessels at a given depth may not be small relative to the axial osmolality gradient, which contradicts the conventional interpretation of countercurrent multiplication in the OM. The region-based mathematical model of the UCM in the rat OM developed by Layton and Layton (35, 36) accounts for the specific organization of the OM by distinguishing four regions centered on a vascular bundle, thereby allowing for preferential interactions among certain tubules and vasa recta. The model predicts significantly differing NaCl and urea concentrations in adjoining regions (Fig. 1) and between tubules and vessels in a given region. In other words, the three-dimensional architecture of the rat OM is thought to generate substantial radial osmolality gradients at each level. Thus, given the significant axial and radial heterogeneities in the OM, the traditional countercurrent multiplication paradigm for the OM concentrating mechanism appears to be incorrect (37).

A satisfactory understanding of the urine concentrating mechanism in the inner medulla (IM) has been a goal of several active research programs, but that understanding has yet to emerge. As described below, although computational models have invalidated, at least in part, several theories of the inner medullary UCM, they have not yet succeeded in predicting the maximal urine osmolalities that have been measured in animals. Urine osmolality can reach ~1,000–2,000 mosmol/kgH₂O in primates, ~3,000 mosmol/kgH₂O in rats, and ~4,000 mosmol/kgH₂O in mice and hamsters (76).

The passive mechanism was first proposed by Stephenson (83) and by Kokko and Rector (31). This mechanism posits that the active transport of NaCl in the OM and the cortex, in combination with the urea cycle, serves to concentrate the IM; it rests on the assumption that the urea permeability of Henle’s loops is very small. If that is the case, the concentration of NaCl should be significantly greater than that of urea in the ascending limb and vice versa in the CD. Thus passive diffusion of NaCl from ascending limbs and of urea from CDs into the inner medullary interstitium should raise the osmolality of the interstitial fluid.
thereby drawing water out of descending limbs and CDs and further concentrating the fluid flowing down in the descending limbs and CDs.

Simulations have shown that for the passive mechanism to operate as initially proposed, the urea permeability of Henle’s loop as well as the NaCl permeability of the descending limb must be small, significantly lower in fact than measured values in the rat, hamster, and chinchilla (76). Using those measured values, existing mathematical models of the UCM are not capable of predicting physiological maximum urine osmolalities. Thus the relevance of the passive mechanism, at least in those species, has been questioned.

Nevertheless, Layton and colleagues (65) recently suggested that the passive mechanism be reconsidered in light of new observations on the IM architecture by Pannabecker and colleagues (62–64, 66). They proposed that the passive mechanism be called instead a “solute-separation, solute-mixing” (SSSM) mechanism, because it requires separation of both NaCl in loops of Henle and urea in CDs and their subsequent mixing in the interstitium and vasculature of the IM (40). Pannabecker and colleagues (61–64, 66) developed a computer-assisted process to reconstruct the vascular and tubular structures of the rat IM. Their findings on the axially variable expression of AQP-1 water channels and CLC-K1 chloride channels along thin limbs of Henle’s loop (61) led to the development of two mathematical models of the UCM that incorporated these data (40). The predictions of the so-called pipe model, which is similar to the passive hypothesis, were in good agreement with in vivo micropuncture studies (67), but the model still failed to predict the very high osmolalities that have been measured in rats (40). More recent observations by Pannabecker and Dantzler (63, 64) indicate that loops and vasa recta are organized around primary clusters of CDs and that the arrangement of the CDs and some of the ascending vasa recta and ascending thin limbs inside the CD clusters forms interstitial nodal spaces (i.e., isolated microdomains) that may serve as solute-mixing compartments (Fig. 2). Their findings suggest that the concentrating mechanism in the IM may consist of three different countercurrent systems, involving different subpopulations of long loops of Henle: two in the outer portions of the IM (one in the central regions of the CD clusters, and another in the intercluster regions), and a third in the inner portion of the IM (65). A mathematical model that accounts for those highly specific anatomical features has yet to be developed.

Such a model will more than likely predict higher urinary osmolalities than current approaches, but it remains unclear whether the SSSM mechanism is the main principle underlying the UCM in the inner medulla. The region-based model of the rat OM, which takes into consideration the preferential interactions between certain types of vessels and tubules in the OM (vide supra), suggests that regionalization augments the axial osmolality gradient in the OM by less than 50% (36). As noted by Layton and colleagues (37), other biophysical principles also may be fundamental to the concentrating mechanism in the IM.

