Transport of plasma proteins across vasa recta in the renal medulla

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ZHANG, WENSHENG, and AURÉLIE EDWARDS. Transport of plasma proteins across vasa recta in the renal medulla. Am J Physiol Renal Physiol 281:F478–F492, 2001.—In this study, we have extended a mathematical model of microvascular exchange in the renal medulla to elucidate the mechanisms by which plasma proteins are transported between vasa recta and the interstitium. In contrast with other work, a distinction was made between the paracellular pathway and the transcellular route (i.e., water channels) in descending vasa recta (DVR). Our model first indicates that concentration polarization on the interstitial side of vasa recta has a negligible effect on medullary function. Our results also suggest that, whereas proteins are cleared from the interstitium by convection, both diffusion and convection play a role in carrying proteins to the interstitium. In those regions where transcapillary oncotic pressure gradients favor volume influx through the paracellular pathway in DVR, diffusion is the only means by which proteins can penetrate the interstitium. Whether the source of interstitial protein is DVR or ascending vasa recta (AVR) is determined by medullary permeability to proteins, and vasa recta reflection coefficients to small solutes and proteins. Finally, our model predicts significant axial protein gradients in the renal medullary interstitium.

microcirculation; medullary interstitium; urine concentration; mathematical model

Several studies have shown that albumin is present in the medullary interstitium in significant concentrations (11, 12, 15). The mechanisms by which this extravascular pool of albumin is generated and maintained have long remained uncertain. Radiolabeled albumin injected in the medullary interstitium is rapidly cleared (12), but it is unclear how. Lymphatics are absent in the inner medulla and sparse in the outer medulla, and the possibility of clearance of albumin by drainage via prelymphatic channels is not supported by experimental evidence (12).

The most likely mechanism is that of protein clearance by the microcirculation itself. Pallone (14) suggested descending vasa recta (DVR) as the source of interstitial proteins and postulated that accumulation of albumin in the interstitium results from convective transport processes. Because the reflection coefficient of DVR to albumin is higher than that of ascending vasa recta (AVR), it is possible in principle to maintain steady fluxes of albumin from DVR through the interstitium to AVR (12). Wang and Michel (25) recently developed a model of microvascular exchange of fluid, plasma proteins, and small solutes among DVR, AVR, and the medullary interstitial fluid (ISF) to examine this hypothesis. Their results suggest that convection may indeed be the main mechanism by which plasma proteins are transported from DVR to AVR via the interstitium.

Their model, however, does not distinguish between two parallel transport pathways in DVR that differ significantly. The first one consists of aquaporin-1 (AQP1) water channels, which are present in DVR only and are impermeable to all solutes; transcellular volume fluxes across water channels cannot, therefore, carry albumin by solvent drag into the ISF. The second route, the paracellular pathway, appears to have a reflection coefficient to small solutes that is close to zero (16) and to favor water transport from the ISF toward the lumen in most parts of the medulla (4). In those regions where the paracellular flux is directed toward the lumen, the convective transport of albumin from DVR to the interstitium is not possible, even though there is overall volume efflux from DVR. The objective of this work was to reexamine the mechanisms of albumin exchange with a model that accounts for the presence of two separate transport pathways in DVR as well as for concentration polarization.

We first evaluated albumin concentration differences between the bulk interstitium and the interstitial side of vasa recta walls (i.e., immediately adjacent to the capillaries) to calculate accurately the driving forces for transcapillary transport. We then used conservation equations in the interstitium to determine both interstitial protein concentrations and the processes by which proteins are transported across vasa recta (i.e., diffusion and/or convection from AVR to DVR or vice versa). Because the latter mechanisms appear to vary according to the values of vasa recta permeability to proteins and reflection coefficient to...
small solutes and macromolecules, corresponding parameter sensitivity studies are conducted.

**Glossary**

- \( A_{im} \): Cross-sectional area of inner medulla
- \( A_{int} \): Cross-sectional area of inner medullary interstitium
- \( AVR \): Ascending vasa recta
- \( C_{r}^{i}, C_{w}^{i} \): Concentration of solute \( i \) in plasma, red blood cells, and interstitium, respectively
- \( C_{hb}, C_{hb}^{i} \): Molar and molal concentrations of hemoglobin in red blood cells, respectively
- \( D \): Vessel diameter
- \( D_{i} \): Diffusivity of solute \( i \)
- \( DVR \): Descending vasa recta
- \( f \): Fractional volume of distribution of urea in red blood cells
- \( f_{p} \): Fraction of capillary surface occupied by pores
- \( F_{VR} \): Fraction of the inner medullary cross-sectional area occupied by vasa recta
- \( H_{i} \): Hydrodynamic hindrance factor for diffusive transport of solute \( i \)
- \( IM \): Inner medulla
- \( INT \): Interstitium
- \( ISF \): Interstitial fluid
- \( J_{i} \): Paracellular molar flux of solute \( i \)
- \( J_{v}, J_{v}^{R} \): Volume fluxes across capillaries and red blood cell membranes, respectively
- \( J_{vp}, J_{vt} \): Paracellular and transcellular volume fluxes across capillaries, respectively
- \( J_{uc}, J_{ur} \): Carrier-mediated transcapillary molar flux of urea, and molar flux of urea across red blood cell membranes
- \( l \): Capillary pore length
- \( L \): Length of renal medulla
- \( L_{im} \): Length of inner medulla
- \( L_{p}, L_{q} \): Hydraulic conductivities of paracellular and transcellular pathways, respectively
- \( L_{R} \): Hydraulic conductivity of red blood cell membrane
- \( N \): Number of vasa recta
- \( N_{c} \): AVR-to-DVR number ratio
- \( OM \): Outer medulla
- \( P, P_{i} \): Hydraulic pressure in plasma and interstitium, respectively
- \( Pe \): Peclet number
- \( P_{v} \): Permeability of capillary wall to solute \( i \)
- \( P_{uc}, P_{ur} \): Permeability of urea transporter in capillary wall and red blood cell membrane, respectively
- \( Q^{P}_{b} \): Blood flow rate
- \( Q^{P}_{r} \): Plasma flow rate
- \( Q^{R}_{b} \): Red blood cell flow rate
- \( r \): Radius
- \( r_{p} \): Capillary pore radius
- \( r_{i} \): Radius of solute \( i \)
- \( RBC \): Red blood cell
- \( u \): Urea
- \( W \): Half-width of slit pore
- \( \Phi \): Solute distribution coefficient
- \( \Gamma \): Red blood cell-to-vessel surface area ratio
- \( \gamma_{i} \): Activity coefficient of solute \( i \)
- \( \Pi_{i} \): Oncotic pressure due to solute \( i \)
- \( \sigma_{i} \): Reflection coefficient of the paracellular pathway to solute \( i \)
- \( \psi_{v}, \psi_{Na}, \psi_{u} \): Generation rate of volume, sodium, and urea, respectively, per unit area of interstitium
- \( a \): Albumin
- \( hb \): Hemoglobin
- \( Na \): Sodium
- \( pr \): Plasma protein
- \( ss \): Small solute (sodium and urea)

**METHODS**

*Mathematical Model*

The fundamental assumptions of our model of renal medullary microvascular transport have been extensively described earlier (4–6). We consider only those vasa recta that are destined for the inner medulla (IM), i.e., those that lie in the center of the vascular bundles and do not perfuse the capillary plexus of the outer medulla (OM). The deposition of NaCl, urea, and water into the IM interstitium from the loops of Henle and the collecting ducts is simulated with generation rates that undergo spatial variation within the IM interstitium. In the vascular bundles, exchanges occur only between vasa recta and the interstitium, so that generation rates are taken to be zero. Plasma and red blood cells (RBC) are considered as two separate compartments. Two transcellular pathways are present in DVR only: AQP1 water channels and urea transporters.

