Modeling exchange of plasma proteins between microcirculation and interstitium of the renal medulla

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Wang, W., and C. C. Michel. Modeling exchange of plasma proteins between microcirculation and interstitium of the renal medulla. Am J Physiol Renal Physiol 279: F334–F344, 2000.—In the absence of evidence for lymphatics in the inner medulla of the kidney, it has been proposed that plasma proteins are cleared by convection out of the medullary interstitial fluid (ISF) directly into the ascending vasa recta (AVR). To clarify this hypothesis we have developed a mathematical model of the microvascular exchange of fluid, plasma proteins, and small solutes among the descending vasa recta (DVR), the AVR, and the ISF. The model represents the DVR and AVR as limbs of a countercurrent exchange loop separated and surrounded by the ISF. Steady-state exchange of fluid and solute are considered by using conservation and exchange equations. We have used values for parameters based on experimental measurements and investigated the effects of the properties of the vasa recta, the flow, and the gradient of small solutes on the distribution of plasma proteins. Results from the model agree reasonably well with experimental measurements, suggesting that convection may account for the clearance of plasma proteins from the renal medulla maintaining their concentration below that of the AVR.

countercurrent exchange; theoretical model; convection

The renal medulla has a highly specialized microvascular bed. Descending vasa recta (DVR) and ascending vasa recta (AVR) run to and from the tip of the papilla as straight and closely packed vessels. In the outer medulla, DVR and AVR are grouped into vascular bundles and are separated from the parallel segments of nephron. In the inner medulla, the microvessels are more evenly distributed. DVR and AVR are both conducting and exchange vessels, and they connect to each other through capillaries at different depths. In addition to their function of delivering oxygen and other nutrients to the tissues, the medullary microcirculation reabsorbs water that has been extracted during the concentration of the urine and transports it back to the rest of the organism (14).

In most microvascular beds, net fluid uptake from tissues to capillaries occurs when the osmotic pressure of the plasma exceeds the sum of the osmotic pressure of the pericapillary fluid and the transcapillary hydrostatic pressure difference (30). In these tissues, there are lymphatics that clear plasma proteins and excessive fluid from the interstitium and maintain the oncotic pressure differences across the capillary walls (13). In the inner medulla of the kidney, however, there is little or no evidence for the existence of lymphatics (1, 33). When labeled albumin is injected into the systemic arterial blood, it appears in the renal medulla in &lt;2 min, which demonstrates that the medullary microcirculation is permeable to plasma proteins (8). If oncotic pressure differences across the AVR are responsible for the clearance of fluid from the inner medulla, the question arises as to what mechanism is involved regarding the simultaneous drainage of plasma proteins from the interstitium to keep its oncotic pressure low.

In a recent review, Michel (14) discussed three possible routes for protein clearance from the inner medulla: 1) proteolysis occurred in the medullary interstitium; 2) proteins were cleared through prelymphatic channels in the interstitium; and 3) proteins entered the AVR by convection. He concluded that the most likely route was through convection into the AVR. In a later paper in the same year, MacPhee and Michel (11) reported that the reflection coefficient of the AVR to albumin is between 0.59 and 0.72, on the basis of their measurements using 15-day-old Sprague-Dawley rats. In the appendix of the same paper, the mechanism of the convective transport of a solute by osmotic flow up its own concentration gradient was presented by using a three-compartment system. They demonstrated how the system could work in theory if two membranes had different properties. Pallone and colleagues (17–19, 24) reported differences in the hydraulic permeability of the DVR (10−6 cm·s−1·cmH2O−1) and AVR (9.2–13.8×10−6 cm·s−1·cmH2O−1) and the reflection coefficient to serum albumin (0.9–0.99 for DVR and 0.75 for AVR). All these findings support the convective mechanism for protein clearance by the AVR. Nevertheless, it remains to be examined whether the proposed convective mechanism can function in the renal...
medulla, where changes in solute concentration exist along the whole length of the DVR and AVR due to fluid filtration and reabsorption.

Previous models of the urinary-concentrating mechanism have generally neglected the vasa recta by assuming that the microvessels offer negligible resistance to the transport of solute and water (9, 31). The medullary microcirculation and its functions in the transport of plasma proteins, for example, are poorly understood. In the present study, we focus on the role of the DVR and AVR on protein clearance from the inner medulla of the kidney. A simplified capillary loop represents the countercurrent arrangement of DVR and AVR. Basic principles governing the transcapillary exchange of small solutes, plasma proteins, and water are used. Nonlinearity introduced by the transcapillary exchange of water and plasma proteins makes it necessary to seek steady-state distributions of solute and flow numerically (2). We pay particular attention to the following questions: 1) whether the convective mechanism for protein clearance by AVR has steady-state solutions when parameters take physiological values; 2) whether the distribution of small solutes and proteins predicted by the model in the steady state agrees with data measured in the renal medulla; and 3) how changes in the flow and the permeability properties of the DVR and AVR influence plasma protein concentration distribution. Some of the features in the renal medulla are purposely left out, e.g., anastomoses between the DVR and AVR and the exponential distribution of small solutes in the interstitium, and we believe that by simplifying the model in this way we are able to focus on the fundamental questions.