It has been postulated that the rhythmic contractions of the pelvic wall contribute to the UCM in the IM. Expanding on a hypothesis first advanced by Schmidt-Nielsen (77), Knepper et al. (30) proposed that hyaluronan, the main component of the medullary interstitial matrix, can use the mechanical energy from the pelvic contractions to lower the interstitial pressure after each contraction and thereby drive water efflux from the descending limb of Henle. This would in turn raise the luminal osmolality above that of the interstitium and generate a single effect for concentration of urine. However, thermodynamic analysis of this process indicates that the pressures exerted on the inner medullary tissue can only account for a small fraction of the concentrating work in the inner medulla (70, 100). Very recently, Pinter and Shohet (69) suggested that pelvic contractions could contribute to the IM osmolality gradient via a different mechanism, one based on the Gibbs-Donnan effect between two interstitial compartments, one containing hyaluronan and the other extravasated plasma albumin. According to their hypothesis, rhythmic pressure increases could squeeze dilute fluid out of the hyaluronan compartment and simultaneously accelerate the outflow of fluid and albumin into the ascending vasa recta from the extravasated plasma albumin compartment. To date, the pressure exerted by pelvic contractions has not been measured, and no mathematical model of the UCM has formally incorporated the role of these contractions. Whether the latter can generate a single effect thus remains to be ascertained.

Several other hypotheses regarding the UCM have been put forward in the past decade or so, but none has been conclusive. Wexler and colleagues (96, 103) investigated the role of the three-dimensional organization of the renal medulla and showed that preferential interactions between tubules and vessels can, in theory, increase papillary tip concentrations of...
The observation two decades ago in spontaneously hypertensive rats that TGF-mediated oscillations are highly irregular, with a pattern suggestive of deterministic chaos (24, 105), has motivated many theoretical studies of the TGF mechanism. Possible reasons for the irregular fluctuations include temporal variations in TGF parameters and interactions between the TGF systems of nephrons originating from a common cortical radial artery. Ongoing work by Layton et al. (38, 39), as well as Marsh, Holstein-Rathlou, and colleagues (8, 51, 52), focuses on nephron-to-nephron coupling and seeks to understand why synchronization patterns are different in normotensive and hypertensive rats. The impact of irregular flow oscillations on NaCl reabsorption across the aldosterone-sensitive distal nephron, where the sodium balance is regulated, has yet to be determined. Thus it is not clear whether irregular pressure and flow patterns contribute to the renal changes in hypertension or whether they are a consequence of those changes.

How is Renal Blood Flow Regulated?

TGF models also have served to investigate the mechanisms underlying the regulation of RBF and GFR. Several theoretical studies have shown that the dynamic autoregulation of RBF is due to the combined action of TGF and the myogenic response (17, 25, 53, 58). Marsh et al. (50) developed a multiscale model of blood flow regulation, which includes a detailed description of Ca\(^{2+}\) dynamics in arteriolar cells, to investigate the nonlinear interactions between the two mechanisms. As shown in Fig. 3, the model predicts autoregulation of single nephron GFR over a broad range of blood pressures. Layton and colleagues investigated how physiological parameters determine the emergence of TGF-mediated oscillations in GFR (42) as well as the effects of limit-cycle oscillations, which can appear spontaneously (29), on fluid and sodium delivery to the distal tubule (43, 59, 71). Sustained perturbations in proximal tubule flow that can initiate or terminate limit-cycle oscillations are predicted to significantly affect the distal delivery of NaCl, as shown in Fig. 4. Other studies have focused on the renal myogenic response (47). A detailed model of afferent arteriole fluid dynamics and myogenic reactivity was developed to examine the importance of nitric oxide advection (80). A recent study suggests that systolic blood pressure, and not

NaCl and urea. The model of Jen and Stephenson (28) demonstrated that the accumulation of an “external” osmolyte in the inner medullary interstitium could also, in principle, enhance the corticomedullary osmolality gradient by driving water out of descending limbs. Thomas and colleagues (22, 87) subsequently showed that, in theory, the accumulation of lactate via anaerobic glycolysis could indeed significantly amplify the IM accumulation of NaCl. However, the concomitant production of protons could abolish this osmotic effect, depending on the buffering ions (90). The efficient IM recycling of lactate by vascular countercurrent exchange requires that the descending vasa recta (DVR) permeability to glucose be low compared to that of other vessels, whereas the DVR permeability to lactate needs to be significantly higher than that to sodium and urea (22). Measurements of these permeabilities would therefore help to assess the lactate hypothesis.