**Conservation and transport equations in vasa recta plasma.** If \( x \) is the axial coordinate along the corticomedullary axis, changes in the plasma flow rate \( (Q^{P}) \) in DVR and AVR at steady state are given by the following equation, based on mass conservation

\[
\frac{dQ^{P}_{c}}{dx} = \pm (J_{c} - \Gamma J_{c}^{R}) \pi ND + \left( \frac{Q^{P}_{r}}{N} \right) \frac{dN}{dx} \quad (1)
\]

where \( J_{c} \) and \( J_{c}^{R} \) are the volume fluxes (per unit membrane area) across the capillary wall and the RBC membrane, respectively, \( \Gamma \) is the cell-to-vessel surface area ratio, \( N \) denotes the number of vessels and \( D \) their diameter, and + and − apply to AVR and DVR, respectively. \( J_{c} \) is the sum of two contributions, the paracellular \( (J_{vp}) \) and transcellular \( (J_{vt}) \) volume fluxes, which are given by
where \( L_p \) and \( L_t \) represent the hydraulic conductivities of the paracellular and transcellular pathways, respectively, \( \Delta P \) is the transcapillary hydraulic pressure difference, \( \Delta \Pi_a \) and \( \Delta \Pi_{pr} \) are the transcapillary oncotic pressure differences due to albumin and all plasma proteins, respectively, and \( \sigma_i \) is the reflection coefficient of the paracellular pathway to albumin. The plasma and interstitial concentrations of solute \( i \) are denoted by \( C_i^p \) and \( C_i^t \), respectively; \( \gamma_i \) is the activity coefficient of \( i \), and \( \sigma_i \) is the reflection coefficient of the paracellular pathway to albumin. Note that reflection coefficients are taken to be one for the solute-impermeable transcellular pathway and that \( J_i \) is zero across AVR, where no AQP1 has been found. The oncotic pressures due to albumin and all plasma protein are calculated as, respectively

\[
\Pi_a = 2.8C_a + 0.18C_a^2 + 0.012C_a^3
\]

\[
\Pi_{pr} = 2.1C_{pr} + 0.16C_{pr}^2 + 0.009C_{pr}^3
\]

where \( C_a \) and \( C_{pr} \) are the albumin and total protein concentration, respectively, in grams per deciliter.

Conservation of solutes to which RBCs are impermeable, such as sodium, albumin, and other proteins, can be written as

\[
\frac{d(Q^iC_i^p)}{dx} = \pm J_i \pi N D + \left( \frac{Q^iC_i^p}{N} \right) \frac{dN}{dx}
\]

where \( J_i \) is the (paracellular) molar flux of solute \( i \) (per unit membrane area) from plasma to interstitium. With the assumption of negligible loss of protein other than albumin to the interstitium, the flux of nonalbumin protein is taken to be zero. Conservation of urea, which is exchanged across the RBC membrane, yields

\[
\frac{d(Q^iC_i^p)}{dx} = \pm (J_u + J_{uc} - \Gamma J^R_i) \pi N D + \left( \frac{Q^iC_i^p}{N} \right) \frac{dN}{dx}
\]

where \( J_u \) and \( J_{uc} \) are the paracellular and carrier-mediated transcapillary molar fluxes of urea, respectively, and \( J^R_i \) is the molar flux of urea across RBCs. The paracellular flux of solute \( i \) \( (i = \text{sodium, albumin, urea}) \) across capillary walls can be written as

\[
J_i = J_{vp}(1 - \sigma_i) \left[ \frac{C_i^p - C_i^t \exp(-Pe)}{1 - \exp(-Pe)} \right]
\]

\[
Pe = \frac{J_{vp}(1 - \sigma_i)}{P_i}
\]

where \( P_i \) is the permeability of the vessel to solute \( i \), and the Pecllet number, \( Pe \), is a measure of the importance of convection relative to diffusion. The carrier-mediated transcapillary and transmembrane fluxes of urea, respectively, are given by

\[
J_{uc} = P_{uc}(C_i^u - C_i^t)
\]

\[
J^R_i = P_{ur}(C_i^u - C_i^t)
\]

where \( P_{uc} \) and \( P_{ur} \) are the permeabilities of the urea transporter in the capillary wall and in the RBC membrane, respectively, and \( C_i^u \) is the RBC concentration of urea.

**Conservation and transport equations in RBCs.** Conservation of mass in RBCs can be expressed as

\[
\frac{dQ^i}{dx} = \frac{d}{dx} \left( \frac{Q^iC_i^p}{N} \right) \frac{dN}{dx}
\]

where \( Q^i \) is the RBC flow rate. If we assume that there is no hydraulic pressure difference across the RBC membrane, \( J^R_i \) is given by

\[
J^R_i = L_m[\Pi_{pr} - \Pi_{hb} - RT \sum \gamma_i(C_i^p - C_i^t)]
\]

where \( L_m \) is the RBC membrane hydraulic conductivity, \( \Pi_{pr} \) and \( \Pi_{hb} \) are the oncotic pressures due to plasma proteins and to hemoglobin in the cells, respectively, and \( C_i^p \) denotes the RBC concentration of solute \( i \). As described in Edwards and Pallone (5), the oncotic pressure due to hemoglobin in RBCs is calculated as

\[
\Pi_{hb} = RT[C_{hb}^m + 0.106(C_{hb}^m)^2 + 0.020(C_{hb}^m)^3]
\]

\[
C_{hb}^m = \frac{C_{hb}}{1 - \bar{v}C_{hb}}
\]

where \( C_{hb} \) and \( C_{hb}^m \) are the molar and molal RBC concentrations of hemoglobin, respectively, and \( \bar{v} = 0.75 \text{ mg/dl} \) is the partial specific volume of hemoglobin.

Conservation of hemoglobin and other nonurea solutes (e.g., potassium, magnesium, and associated intracellular anions) in RBCs yields

\[
\frac{d(Q^hC_{hb}^m)}{dx} = \frac{d}{dx} \left( \frac{Q^hC_{hb}^m}{N} \right) \frac{dN}{dx}
\]

\[
J = \text{hemoglobin, other nonurea solutes}
\]

The RBC concentration of urea can be obtained on the basis of the conservation equation

\[
\frac{d(Q^iC_i^p)}{dx} = \pm (J_u + J_{uc} - \Gamma J^R_i) \pi N D + \left( \frac{Q^iC_i^p}{N} \right) \frac{dN}{dx}
\]

where \( f \) is the fractional volume of distribution of urea within RBCs, taken to be 0.86.

**Conservation equations in interstitium.** As described in Edwards et al. (4), the deposition of NaCl, urea, and water into the medullary interstitium from the loops of Henle and collecting ducts is simulated with generation rates that undergo spatial variation within the IM interstitium. The interstitial hydraulic pressure (\( P^t \)) and small solute concentrations (\( C_i^t \) and \( C_i^t \)) are determined by considering that, at any location along the corticomedullary axis, the sum of the fluxes from DVR and AVR, weighted according to their respective surface area, must be equal and opposite to the rate of generation in the interstitium

\[
[(J_{vp})(x) + J_{uc}(x)]N(x)\pi D_{DVR} + [J_{vp}(x)N(x)\pi D]_{AVR}
\]

\[
+ A_{ur}(x)\Psi_{ur}(x) = 0
\]

\[
[J_{Na}(x)N(x)\pi D]_{DVR} + [J_{Na}(x)N(x)\pi D]_{AVR}
\]

\[
+ A_{ur}(x)\Psi_{Na}(x) = 0
\]

\[
[(J_{u}(x) + J_{uc}(x))N(x)\pi D]_{DVR} + [J_{u}(x)N(x)\pi D]_{AVR}
\]

\[
+ A_{ur}(x)\Psi_{u}(x) = 0
\]
where \( A_{\text{int}} \) is the cross-sectional area of the medullary interstitium (in cm\(^2\)), and \( \psi_v, \psi_{\text{Na}}, \) and \( \psi_a \) are the local generation rates of volume, sodium, and urea, respectively, per unit area of interstitium. The latter three terms are taken to be zero in the OM, where in the vascular bundles the exchange of water, sodium, and urea can occur only between vasa recta and interstitium.

The cross-sectional area of the IM interstitium is calculated on the basis of that of the inner medulla, \( A_{\text{im}}(6) \)

\[
A_{\text{im}} = (0.25X_{\text{im}} + 0.05)A_{\text{im}}
\]

\[
A_{\text{im}} = 0.175 - 0.3883X_{\text{im}} + 0.2606X_{\text{im}}^2 - 0.04193X_{\text{im}}^3
\]

where \( X_{\text{im}} \) is the dimensionless IM axial coordinate based on the length of the IM.

Concentration polarization: annular space model. As water is reabsorbed from the interstitium into AVR, the accumulation of albumin near the AVR wall on the interstitial side, a phenomenon known as concentration polarization, reduces the transcapillary oncotic pressure difference and therefore decreases the driving force for water reabsorption. Conversely, during volume efflux from DVR, the concentration of albumin on the interstitial side of the DVR wall will be lower than that averaged radially over the interstitium; i.e., reverse polarization will occur, leading to a decreased rate of fluid filtration. Polarization (or its reverse) is not expected to be significant within vasa recta, due to the presence of RBCs, which create a circulatory flow that homogenizes plasma concentrations (3).