**Transport of Fluid and Solute in and Across Vasa Recta**

In the renal medulla, DVR and AVR are a few micrometers apart. They run parallel to each other for several millimeters and form a countercurrent exchange system. We consider the vessels to be simple loops bearing a constant relationship to each other and to the neighboring nephron segments. The model includes DVR, AVR, and a common interstitium as sketched in Fig. 1. The length of the unit is \( L \), and its cross-sectional area is \( S \). The countercurrent exchange loop runs from the junction between the inner and outer medulla, \( x = 0 \), to the tip of papilla, \( x = L \). DVR and AVR have different properties, e.g., cross-sectional area \( (S_1 \text{ and } S_2) \), solute permeability, and water conductivity. There are also more AVR than DVR in the medulla and the ratio of the two, \( \lambda \), is between 1.7 and 2.3 (22).

Protein-free fluid entering the interstitial fluid (ISF) from neighboring nephrons is considered in the model, which, in the steady state, satisfies volume conservation in the interstitium. We assume a linear distribution of small solutes with the depth, \( x \), in the interstitium, which is maintained by the input of small solutes from the neighboring nephron segments. The linear distribution of small solute in the ISF is used here not only for its simplicity but also for its good agreement with experimental data reported by Koepsell et al. (6) over 85% of the length of the renal medulla, i.e., between \( x = 0 \) and \( x = 0.85 \).

On the basis of data from the renal medulla of the rat and hamster (4, 5, 12), \( L \) is between 5 and 10 mm, radii of the DVR and AVR are 7 and 11 \( \mu \)m, respectively, and the cross-sectional area of the ISF is approximately the same as that of DVR. Flow velocity in vasa recta \( (\mu) \) is between 100 and 1,000 \( \mu \)m/s, and the value varies along the vessel as water filtration and reabsorption occur. The diffusion coefficient of small solutes, e.g., \( \text{Na}^+ \), in plasma is \( 10^{-5} \) cm\(^2\)/s, and, in the ISF, is slightly smaller. The diffusion coefficient for plasma proteins, e.g., albumin, in plasma is \( 6 \times 10^{-7} \) cm\(^2\)/s and may decrease to \( 1-6 \times 10^{-8} \) cm\(^2\)/s in the ISF. Considering the small diameters of the microvessels, \( d \), and low flow velocities in them, \( u \), the Reynolds number of the flow, \( u_d^2/\mu \), is very small, where \( \rho \) is the density of the plasma and \( \mu \) is its viscosity. Order of magnitude analysis reveals that (34, 35), in vasa recta, solute...
diffusive transport in the axial direction is negligible compared with that by convection; flow velocity in the radial direction of the vasa recta is very small compared with that in the axial direction; and changes in solute concentration in the radial direction are negligibly small compared with those in the axial direction. As far as solute transport is concerned, we also neglect details of the velocity profile in the vasa recta and use averaged velocities. In the interstitium, transport of fluid and solute is dominantly in the direction normal to the axis of the unit between the neighboring DVR and AVR. Transport in the axial direction, by comparison, is negligible, mainly because the length of the renal medulla is several thousand times greater than the distance between adjacent vessels. This assumption is reexamined for its consistency later in this paper when the concentrations of solute are solved. 

Governing equations for this countercurrent exchange system are the following: 

Transcapillary exchange of water. 

In DVR 

$$J_{v1} = L_{p1}[p_1 - p_0 + \sigma_s RT(C_{s0} - C_{s1}) + \sigma_{p1}(P_0 - P_1)]$$ (1) 

and AVR 

$$J_{v2} = L_{p2}[p_2 - p_0 + \sigma_s RT(C_{s0} - C_{s2}) + \sigma_{p2}(P_0 - P_2)]$$ (2) 

where $J_v$ represents the rate of transcapillary fluid flux per unit surface area; $p$ is the hydrostatic pressure; $C_s$ is the concentration of small solutes; $L_p$ is the hydraulic permeability of the vessel; and $\sigma_s$ and $\sigma_p$ are reflection coefficients of the vessel to small solutes and plasma proteins, respectively. $RT$ is the product of the universal gas constant and the absolute temperature, and subscripts 0, 1, and 2 represent values for the ISF, DVR, and AVR, respectively. $P$ is the osmotic pressure of the plasma proteins 

$$\Pi = \alpha_1 C_p + \alpha_2 C_p^2 + \alpha_3 C_p^3$$ (3) 

At 37°C, $\alpha_1 = 2.1$, $\alpha_2 = 0.16$, and $\alpha_3 = 0.009$, where $C_p$ is the concentration of plasma protein (in g/100 ml), and $\Pi$ is measured in millimeters mercury (7).

Transcapillary exchange of plasma proteins (27). 