Why Are Tubuloglomerular Feedback-Mediated Oscillations Irregular in Hypertensive Rats?

Macroscopic models of solute and water transport in the kidney also have been developed to examine other aspects of renal function, such as tubuloglomerular feedback (TGF), renal perfusion, and medullary oxygenation. The TGF is thought to play a fundamental role in balancing the glomerular filtration rate (GFR) with transport rates across tubular epithelia and in maintaining a relatively constant delivery of water and solutes to the distal nephron. In conjunction with the myogenic mechanism, the TGF also participates in the autoregulation of renal blood flow (RBF) and protects the kidney against sudden or sizeable fluctuations in blood pressure (78). The TGF and myogenic mechanisms each generate oscillations in tubular fluid flow, at respective frequencies of 20–40 and 100–200 mHz. Since both mechanisms are mediated by constriction of the afferent arteriole, they interact: TGF modulates the amplitude and the frequency of the myogenic oscillation (81).
mean blood pressure, is the primary determinant of the myogenic response of the afferent arteriole (104). Models of the medullary microvasculature have examined the contribution of vasa recta to the urine concentrating mechanism (12, 60) and the transport of nitric oxide, a potent vasodilator, in the medulla (107, 109). The contractility of resistance vessels such as DVR is regulated by the variations in intracellular Ca$^{2+}$ concentration in both endothelium and smooth muscle. Some of our studies have focused on calcium transport dynamics in pericytes, the smooth muscle cells that impart contractile properties to DVR. In contrast with typical cellular representations, our pericyte model takes into account the microdomains formed through close association of the sarcoplasmic reticulum (SR) with the overlying plasma membrane (Fig. 5). Variations in microdomain Na$^{+}$ pump activity, such as those induced by ouabain, are predicted to modulate both the loading of Ca$^{2+}$ into SR stores and cytosolic Ca$^{2+}$ concentrations (14). These studies have elucidated the mechanisms by which ouabain and angiotensin II affect Ca$^{2+}$ signaling in pericytes (13, 15). A multiscale model linking cellular events to changes in vessel contractility and overall blood flow in the renal medulla has yet to be built.

**How is Kidney Oxygenation Regulated?**

Both acute and chronic renal diseases are characterized by tissue hypoxia (2, 18). The availability of oxygen (O$_2$) in the cortex and the medulla depends on the balance between supply and demand; that is, O$_2$ distribution is regulated by renal perfusion on one hand and renal metabolic requirements (particularly for active NaCl reabsorption across thick ascending limbs) on the other hand. Evans et al. (16) recently argued that arterial-to-venous (AV) oxygen shunting could play an important role in the dynamic regulation of kidney oxygenation as well as the development of renal hypoxia in kidney disease. They proposed that RBF-dependent changes in AV O$_2$ shunting may explain why renal oxygen tension (PO$_2$) remains stable when RBF is varied within physiological ranges (±30% relative to basal levels) and oxygen consumption does not vary significantly. The evidence in favor of such a mechanism remains indirect thus far. Modeling studies have shown that the countercurrent arrangement of DVR and AVR in the medulla results in O$_2$ shunting from DVR to AVR (108), similar to AV oxygen shunting in the cortex, and significantly limits O$_2$ delivery to the deep medulla. Our recent model of oxygen transport in the OM (3, 4) suggests that the structural organization of the OM results in significant PO$_2$ gradients in both the axial and radial directions (Fig. 6). The segregation of DVR, the main supply of O$_2$, at the center and immediate periphery of the vascular bundles limits O$_2$ reabsorption from long DVR, thereby preserving O$_2$ delivery to the IM but severely restricting O$_2$ distribution to the interbundle region where thick ascending limbs are located. The model predicts that, as a result, the concentrating capacity of the OM is significantly reduced. Further theoretical and experimental studies are needed to elucidate the contribution of cortical AV shunting to the regulation of intrarenal oxygenation.

**How Selective Is the Glomerular Filtration Barrier?**

The filtration of blood by glomerular capillaries has been the object of a large modeling effort, which has significantly improved our understanding of glomerular function in both health and disease. The models developed by Deen, Myers, and colleagues have served to elucidate the mechanisms of hypofiltration in healthy, aging subjects (23), as well as the ultrastructural basis underlying a number of disorders, such as minimal change and membranous nephropathy (9, 82), IgA nephropathy (45), and preeclampsia (34). Nevertheless, the respective contribution of the three different components of the glomerular capillary wall, namely, the endothelium, the glomerular basement membrane, and the podocyte layer, remains a matter of controversy, as briefly reviewed in Ref. 54. The significance of the recently identified subpodocyte space (SPS), which covers ~60% of the filtering portion of the glomerular filtration surface (55), also merits further investigation. A mathematical model of flow through the SPS predicts...
that its resistance is greater than that of the glomerular filtration barrier at physiological pressures and suggests that podocytes could play a role in regulating the rate of glomerular filtration across at least a part of the barrier by modulating the dimensions of the SPS (56).