Transport of fluid and solutes in the interstitium is predominantly in the radial direction (i.e., normal to the corticomedullary axis); not only do the orientation and density of lipid-laden IM interstitial cells appear to hinder axial diffusion (10), but the length of the renal medulla is about a thousand times the distance between adjacent vasa recta. In our analysis, interstitial transport in the axial direction is therefore deemed negligible compared with radial diffusion and radial convection.

To assess the effects of concentration polarization at a given depth in the medulla, we used a one-dimensional, cylindrical model of polarization in the radial direction, following the approach of Lee (9). The objective was to estimate the albumin concentration difference between the bulk interstitium and in the interstitium immediately adjacent to the capillary membrane. With the assumption that each vasa recta can be represented as a cylinder embedded in a coaxial, conic interstitium, as shown in Fig. 1, conservation of albumin in the annular space (i.e., in the interstitium) is written as

\[
\frac{1}{r} \frac{\partial}{\partial r} (rJ_a) = \frac{1}{r} \frac{\partial}{\partial r} \left[ \left( \nu C_a - \frac{D_a}{r} \frac{\partial}{\partial r} (rC_a) \right) \right] = 0
\]

where \( J_a, C_a, \) and \( D_a \) are the flux, concentration, and diffusivity of albumin in the interstitium, respectively, and \( \nu \) is the fluid velocity. Conservation of water implies that

\[
rv = \text{constant} = r_a \nu_a
\]

where \( r_a \) is the radius of the inner cylinder (i.e., of DVR or AVR) and \( \nu_a \) is the (known) velocity at that boundary. Equations 15 and 16 can be combined to yield

\[
\frac{\partial^2 C_a}{\partial r^2} + \frac{1}{r} \frac{\partial}{\partial r} \left( 1 - r_a \nu_a \right) \frac{\partial C_a}{\partial r} = 0
\]

Given the bulk interstitial albumin concentration, \( C_{\text{im}} \), the following boundary conditions have to be satisfied

\[
\text{at } r = r_B, \quad C_a = C_{\text{im}}
\]

\[
\text{at } r = r_A, \quad \nu C_a - D_a \frac{\partial C_a}{\partial r} = J_a
\]

where \( r_B \) is the outer radius, and \( J_a \), the (specified) transcapillary flux of albumin, is constant in the \( r \)-direction in the annular space (see Eq. 15). The differential equation Eq. 17, coupled with the boundary conditions (Eq. 18, a and b), has an explicit solution

\[
C_a(r) = \left( C_{\text{im}} - J_a/\nu_a \frac{r_B}{r_a} \right) \left( \frac{r}{r_B} \right)^{1-\sigma_a} + J_a/\nu_a
\]

\[
Pe_a = \frac{r_a \nu_a}{D_a}
\]

By substituting \( r = r_A \) into Eq. 19, the albumin concentration at the vasa recta wall, \( C_w \), can be determined.

If diffusion is negligible across the capillary wall, the transcapillary flux of albumin \( J_a \) is directly proportional to the paracellular water flux (see Eq. 24 below in the limit when \( Pe_a \to \infty \)). In AVR where there are no water channels, the paracellular water flux (per unit membrane area) is equal to \( \nu_A \), so that \( J_a = (1 - \sigma_a) C_{\text{im}} \nu_A \) in that limit and the wall-to-bulk albumin concentration ratio is given by

\[
\frac{C_w}{C_{\text{im}}} = \frac{1}{1 + \sigma_a \left( \frac{r_B}{r_A} \frac{\nu_w}{\nu_A} - 1 \right)}
\]

where \( \sigma_a \) is the reflection coefficient of vasa recta to albumin. When water flows from the interstitium toward AVR, \( Pe_a \) is negative, and the concentration ratio is >1. The interstitial oncotic pressure at the AVR wall is, therefore, greater than that which would be calculated based on the bulk interstitial concentration. Polarization thus reduces the driving force for volume flux toward AVR, thereby limiting fluid uptake.

In DVR, even when convection is highly dominant, \( J_a \) is not directly proportional to \( \nu_A \), because there is a transcellular component to the water flux and water channels are impermeable to albumin. Equation 19, with \( r = r_A \), cannot therefore be reduced to Eq. 20. It can be shown, however, that \( C_w \) is less than \( C_{\text{im}} \) when water flows out of DVR. The reduction in the interstitial oncotic pressure then serves to limit volume efflux.
**Interstitial space size calculations.** Because both the number of AVR and their diameters are greater than those of DVR, the average distance between the bulk of the interstitium and the capillary wall (i.e., DVR, the average distance between the bulk of the interstitium and their diameters are greater than those of AVR) is different for AVR and DVR. At every depth and for each type of vessel, \( r_b \) is approximated using the equation

\[
N_A r_b^3 = N_D r_c^3 + A_{\text{int}} \quad (21)
\]

Because we consider only those vasa recta that are destined for the IM, the number of vasa recta in the OM remains constant. In the IM, the number of DVR and AVR is given by

\[
N_{\text{DVR}}(x) = \frac{F_{\text{VR}} A_{\text{int}}(x)}{(D_{\text{DVR}}^2 + N_D D_{\text{VR}}) \pi / 4} \quad (22)
\]

\[
N_{\text{AVR}}(x) = N_A N_{\text{DVR}}(x)
\]

where \( F_{\text{VR}} \), the fraction of the inner medullary cross-sectional area occupied by vasa recta, and \( N_A \), the AVR-to-DVR number ratio, are taken to be constant and equal to 0.3 and 2.55, respectively (26). With those assumptions, \( r_b/r_c \) remains constant between 1.3 at the OM-IM junction and 2.4 at the papillary tip for DVR and between 1.1 and 1.5 at the same boundaries for AVR. (Note that, even though \( r_b/r_c \) is constant and \( A_{\text{int}} \) decreases along the corticomedullary axis, the number \( N \) of vessels decreases more rapidly, which is why the ratio \( r_b/r_c \) increases.) In the OM, we assume that \( r_b/r_c \), remains constant and equal to its value at the OM-IM junction. In those simulations of concentration polarization, the diffusivity of albumin in the interstitium, \( D_a \), is estimated to be ten times smaller than that in water (8).

**Albumin interstitial concentration.** In our previous approaches (4, 6), the interstitial concentration of albumin was taken to be fixed and constant along the corticomedullary axis. The issue of albumin polarization having been addressed, the transport of albumin may now be modeled more rigorously. An interstitial mass conservation equation can be written to determine the concentration of albumin in the interstitium. If there are no interstitial sources or sinks of albumin (such as transcytosis, proteolysis, or lymphatic drainage), the amount of albumin carried from DVR and AVR can be written to determine the concentration of albumin in the interstitium:

\[
(J_a N_A d)_{\text{DVR}} + (J_a N_A d)_{\text{AVR}} = 0 \quad (23)
\]

where \( J_a \) is the transcapillary flux of albumin. Implicit in Eq. 23 is the assumption that axial transport in the interstitium is negligible, as discussed earlier. The albumin flux can be written as

\[
J_a = J_{\text{wp}}(1 - \sigma_a) \left[ C_a^p - C_a^w \exp(-P_e) \right] \frac{1 - \exp(-P_e)}{1 - \exp(-P_e)} \quad (24)
\]

where \( P_e \), the Peclet number, is given by Eq. 6. Note that Eq. 24 includes the interstitial concentration of albumin immediately adjacent to the capillary wall, \( C_a^w \), which is related to the bulk interstitial concentration, \( C_a^b \), as described in Concentration Polarization. At every depth along the corticomedullary axis, as flow rates and concentrations in plasma are determined, Eq. 23, which relates albumin concentrations in vasa recta to \( C_a^w \), is solved to determine interstitial albumin concentrations.

**Parameter selection.** Parameter values for our model are given in Table 1. The hydraulic pressure \( P \) is assumed to remain constant in AVR and IMDVR, with fixed values of 7.8 and 9.2 mmHg, respectively. In OMDVR, \( P \) is assumed to decrease linearly from 20 to 9.2 mmHg (5). The fraction of the filtered load recovered by IM vasa recta for water, NaCl, and urea is taken as 1, 1, and 40%, respectively; the filtered load is calculated as described in Edwards et al. (4), based on the values of corticomedullary DVR concentrations and whole kidney glomerular filtration rate (GFR) that are given in Table 1. In the baseline case, the interstitial area-weighted generation rate of water decreases linearly between the OM-IM junction and the papillary tip, whereas those of sodium and urea increase linearly and exponentially, respectively (4).

**Permeability of vasa recta to albumin.** The permeability of AVR to albumin is \(<10^{-6}\) cm/s and is therefore too low to be measured by present methods (14). If we assume that the paracellular pathway consists of parallel pores of uniform size, estimates of pore dimensions can be obtained using pore

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**Table 1. Parameter values**

<table>
<thead>
<tr>
<th>Parameter values*</th>
<th>DVR</th>
<th>AVR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transport parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paracellular hydraulic conductivity, ( L_a ), cm·s⁻¹·mmHg⁻¹</td>
<td>1.8×10⁻⁶</td>
<td>12.5×10⁻⁶</td>
</tr>
<tr>
<td>Transcellular osmotic hydraulic conductivity, ( L_e ), cm·s⁻¹·mmHg⁻¹</td>
<td>1.0×10⁻⁷</td>
<td></td>
</tr>
<tr>
<td>Hydraulic conductivity of RBC membrane, ( L_p ), cm·s⁻¹·mmHg⁻¹</td>
<td>2.1×10⁻⁸</td>
<td>2.1×10⁻⁸</td>
</tr>
<tr>
<td>Paracellular permeability to sodium, cm/s</td>
<td>75×10⁻⁵</td>
<td>113×10⁻⁵</td>
</tr>
<tr>
<td>Paracellular permeability to urea, cm/s</td>
<td>75×10⁻⁵</td>
<td>113×10⁻⁵</td>
</tr>
<tr>
<td>Carrier-mediated permeability of capillary wall to urea, ( P_{uw} ), cm/s</td>
<td>285×10⁻⁵</td>
<td></td>
</tr>
<tr>
<td>Carrier-mediated permeability of RBC membrane to urea, ( P_{ur} ), cm/s</td>
<td>160×10⁻⁵</td>
<td>160×10⁻⁵</td>
</tr>
<tr>
<td>Paracellular reflection coefficient to albumin</td>
<td>0.89</td>
<td>0.70</td>
</tr>
<tr>
<td>Baseline paracellular permeability to albumin, cm/s</td>
<td>1×10⁻⁷</td>
<td>1×10⁻⁶</td>
</tr>
</tbody>
</table>

**Physical dimensions**

| DVR diameter, \( D_v \), \( \mu \)m | 15.6 |
| AVR diameter, \( D_v \), \( \mu \)m | 20.0 |
| Total length of medulla, mm | 7.8 |
| Length of inner medulla, mm | 5.9 |

**Boundary conditions**

| Initial single vessel blood flow rate, nl/min | 10 |
| Initial hematocrit | 0.25 |
| Initial albumin plasma concentration, g/dl | 3.9 |
| Initial other plasma protein concentration, g/dl | 2.9 |
| Initial sodium plasma concentration, mmol/l | 150 |
| Initial urea plasma concentration, mmol/l | 5 |
| Initial urea RBC concentration, mmol/l | 5 |
| Initial hemoglobin RBC concentration, mmol/l | 5.1 |
| Initial RBC concentration of other nonurea solutes, mmol/l | 292 |
| Whole kidney glomerular filtration rate, \( \mu \)l/min | 784 |

*See Refs. 5 and 6 (with the change between 4 and 6). DVR, descending vasa recta; AVR, ascending vasa recta; RBC, red blood cells; Initial, at the corticomedullary junction in DVR.
theory and other available measurements, and the permeability of vasa recta to albumin may be calculated using pore theory as well. Calculations are made for both cylindrical and slit pores.

For cylindrical pores, the (osmotic) reflection coefficient in the absence of electrical interactions between the solute and pore wall is given by (2)

$$\sigma = (1 - \Phi)^2$$

(25)

$$\Phi = (1 - r_p/r_p)^2$$

where \( r_s \) and \( r_p \) are the radii of the solute and pore, respectively, and \( \Phi \) is the distribution coefficient, i.e., the ratio of the average intrapore concentration to that in bulk solution at equilibrium. The reflection coefficient of DVR to albumin (\( r_s = 3.5 \) nm) has been measured as 0.89 (23), yielding 4.6 nm as the pore radius. In AVR, where the average value of \( r_s \) is ~0.70 (12, 14), the pore radius is calculated to be 5.9 nm. Even if there are electrical interactions between the negatively charged albumin and the endothelial glyocalyx, these values should represent reasonable order-of-magnitude estimates of \( r_p \).

For slit pores, the osmotic reflection coefficient can be written as (2)

$$\sigma = 1 - \frac{1}{2} \Phi + \frac{1}{2} \Phi^3$$

(26)

$$\Phi = 1 - r_p/W$$

where \( W \), the half-width of the slit, is calculated to be 3.8 nm in DVR and 4.4 nm in AVR, following the procedure described immediately above.

The permeability \( P_i \) of the porous pathway to a given solute \( i \) can be written as

$$P_i = \frac{H_i D_i f_i}{l}$$

(27)

where \( D_i \) is the solute diffusivity in dilute bulk solution, the coefficient \( H_i \) expresses the hydrodynamic hindrance to diffusive solute transport, \( f_i \) is the fraction of capillary surface occupied by pores, and \( l \) is the pore length. The permeability of the paracellular pathway to urea (or sodium) being known, the permeability to albumin can then be calculated as

$$P_a = P_u \left( \frac{H_u}{H_a} \right) \left( \frac{D_u}{D_a} \right)$$

(28)

where the subscripts \( a \) and \( u \) refer to albumin and urea \( (r_s = 0.28 \) nm), respectively. An expression for \( H_i \), for uncharged solutes in cylindrical pores is given by Bungay and Brenner (1) as a function of \( \lambda = r_s/r_p \)

$$H_i = \frac{6\pi(1 - \lambda)^2}{K_i}$$

(29)

$$K_i = \frac{9}{4\pi^2 \sqrt{2(1 - \lambda)^{-3/2}}} \left[ \frac{1}{60} - \frac{73}{10^6} (1 - \lambda) + \frac{77.293}{50.400} (1 - \lambda)^2 \right]$$

$$- 22.5083 - 5.6117\lambda - 0.3363\lambda^2$$

$$- 1.216\lambda^3 + 1.647\lambda^4$$

In slit pores, with \( \lambda = r_p/W, H_i \) can be determined as (2)

$$H_i = (1 - \lambda) \left[ 1 - 0.004\lambda + 0.418\lambda^2 + 0.214\lambda^3 - 0.169\lambda^4 \right]$$

(30)

The diffusivity of albumin in dilute bulk solution is calculated using the Stokes-Einstein equation, yielding \( 9.3 \times 10^{-7} \) cm²/s, and that of urea is estimated as \( 2.0 \times 10^{-5} \) cm²/s on the basis of the Wilke-Chang correlation for small solutes (20). In this manner, the permeability to albumin of DVR and AVR is calculated to be \( 5.6 \times 10^{-8} \) and \( 9.9 \times 10^{-7} \) cm²/s, respectively, assuming that the pores are cylindrical and \( 1.3 \times 10^{-6} \) and \( 5.4 \times 10^{-6} \) cm²/s, respectively, in the case of slit pores. A range of parameter values for \( P_a \) must therefore be explored.

**Numerical Methods**

In the microcirculation, nine variables must be determined along both DVR and AVR: plasma flow rate, RBC flow rate, albumin plasma concentration, other protein plasma concentration, sodium plasma concentration, urea plasma concentration, urea RBC concentration, hemoglobin RBC concentration, and the RBC concentration of other nonurea solutes. *Equations 1, 4, 5, 8, 11, and 12* form the corresponding set of ordinary differential equations (ODEs) that need to be integrated to determine the profiles of these variables. The initial values in DVR at the corticomedullary junction are specified (see Table 1). At the papillary tip, i.e., at the entrance to AVR, DVR and AVR values have to match.

The set of ODEs expressing mass conservation in DVR and AVR is highly coupled. At each point along the corticomedullary axis, evaluating fluxes across DVR requires that values in the interstitium and in AVR be known, and vice versa. However, the ODEs cannot be simply integrated simultaneously along DVR and AVR, because boundary values for flow rates and concentrations in AVR at the papillary tip are not known until differential equations for DVR have been integrated along the entire axis. Hence, we used the following approach.