The selectivity of the glomerular filtration barrier to albumin and the origin of proteinuria are the object of an ongoing debate (5, 6, 27) to which mathematical models have contributed. Historically, the glomerular filter has been thought to be nearly impermeable to albumin (with a glomerular sieving coefficient, or GSC, lower than 0.001) because of its large charge selectivity. The polyanionic glycoproteins that bind to the endothelial fenestrations, the glomerular membrane, and the epithelial cells are believed to strongly repel polyanions (54). However, Comper and colleagues (74, 75) have argued instead that albumin filtration is essentially determined by size selectivity alone and that the albumin GSC is orders of magnitude higher, $-0.04$. According to their hypothesis, the large amounts of filtered protein are then rapidly and efficiently removed from the tubular lumen by proximal tubular (PT) cells via endocytosis (75). This viewpoint has significant implications for the treatment of nephrotic syndrome, because it implies that albuminuria is primarily a tubular defect, not a glomerular defect (5, 7), but it remains highly controversial (5, 6, 27). The arguments and findings of Comper and colleagues have been challenged at different levels, in particular by recent measurements of albumin GSC (68, 85) and by a mathematical model of albumin reabsorption in the proximal tubule (44). To be consistent with micropuncture measurements of PT albumin concentrations, the filtered load of albumin obtained assuming a GSC of 0.04 would have to be reabsorbed in the first millimeter or so of tubule (6). However, the model of Lazzara and Deen (44) suggests that mass transfer limitations are such that albuminuria is primarily a tubular defect, not a glomerular defect (5, 7), but it remains highly controversial (5, 6, 27). The arguments and findings of Comper and colleagues have been challenged at different levels, in particular by recent measurements of albumin GSC (68, 85) and by a mathematical model of albumin reabsorption in the proximal tubule (44). To be consistent with micropuncture measurements of PT albumin concentrations, the filtered load of albumin obtained assuming a GSC of 0.04 would have to be reabsorbed in the first millimeter or so of tubule (6).

How is Epithelial Solute Transport Regulated?

At the microscale, the reabsorption or secretion of water and solutes along the different nephron segments is mediated by epithelial transport processes. Given the many different types of channels, transporters, exchangers, and pumps that are present in a given cell and the coexistence of different cell types in some renal epithelia, mathematical models of tubular epithelial transport are necessary to understand how Na$^+$, K$^+$, Cl$^-$, and acid-base fluxes are coupled and how overall cell function is regulated by molecular events. A significant body of such modeling studies, reviewed in Ref. 99, has generally been successful in predicting in vitro and in vivo transport rates while also elucidating transport pathways and the effects of hormones and drugs.

In a 2003 review of mathematical models of renal epithelial transport, Weinstein (99) summarized fundamental questions that had yet to be answered. The latter included the relative contribution of the paracellular and transcellular routes for water transport in the PT, the mechanisms underlying perfusion-absorption balance, the magnitude of in vivo and in vitro K$^+$ fluxes in the CD, and the specific Cl$^-$ exit pathways in the OMCD. Since then, progress has been made on several of these issues.

Experimental studies investigating perfusion-absorption balance, i.e., the modulation of epithelial Na$^+$ reabsorption by luminal flow, had shown that increases in fluid velocity recruit new Na$^+$/H$^+$ exchangers into the luminal membrane (48, 72). Guo et al. (20) postulated that the PT brush-border microvilli could act as a mechanosensor of fluid flow. Indeed, later experiments demonstrated that Na$^+$ and HCO$_3^-$ reabsorption varies proportionally with the torque exerted on the microvilli (10, 11). The recent rat PT model developed by Weinstein et al. (102) incorporated these findings by relating the density of luminal and/or peritubular transporters to the magnitude of the microvillus torque. An important conclusion of this work was that scaling the density of luminal transporters alone could not explain experimental observations, i.e., coordinated regulation of both luminal and peritubular transporters to the magnitude of the microvillus torque. Another recent model of PT cell homeostasis that is based on optimal control theory also suggests that to minimize variations in cell volume and composition during perfusion-absorption balance, the cell must regulate both luminal and peritubular transporter expression (101). Experimental studies are needed to elucidate the mechanisms underlying luminal-peritubular cross talk.