An initial guess was made for the profiles in AVR of the nine variables along the entire corticomedullary axis. The set of ODEs (Eqs. 1, 4, 5, 8, 11, and 12) was then numerically integrated along DVR; at each step along the corticomedullary axis, algebraic equations were solved to determine the interstitial hydraulic pressure as well as sodium, urea, and albumin interstitial concentrations (Eqs. 13, a–c, and 23). Once papillary tip values were obtained, the same set of differential equations was numerically integrated back up along AVR, and AVR flow rates and concentration values were updated. This process was iterated until the normalized difference between the current and previous estimates of each variable in AVR at any \( x \) was \( <10^{-5} \). Tests demonstrating mass conservation are described in the APPENDIX.

ODEs were integrated along vasa recta by use of Gear’s method, which is a self-adaptive, multistep, predictor-corrector method for stiff ODEs. At each value of \( x \), the system of three or four nonlinear algebraic equations (Eqs. 13, a–c, and 23) was solved using a modified Powell hybrid method. This algorithm, which is a variation of Newton’s method, uses finite difference approximations to the Jacobian and avoids large step sizes or increasing residuals (13). Simulations were performed on an Alpha PC64 workstation. Convergence was typically achieved in 5 h.

When the effects of concentration polarization are assessed, the incorporation of Eq. 19 into the simulations of medullary microvascular transport is complicated by the fact that \( v_A \), and hence \( P_{ea} \) and \( J_{ea} \), are themselves functions of \( C_A^0 \) through the interstitial oncotic pressure term in the paracellular and transcellular volume fluxes (Eqs. 2 and 3). At each integration step along DVR and AVR, we first calculated the volume fluxes on the basis of the bulk interstitial concentration of albumin. The albumin interstitial concentration immediately adjacent to the walls was then determined using...
Eq. 19, and the volume fluxes were calculated anew on the basis of this value. The latter two steps were iterated until convergence was achieved.

RESULTS

We first examined the extent to which concentration polarization in the medullary interstitium affects flow rates and concentration profiles in vasa recta; for simplicity, the bulk interstitial concentration of albumin was assumed to be constant and known in those calculations. We then eliminated that hypothesis and used instead conservation equations in the interstitium to determine protein interstitial concentrations and the mechanisms by which proteins are exchanged between vasa recta and the interstitium. In the absence of measurements for certain capillary wall permeabilities and reflection coefficients, parameter sensitivity studies were performed in which a range of possible values was explored.

Albumin Concentration Polarization

The AVR-to-interstitium albumin concentration difference is a major determinant of fluid reabsorption into the microcirculation. To evaluate this driving force, the effects of concentration polarization must be taken into consideration, because polarization significantly reduces the oncotic pressure gradient across AVR walls. We had previously postulated that the accumulation of albumin on the interstitial side of the AVR wall is high enough to eliminate the oncotic pressure difference due to albumin (4). The more rigorous approach to concentration polarization developed here allowed us to test this hypothesis as well as to examine the effects of reverse polarization at DVR walls. During volume efflux from DVR, interstitial concentrations adjacent to the membrane are smaller than those in the bulk, thereby increasing oncotic pressure gradients across DVR walls.

Results based on the present model of polarization were compared with those obtained in two cases: 1) concentration polarization and its reverse are negligible (the “no-polarization” hypothesis); and 2) the accumulation of albumin on the interstitial side of the AVR wall is so significant that albumin oncotic pressure differences across that barrier vanish entirely (the no-AVR-ΔIa hypothesis). The bulk interstitial concentration of albumin, C_a^I, was kept fixed, either at 3.4 g/dl, as measured by Pallone (15) or at 1 g/dl, as reported by MacPhee and Michel (12). To maintain high osmolalities at the papillary tip, we varied only the spatial distributions of the interstitial area-weighted generation rate of urea. As described in the previous section, the set of differential equations (Eqs. 1, 4, 5, 8, 11, and 12) was numerically integrated along vasa recta to obtain flow rates and concentration profiles in plasma; at each step, the algebraic equations (Eq. 13, a–c) had to be solved to yield interstitial values. When polarization is accounted for, the albumin interstitial concentration at the wall was related to that in the bulk through Eq. 19. Results are shown in Table 2.

Reverse polarization at the DVR wall increases the transcapillary albumin oncotic pressure difference, thereby reducing water efflux from DVR; the rise in sodium and urea concentrations along the corticomedullary axis is therefore less accentuated. Polarization at the AVR wall has the same effect: a reduced ΔIa limits water influx into AVR and, hence, efflux from DVR, since the interstitial water balance must be maintained; sodium and urea concentrations thus remain lower. Consequently, as shown in Table 2, the osmolality at the papillary tip is always overestimated when concentration polarization and its reverse are neglected and systematically underpredicted if ΔIa across AVR walls is omitted.

In the former case, however, the error remains small, <2%, and the lower the C_a^I, the smaller the error, because differences between interstitial concentrations in the bulk and near the capillary walls then have less of an effect on oncotic pressure gradients (see Eqs. 2 and 3). If the assumption that ΔIa can be neglected across AVR walls is employed rather than our present approach, the discrepancy can be as high as 15%, suggesting that the no-AVR-ΔIa hypothesis, which we used previously (4), is an overly simplifying assumption.

Given the uncertainty in model geometry and in parameter values such as generation rates and albumin permeability, errors on the order of 2% are not very significant. The annular space model developed here, although based on an idealized representation of the medulla, therefore suggests that the effects of concentration polarization in the renal medulla can be neglected, as they will be in the remainder of this study.

Transport Mechanisms of Plasma Proteins Across Vasa Recta

Paracellular and transcellular volume fluxes. AQP1 water channels in DVR are impermeable to all solutes

Table 2. Effect of concentration polarization on osmolality at the papillary tip

<table>
<thead>
<tr>
<th>Case*</th>
<th>Osmolality at Papillary Tip, mosmol/l (% contributed by urea)</th>
<th>No polarization</th>
<th>Polarization (present model)</th>
<th>No-AVR-ΔIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exponential urea increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_a^I = 3.4 g/dl</td>
<td>1210</td>
<td>1193</td>
<td>1155</td>
<td></td>
</tr>
<tr>
<td>(51.6)</td>
<td>(51.7)</td>
<td>(51.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exponential urea increase</td>
<td>1134</td>
<td>1127</td>
<td>954</td>
<td></td>
</tr>
<tr>
<td>C_a^I = 1.0 g/dl</td>
<td>(51.5)</td>
<td>(51.4)</td>
<td>(49.7)</td>
<td></td>
</tr>
<tr>
<td>Linear urea increase</td>
<td>1040</td>
<td>1019</td>
<td>984</td>
<td></td>
</tr>
<tr>
<td>C_a^I = 3.4 g/dl</td>
<td>(45.8)</td>
<td>(45.7)</td>
<td>(45.6)</td>
<td></td>
</tr>
<tr>
<td>Linear urea increase</td>
<td>960</td>
<td>957</td>
<td>842</td>
<td></td>
</tr>
<tr>
<td>C_a^I = 1.0 g/dl</td>
<td>(45.5)</td>
<td>(45.5)</td>
<td>(44.6)</td>
<td></td>
</tr>
</tbody>
</table>

*The interstitial area-weighted generation rate of urea is taken to increase either linearly or exponentially. In those simulations, the bulk interstitial concentration of albumin, C_a^I, is fixed.

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Because small solutes such as sodium and urea are more concentrated in the medullary interstitium than in DVR, osmotic pressure gradients drive water from DVR toward the interstitium through this transcellular pathway (i.e., $J_{vp} > 0$). The reflection coefficient to small solutes of the paracellular pathway ($\sigma_{ss}$), however, is close or equal to zero (16), so that osmotic pressure gradients have little to no effect on $J_{vp}$. Transcapillary protein concentration differences are therefore the dominant driving force across that route, and water moves in the opposite direction through the paracellular pathway, i.e., from the interstitium toward DVR (Eq. 2, a and b).

Shown in Fig. 2 are the paracellular and transcellular water fluxes across DVR and AVR when albumin interstitial concentration is specified and with the assumption that $\sigma_{ss}$ is zero. Generation rates are those of the baseline case, parameter values are given in Table 1, and $C_I$ is fixed at 3.4 g/dl, as measured by Pallone (15). As illustrated in Fig. 2, the paracellular flux of water across DVR is positive only near the corticomedullary junction; it is negative, i.e., directed toward the capillary lumen, throughout most of the medulla. With a smaller interstitial albumin concentration, in the range of 1 g/dl as measured by MacPhee and Michel (12), albumin concentration gradients across DVR are even larger, resulting in more water influx through the paracellular route.

Because there can be no transport of albumin across AQP1, solvent drag is effective only across paracellular routes and will therefore carry albumin away from the interstitium in most of the medulla and toward both DVR and AVR. Hence, it is unlikely that convective transport can solely explain the presence of protein in the medullary interstitium.

Transport of albumin and other plasma proteins. To understand the mechanisms by which albumin appears in the medullary interstitium, albumin concentration in the ISF was then calculated on the basis of interstitial mass conservation (Eq. 23) instead of being specified. The permeability of DVR and AVR to albumin was initially taken as $1 \times 10^{-7}$ and $1 \times 10^{-6}$ cm/s, respectively; we assumed that $\sigma_{ss} = 0$, and all other parameters were set to their baseline value (Table 1). The resulting concentration profile is shown in Fig. 3A. Transcapillary fluxes of water and albumin are shown in Fig. 3, B and C, respectively, and Pe values for albumin are given in Fig. 3D. A positive flux of albumin across DVR (or AVR) walls indicates that albumin is carried from DVR (or AVR) into the interstitium, and vice versa. In addition, the greater the absolute value of Pe, the greater the importance of convection relative to diffusion.

Near the corticomedullary junction, water is drawn out of the lumen through both pathways in DVR; in that region, albumin is carried mainly by convection out of DVR and into AVR, and the concentration of albumin increases simultaneously in interstitium and DVR. Below that upper region, the DVR paracellular flux of water is reversed, and diffusion out of AVR and convection into DVR account for the presence of albumin in the interstitium. Indeed, even though there is volume influx into AVR, the Pe for AVR is small, and diffusion of albumin down its concentration gradient (i.e., from AVR toward the interstitium) dominates; solvent drag then carries albumin into DVR, as Fig. 3D suggests.

Before the OM-IM junction, as water reabsorption into AVR decreases, there is less and less solvent drag into AVR to oppose diffusion out of AVR, and $C_I$ thus rises (right before the boundary, there is actually some water efflux from AVR, so that both solvent drag and diffusion carry albumin from AVR into the interstitium). After the OM-IM junction, conversely, the increase in water influx into AVR (due to volume generation rate in the interstitium) leads to a decrease in $C_I$. Toward the papillary tip, water fluxes are much reduced as the generation rate for water decreases to zero, and $C_I$ increases rapidly again. The volume average interstitial concentration of albumin is 1.21 g/dl in the entire medulla and 0.94 g/dl in the IM only.

We have until now assumed that there is negligible efflux of protein other than albumin from plasma (4, 6), but other investigators (25) do not distinguish between albumin and other proteins. If vasa recta are also permeable to other plasma proteins, the interstitial concentration of protein ($C_{pr}$) is likely to be higher on average. To examine this hypothesis, we assumed, in the absence of data, that the transport properties characterizing all plasma proteins (i.e., reflection coeffi-

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Fig. 2. Transcapillary volume fluxes across descending (DVR) and ascending vasa recta (AVR) based on the circumference of all vessels (i.e., $J_{vp} = D$, as in Eq. 1), as a function of position along the corticomedullary axis. $x/L$ represents the total length of the medulla. The junction between the outer medulla (OM) and the inner medulla (IM) corresponds to $x/L = 0.24$. The sharp bends at this junction are due to anatomical changes and the sudden reabsorption of water and solutes from the loops of Henle and the collecting duct in the IM. The interstitial concentration of albumin is fixed at 3.4 g/dl. The permeability to albumin of DVR ($P_{vp}^I$) and AVR ($P_{vp}^I$) is taken to be $1 \times 10^{-7}$ and $1 \times 10^{-6}$ cm/s, respectively, and the reflection coefficient of the transcellular pathways to small solutes ($\sigma_{ss}$) is zero. Because the paracellular flux of volume across DVR is directed mostly toward the capillary lumen, it is unlikely that albumin is carried to the interstitium only by solvent drag from DVR.
cient, permeability) were equal to those of albumin, and the interstitial mass balance for albumin (Eq. 23) was taken to apply to all proteins. All other parameter values were identical to those used in the previous simulation. We also confirmed that concentration polarization is negligible when all plasma proteins, not just albumin, can be transported to the interstitium. Results are shown in Fig. 4 (case A). Variations in $C_{pr}$ along the corticomedullary axis are similar to those in $C_a$ when albumin is taken to be the only plasma protein that can be exchanged across vasa recta, and the mechanisms by which all proteins are transported to and from the interstitium are also as described in Fig. 3. The interstitial concentration of albumin ($C_{a}$) is calculated on the basis of an interstitial balance (Eq. 23), assuming that other plasma protein cannot be exchanged across vasa recta. The permeability to albumin of DVR and AVR is taken to be $1 \times 10^{-7}$ and $1 \times 10^{-6}$ cm/s, respectively, and $\sigma_{w} = 0$. Other parameters are those of the baseline case. A: albumin concentration in DVR, AVR, and interstitium, divided by its initial value in DVR at the corticomedullary junction. B: transcapillary volume fluxes across vasa recta, based on the circumference of all vessels. C: transcapillary albumin fluxes across vasa recta, based on the circumference of all vessels. D: albumin Peclet number (Pe). After the sign change in the DVR paracellular volume flux near the corticomedullary junction, albumin enters the interstitium by diffusing out of AVR and is then carried by convection into DVR.
by both convection and diffusion out of DVR for a short distance beginning at the corticomedullary junction.

Avr (avr) is a capillary network in the renal medullary interstitium. The interstitial concentration of protein is higher, at least 5 cm/s (based on slit pore theory). Conversely, with \( \alpha_a = 0.78 \) in AVR, the permeability of AVR to albumin is calculated to be only 4.5 \times 10^{-7} \text{ cm/s} (assuming that the pores are cylindrical).

We therefore explored a broad range of values for the permeability of AVR to plasma proteins, using the same technique as for DVR. Results are summarized in Tables 3 and 4.

Increasing the permeability of AVR to plasma proteins to 1 \times 10^{-5} \text{ cm/s} results in larger interstitial protein concentrations but does not affect the mechanisms by which proteins are exchanged across vasa recta, even if \( P_{pr}^{\text{av}} \) also increases to 1 \times 10^{-4} \text{ cm/s}. That

### Table 3. Effect of permeability of DVR and AVR to plasma proteins on the average protein concentration in the renal medullary interstitium

<table>
<thead>
<tr>
<th>( P_{pr}^{\text{av}} )</th>
<th>( 1 \times 10^{-7} )</th>
<th>( 1 \times 10^{-6} )</th>
<th>( 2 \times 10^{-6} )</th>
<th>( 5 \times 10^{-6} )</th>
<th>( 1 \times 10^{-5} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{pr}^{\text{av}} )</td>
<td>0.76</td>
<td>2.24</td>
<td>3.32</td>
<td>4.67</td>
<td>5.41</td>
</tr>
<tr>
<td>1 \times 10^{-8}</td>
<td>0.76</td>
<td>2.25</td>
<td>3.32</td>
<td>4.67</td>
<td>5.41</td>
</tr>
<tr>
<td>1 \times 10^{-7}</td>
<td>0.77</td>
<td>2.25</td>
<td>3.32</td>
<td>4.67</td>
<td>5.41</td>
</tr>
<tr>
<td>1 \times 10^{-6}</td>
<td>2.65</td>
<td>3.54</td>
<td>4.75</td>
<td>5.44</td>
<td></td>
</tr>
</tbody>
</table>

Permeabilities of DVR and AVR to plasma proteins (\( P_{pr}^{\text{av}} \) and \( P_{pr}^{\text{av}} \), respectively) are given in cm/s and interstitial protein concentrations in g/dl. The reflection coefficient of DVR and AVR to small solutes is taken to be zero.