A new model of transport along the entire distal nephron has clarified the locus of K$^+$ secretion (97). The model predicts that K$^+$ secretion occurs primarily along the connecting tubule (CNT), that is, about five times the load delivered to the distal nephron. Thus the resulting increase in luminal K$^+$ concentrations drives diffusive K$^+$ reabsorption in the downstream medullary segments; model results predict that one-half of the
secreted $K^+$ is reabsorbed before the final urine, in agreement with micropuncture measurements (49).

**How Do Antihypertensive Thiazides Operate In the Distal Nephron?**

All known Mendelian forms of hypertension and hypotension are associated with alterations in renal salt reabsorption, mainly in the distal nephron (46). Thiazides, which inhibit NaCl cotransport in the distal convoluted tubule (DCT), are often favored in the treatment of hypertension, because they reduce sodium reabsorption, plasma volume, and blood pressure. Nevertheless, the use of thiazides as the first-line treatment of hypertension remains controversial because of their negative side effects (73): thiazides exacerbate features of metabolic syndrome, increase the risk for developing diabetes, and generate acid-base disturbances. A better understanding of the underlying mechanisms could guide strategies to improve antihypertensive treatments.

The distal nephron model developed by Weinstein (97) was used to investigate the pathways leading to metabolic alkalosis with thiazides and furosemide and to metabolic acidosis with thiazides and furosemide. Experimental findings in the rabbit CCD also suggest that the most important Cl$^-$ transport pathway is through the $\beta$-cell (79). However, current mathematical models predict that the Cl$^-$ flux is predominantly paracellular in the CCD (84, 98). Further studies are needed to determine fully the secretion by the $\beta$-cells, thereby blunting urine acidification. A similar effect is predicted in response to furosemide, i.e., the model indicates that the increased delivery of NaCl to the CNT produces significant HCO$_3^-$ secretion by $\beta$-cells so that the urine pH rises to 6.23 (97). In contrast, experimentally furosemide was found to lower the urine pH from 6.02 to 5.16 in rat micropuncture studies (26). Several hypotheses were examined in an attempt to resolve this discrepancy. The most plausible is that furosemide induces a very significant upregulation of CNT $\alpha$-cell transport, perhaps as a result of increased luminal flow. Thus not only the model but also several experimental findings (reviewed in Ref. 97), suggest an adaptive response to furosemide diuresis.

Thiazides also have been shown to inhibit NaCl reabsorption by $\sim$50% in the rat and mouse cortical collecting duct (CCD), downstream of the DCT, via an electroneutral pathway that is distinct from the amiloride-sensitive electrogenic pathway (45a, 86). The molecular target of thiazides in the CCD remains uncertain, but the electroneutral pathway is likely to involve pendrin, the apical Cl$^-$/HCO$_3^-$ exchanger expressed by intercalated $\beta$-cells Chloride reabsorption is abolished in pendrin knockout mice (95), and these mice are protected against hypertension induced by the aldosterone analog deoxycorticosterone pivalate (92). Experimental findings in the rabbit CCD also suggest that the most important Cl$^-$ transport pathway is through the $\beta$-cell (79). However, current mathematical models predict that the Cl$^-$ flux is predominantly paracellular in the CCD (84, 98). Further studies are needed to determine fully the...
ionic transport pathways in the CCD and to characterize their response to thiazides.

Conclusions

Mathematical models of renal transport continue to significantly enhance our understanding of kidney function and dysfunction. Inevitably, further progress in many areas is conditional on new experimental advances. The complexity of the kidney is such that mathematical models of renal function are highly dependent on in vivo and in vitro measurements, some of which become clear objectives only in light of the models themselves. Thus an important challenge for modelers is how to make their work more accessible, their hypotheses and suggestions more widely read, and their tools more useful to experimental researchers. The Renal Physiome Project seeks to make a major effort to facilitate access to quantitative kidney data (http://physiome.ibisc.fr/qkdb/) and to make mathematical models of the kidney part of the normal toolbox of renal research laboratories (21, 88, 89). Whether through this interface or another, greater feedback between modelers and experimentalists should increase the pace of progress toward a common goal, an improved understanding and treatment of kidney diseases.

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DISCLOSURES

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