### Table 4. Transport mechanisms of plasma proteins between vasa recta and interstitium

| \( P_{pr}^{\text{av}} \) | \( P_{pr}^{\text{av}} \) | \( \alpha_{\text{pr}}^{\text{av}} \) | \( \alpha_{\text{pr}}^{\text{av}} \) | \( \alpha_{\text{pr}}^{\text{av}} \) | \( \alpha_{\text{pr}}^{\text{av}} \) | Transport Mechanisms of Proteins
|-----------------|------------|------------|------------|------------|------------|----------------------------------|
| \( 1 \times 10^{-7} \) | \( 1 \times 10^{-6} \) | 0 | 0 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-7} \) | \( 1 \times 10^{-6} \) | 0 | 0 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-6} \) | \( 1 \times 10^{-6} \) | 0 | 0 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-5} \) | \( 1 \times 10^{-5} \) | 0.014 | 0.009 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-4} \) | \( 1 \times 10^{-5} \) | 0.014 | 0.009 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-6} \) | \( 1 \times 10^{-6} \) | 0.014 | 0.009 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-5} \) | \( 1 \times 10^{-5} \) | 0.014 | 0.009 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-6} \) | \( 1 \times 10^{-6} \) | 0.014 | 0.009 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-5} \) | \( 1 \times 10^{-5} \) | 0.014 | 0.009 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-6} \) | \( 1 \times 10^{-5} \) | 0.014 | 0.009 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-5} \) | \( 1 \times 10^{-5} \) | 0.014 | 0.009 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-6} \) | \( 1 \times 10^{-5} \) | 0.014 | 0.009 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-5} \) | \( 1 \times 10^{-5} \) | 0.014 | 0.009 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR
| \( 1 \times 10^{-6} \) | \( 1 \times 10^{-5} \) | 0.014 | 0.009 | 0.89 | 0.70 | Diffusion out of AVR and convection into DVR

\( \alpha_{\text{pr}}^{\text{av}} \) and \( \alpha_{\text{pr}}^{\text{av}} \) are the reflection coefficients to small solutes of DVR and AVR, respectively. \( \alpha_{\text{pr}}^{\text{av}} \) and \( \alpha_{\text{pr}}^{\text{av}} \) are the reflection coefficients to plasma proteins of DVR and AVR, respectively. \( \alpha_{\text{pr}}^{\text{av}} \) and \( \alpha_{\text{pr}}^{\text{av}} \) are the reflection coefficients to plasma proteins of DVR and AVR, respectively. §In all cases, proteins are carried by both convection and diffusion out of DVR for a short distance beginning at the corticomedullary junction.
is, proteins enter the interstitium mostly by diffusing out of AVR (results not shown).

Conversely, if $P_{pr}^D$ is fixed at $1 \times 10^{-6}$ cm/s, increasing the permeability of DVR to proteins by a factor of 10 significantly reduces the corresponding DVR Pe but does not affect water fluxes. As a consequence, the diffusive flux of proteins out of DVR begins to overcome the convective flux into DVR about halfway down the corticomedullary axis; that is, when transcapillary protein concentration differences have become very large. For $x/L > 0.45$, proteins enter the interstitium by diffusing out of DVR, and they are carried away to AVR by solvent drag, as shown in Fig. 4 (case B). Overall, interstitial protein concentrations are then higher, as illustrated in Table 3.

These results suggest that the mechanisms underlying protein transport are very much dependent on the (unknown) value of vasa recta permeability to proteins.

Reflection Coefficient of Paracellular Pathways to Small Solutes

If the osmotic reflection coefficient of the paracellular pathway in DVR to sodium and urea is close to, but not equal to, zero, will small solute concentration gradients be large enough to reverse the direction of the paracellular volume flux in DVR? To examine how nonzero osmotic reflection coefficients would affect albumin transport, we estimated the reflection coefficient of the paracellular pathway to small solutes on the basis of solvent drag, as shown in Fig. 4 (case B). Overall, interstitial protein concentrations are then higher, as illustrated in Table 3.

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thus constitutes the main source of proteins in the IM interstitium, as shown in Fig. 5 (case B).

Reflection Coefficient of Paracellular Pathways to Albumin

Another parameter that may play an important role in determining the direction of the paracellular water flux across the DVR wall is the reflection coefficient of vasa recta to albumin. The higher the reflection coefficient of vasa recta to albumin, the larger the effect of transcapillary oncotic pressure differences on the paracellular flux (Eq. 2a) and the greater the fluid reabsorption into the lumen through the paracellular route. To draw more water out of DVR and into AVR so as to maximize convective transport, the reflection coefficient of DVR to albumin (or to all plasma proteins) therefore has to be decreased and that of AVR increased. A value as high as 0.78 has been measured for the reflection coefficient of AVR to albumin (14); therefore, we chose an upper bound of 0.80 for the reflection coefficient of AVR to all plasma proteins ($\sigma_{pr}^A$) and a lower bound of 0.85 for that of DVR ($\sigma_{pr}^D$).

If the reflection coefficient of vasa recta to small solutes is taken to be zero, decreasing $\sigma_{pr}^D$ and increasing $\sigma_{pr}^A$ as described above has a small effect on paracellular water fluxes but does not alter significantly the transport mechanisms of proteins (Table 4).

However, if the reflection coefficient of DVR and AVR to sodium and urea is assumed to be equal to 0.014 and 0.009, respectively, transcapillary oncotic pressure gradients due to small solutes favor water efflux from DVR; decreasing $\sigma_{pr}^A$, then, sufficiently reduces the effect of oncotic pressure gradients across DVR walls to change the direction of the paracellular flux of water along the corticomedullary axis in the IM. At large depths, there is volume efflux from DVR for all values of vasa recta permeability to proteins. As a result, DVR and AVR protein concentration values near the papillary tip increase by a factor of ~1.3. As blood flows down along the corticomedullary axis, proteins first diffuse out of AVR into the interstitium and are carried by solvent drag into DVR. When the paracellular flux of water is reversed, convection and diffusion from DVR become the mechanisms by which proteins enter the interstitium. Results are summarized in Table 4.

The Effect of Water Channels

Experimental observations strongly support the hypothesis that NaCl gradients drive water flux exclusively across a water-only pathway such as that provided by AQP1. Pallone et al. (16) have shown that prolonged incubation of OMDVR with pCMBS, a mercurial agent that inhibits AQP1 water channel activity, eliminates the osmotic volume flux induced by transmural NaCl gradients; this inhibition can be reversed by the addition of dithiothreitol. In separate microperfusion studies of molecular sieving of $^{22}$Na and $[^3]$Hraf-finose by DVR, Pallone and Turner (18) concluded that the collectate-to-perfusion ratios of $^{22}$Na and $[^3]$Hraf-finose are best simulated by a small solute reflection coefficient of 1.0 when transmural gradients of NaCl drive water flux. If AQP1 water channels are impermeable to small solutes, they will, a fortiori, be impermeable to larger proteins.

In modeling the exchange of plasma proteins between the microcirculation and interstitium, Wang and Michel (25) did not take into explicit consideration the presence of AQP1 water channels in DVR. The authors did not distinguish between the paracellular and the transcellular pathways, and the reflection coefficients for the joint route that they considered instead were an average over the two separate pathways (18, 25), which amounts to lumping $J_{vp}$ and $J_{vt}$ together. Because there is overall volume efflux from DVR (i.e., $J_{vp} + J_{vt} > 0$) and because this joint route is permeable to proteins, it is not surprising that the authors found that the convective flux of proteins from DVR into the interstitium can balance their clearance by convection into AVR throughout the medulla.

To compare our approach with that of Wang and Michel, we performed similar simulations in which the paracellular and transcellular pathways were lumped together. The water permeability of the joint route was taken as $1.8 \times 10^{-6} \text{cm} \cdot \text{s}^{-1} \cdot \text{mmHg}^{-1}$ and the average reflection coefficient of DVR to small solutes as 0.05 (18). Other parameter values were those given in the baseline case (Table 1). Results are shown in Figs. 6 and 7.

As expected, if no distinction is made between the paracellular and transcellular pathways in DVR, there is water efflux across this joint route almost throughout the medulla, except around the OM-IM junction, as shown in Fig. 6. With the exception of...
that region, proteins are carried by convection (and to a lesser extent by diffusion) from DVR into the ISF and then into AVR. In contrast with the results obtained by Wang and Michel, however, we found that changes in the permeability of AVR to plasma proteins do affect mean C_{pr} values, as illustrated in Fig. 7, because around the OM-IM junction, proteins enter the interstitium by diffusing out of AVR. Average interstitial protein concentrations are given in Table 5.

**DISCUSSION**

In this study, we have taken into consideration the effect of protein concentration polarization and its reverse at AVR and DVR walls by assuming that the interstitium can be represented as an annular space around each vasa recta and by determining the radial changes in water fluxes and solute concentrations. This model suggests that concentration polarization has a small effect on variations in fluxes and concentrations along the corticomedullary axis; in all the cases that we examined, the difference in osmolality at the papillary tip between this model and the no-polarization hypothesis was <2%. Conversely, assuming that oncotic pressure differences due to albumin are negligible across AVR walls because of polarization, as we had previously done (4), yields more significant errors.

The most common hypothesis to explain the presence of a significant pool of albumin in the ISF has been that plasma proteins are transported by convection from DVR to AVR through the interstitium. The recent theoretical work of Wang and Michel (25) appears to confirm this assumption. The study by these authors, however, does not take into consideration the different properties of the paracellular and transcellular routes in DVR. Because there is overall volume efflux from descending vasa recta, they conclude that solvent drag can indeed carry proteins into the interstitium. A careful analysis of transcapillary volume fluxes across each pathway, however, reveals that, across the paracellular route, water can be reabsorbed into DVR. Indeed, transcapillary oncotic pressure gradients drive water into the lumen, and the reflection coefficient of the paracellular pathway to sodium and urea may be too small for small solute concentration differences to counterbalance that effect. Because the transcellular route (i.e., AQP1) is impermeable to solutes, convection from DVR cannot be the sole mechanism by which proteins are transported into the interstitium.

Our results suggest that both diffusion and convection play a role in carrying proteins to the interstitium and that whether proteins come from DVR or AVR depends on certain parameter values and can vary with depth along the corticomedullary axis. In the absence of experimental data, permeability of vasa recta to proteins and reflection coefficients were varied over a broad range.

If the reflection coefficient of vasa recta to small solutes is zero, as suggested by Pallone et al. (16), the paracellular flux of water across DVR (J_{vp}) is directed toward the lumen (except for a small region near the corticomedullary junction), so that solvent drag carries proteins both into DVR and AVR. The only possible source of interstitial proteins is, therefore, diffusion. If the permeability of DVR to proteins (P_{pr}) is <1 x 10^{-6} cm/s, proteins diffuse out of AVR throughout the medulla. If P_{pr} is ≥1 x 10^{-6} cm/s (and if P_{pr} is of the same order of magnitude), half-way down the corticomedullary axis, diffusion out of DVR becomes more favorable.

Pore theory suggests that the reflection coefficient of vasa recta to small solutes is on the order of 0.01. With this assumption, osmotic pressure differences due to sodium and urea can possibly reverse the direction of the paracellular volume flux across DVR in some regions along the corticomedullary axis, especially if the reflection coefficient of DVR to protein is low, thereby reducing the effect of transcapillary oncotic pressure gradients across DVR walls. At small depths, proteins always diffuse out of AVR and enter DVR by solvent drag. After the point where J_{vp} changes sign, the source of interstitial proteins becomes DVR; the relative importance of convection and diffusion in the total protein flux depends on the value of the permeability of vasa recta to proteins. Even when J_{vp} is never reversed, in certain parts of the medulla where transcapillary protein concentration differences are very large, diffusion out of DVR can become more favorable than that out of AVR (because protein concentrations are lower in AVR than DVR). In those regions as well, the net flux of protein is then directed from DVR to AVR via the interstitium.
Our results thus indicate that the values of vasa recta permeability to proteins and reflection coefficient to both small solutes and macromolecules determine the mechanisms by which plasma protein are carried to and cleared from the medullary interstitium.

Our calculations also suggest that the concentration of proteins in the interstitium undergoes significant variations along the corticomedullary axis, which may explain the wide range of protein concentration measurements in the ISF (12, 15). Given both the magnitude of the spatial variations in $C_{Pr}$ and the broad range in the experimental data, we did not attempt to match our calculated values with measured ones to infer the value of transport parameters that have not been measured, such as the permeability of vasa recta to albumin and the reflection coefficient of the paracellular pathways to sodium and urea.

Nevertheless, some agreement between our predictions and other experimental data can be noted. In all cases shown in Figs. 4 and 5, plasma protein concentrations in DVR are 7–50% higher in the papilla than at the corticomedullary junction. Because we assumed that the concentration of plasma proteins entering DVR is 1.4 times that of arterial plasma (i.e., the glomerular filtration fraction is 0.3), DVR concentrations of plasma proteins are predicted to be 1.5–2.1 times higher in the papilla than in systemic blood, which is consistent with experimental observations (19, 21).

We have not considered any active mechanisms for protein transport in this study. Although there is no direct evidence that albumin is broken down or taken up by cells in the medulla, active transendothelial transport of albumin has been demonstrated in vivo. Cultured porcine pulmonary artery endothelial cells actively transport albumin from interstitium to lumen (22). After absorption onto specific binding sites, albumin-gold complexes are carried in transcytotic vesicles across the capillary endothelium of the mouse lung, heart, and diaphragm (7). The counterconvective transport of albumin across venular endothelium has also been observed in rat lung (24). Hence, it is possible that active mechanisms may also be involved.

Along the corticomedullary axis, DVR terminate and give rise to capillaries that either join existing AVR returning from deeper regions of the medulla or form new AVR. Terminal DVR and this interposed capillary plexus are known to be fenestrated (17). It is thus possible that proteins are also exchanged across the intervening capillaries, as suggested by Wang and Michel (25).

In summary, our results suggest that proteins are carried to the medullary interstitium by diffusion from AVR or by either diffusion or convection from DVR, depending on medullary depth and the values of key parameters such as vasa recta permeability to proteins and reflection coefficients to small solutes and proteins.

**APPENDIX**

*Tests Demonstrating Mass Conservation*

The total amount of water, sodium, and urea recovered by vasa recta can be calculated explicitly and compared with the numerical value obtained from simulations. As described in Edwards et al. (4), the total volume recovered by vasa recta, $V_{RRv}$, is given by

$$V_{RRv} = Q_{AVR}^b(0) - Q_{DVR}^b(0)$$

$$= L_{im}A_{im}(0) \int_0^{X_{im}} (0.25X_{im} + 0.05)\Psi(X_{im})dX_{im} \quad (A1)$$

where $Q_{av}^b$ is the total blood flow rate and $L_{im}$ is the length of the inner medulla. *Equation A1*, derived for water, is also applicable to sodium and urea; $Q_{av}^b$ needs to be replaced by the solute mass flow rate, $Q_{av}^bC_{av}^{\text{Na}}$ for sodium, $Q_{av}^bC_{av}^{\text{U}}$ for urea, and $\Psi$ by $\psi_{Na}$ or $\psi_U$.

The right-hand side of *Eq. A1* can be calculated explicitly, given the interstitial generation rate $\Psi$. The analytical result can then be compared with both the value yielded by the numerical integration of *Eq. A1* and the numerical value of the difference in the amount of water (or solute) between AVR and DVR at the corticomedullary junction, i.e., the left-hand side of *Eq. A1*. Representative results are given in Table 6.

As indicated above, the difference between the analytical and the numerical results is always $< 1\%$, more often $< 0.5\%$. Similar results are obtained with differential spatial distributions of generation rates (results not shown).

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Table 6. Vasa recta recovery of volume, sodium, and urea: comparison between analytical and numerical results

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<td>Water, $\text{m}^{-1}$</td>
<td>$\Psi_{W}(X_{im}) = 1.90 \times 10^{-2}(1 - X_{im})$</td>
<td>$1.307 \times 10^{-4} \text{cm}^2/\text{s}$</td>
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<tr>
<td>Sodium, $\mu\text{mol} \cdot \text{cm}^{-3} \cdot \text{s}^{-1}$</td>
<td>$\Psi_{Na}(X_{im}) = 1.75(X_{im})$</td>
<td>$1.960 \times 10^{-2} \mu\text{mol/s}$</td>
<td>$1.957 \times 10^{-2} \mu\text{mol/s}$</td>
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<tr>
<td>Urea, $\mu\text{mol} \cdot \text{cm}^{-3} \cdot \text{s}^{-1}$</td>
<td>$\Psi_{U}(X_{im}) = 5.88\exp(6X_{im} - 1)$</td>
<td>$2.613 \times 10^{-2} \mu\text{mol/s}$</td>
<td>$2.614 \times 10^{-2} \mu\text{mol/s}$</td>
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RHS and LHS stand for right-hand side and left-hand side, respectively. With the specified interstitial generation rates, the fraction of the filtered load recovered by IM vasa recta for water, NaCl, and urea is equal to 1, 1, and 40%, respectively.
REFERENCES