In DVR 

$$J_{p1} = (1 - \sigma_{p1})J_{v1} \left( C_{p1} + \frac{C_{p1} - C_{p0}}{e^{1 - \sigma_{p1}/\lambda_s}P_{p1} - 1} \right)$$ (4) 

and AVR 

$$J_{p2} = (1 - \sigma_{p2})J_{v2} \left( C_{p2} + \frac{C_{p2} - C_{p0}}{e^{1 - \sigma_{p2}/\lambda_s}P_{p2} - 1} \right)$$ (5) 

where $J_p$ is the rate of transcapillary flux of proteins per unit surface area, and $P_p$ is the permeability of vasa recta to proteins. 

Transcapillary exchange of small solutes. 

In DVR 

$$J_{s1} = P_{s1}(C_{s1} - C_{s0}) + (1 - \sigma_{s1})J_{v1}C_{s1}$$ (6) 

and AVR 

$$J_{s2} = P_{s2}(C_{s2} - C_{s0}) + (1 - \sigma_{s2})J_{v2}C_{s0}$$ (7) 

where $J_s$ is the rate of small solute transcapillary flux per unit surface area, and $P_s$ is the permeability of vasa recta to small solutes. 

Flow velocity in vasa recta. Changes in $u$ satisfy volume conservation. 

In DVR 

$$\frac{du_1}{dx} = -\frac{2J_{v1}}{r_1}$$ (8) 

and AVR (u_2 is positive in the direction of flow, i.e., in the x direction) 

$$\frac{du_2}{dx} = \frac{2J_{v2}}{r_2}$$ (9) 

where $r_1$ and $r_2$ are radii of the DVR and AVR. 

Concentration of small solutes. 

Changes in protein concentration satisfy mass conservation. 

In DVR 

$$\frac{d(u_1C_{s1})}{dx} = -\frac{2J_{v1}}{r_1}$$ (10) 

and AVR 

$$\frac{d(u_2C_{s2})}{dx} = \frac{2J_{v2}}{r_2}$$ (11) 

In the ISF, concentration of small solutes is assumed to increase linearly with $x$ 

$$C_{s0} = C_s^0 + Gx$$ (15) 

where $C_s^0$ is the concentration of small solutes, $G$ is the gradient of the small solute concentration, and $C_s^0$ is the value of $C_s^0$ at $x = 0$. 

Boundary conditions: 

At $x = 0$ 

$$C_{s1} = C_s^0$$ (16) 

$$C_{p1} = C_p^0$$ (17) 

$$u_1 = U_0$$ (18) 

and at $x = L$ 

$$C_{s1} = C_{s2}$$ (19) 

$$C_{p1} = C_{p2}$$ (20) 

$$S_1u_1 = \lambda S_2u_2$$ (21)
Numerical Procedure

The nonlinear, multivariable, and interactive problem is solved numerically for steady-state distributions of plasma proteins, small solutes, and flow velocities. Two special features in our numerical treatment should be emphasized.

1) We solve for the steady-state concentration of proteins and small solutes in two separate iterative loops, i.e., under initial values of small solute concentration, we solve for a steady-state distribution of protein concentration. This distribution is then used to solve for a new steady-state concentration distribution of small solutes and so on, until the final steady-state concentration for both proteins and small solutes is reached.

2) Relaxation is applied when the values of the small solute concentration are updated in each iteration to prevent overshooting. In the system, the concentration of small solutes is much higher than that of plasma proteins. Relatively small changes in the small solute concentration can lead to significant changes in the osmotic pressure across the DVR and the AVR. Relaxation is found to be a useful technique in our calculation for results to converge rapidly.

The flow chart of the computation is shown in Fig. 2. In the calculation, initial concentrations of plasma proteins in the DVR, AVR, and ISF are

\[ C_{p1} = C_{p2} = C_{p0} = C_p \]

and the initial concentrations of small solutes in the DVR and AVR are

\[ C_{s1} = C_{s0} - (1-x)\delta_1 \]
\[ C_{s2} = C_{s0} + (1-x)\delta_2 \]

where \( \delta_1 \) and \( \delta_2 \) are concentration differences between vasa recta and interstitium at \( x = 0 \).

The program is written in Fortran, and calculations are carried out on a UNIX workstation Silicon Graphics O2. The length of the unit is equally divided into 2,000 segments. Under normal conditions, it takes between 5 and 10 min for results to reach a steady state.

Results and Discussion

We have investigated effects of different parameters on plasma protein distribution in the DVR, AVR, and ISF. These parameters include the flow velocity into the DVR, \( U_0 \); the concentration gradient of small solutes in the ISF, \( G \); the reflection coefficient of the DVR and AVR to protein, \( \sigma_{p1} \) and \( \sigma_{p2} \), respectively; and the hydraulic permeability of the DVR and AVR, \( L_{p1} \) and \( L_{p2} \). As stated earlier, we have paid particular attention to the convective mechanism for the clearance of plasma proteins from the ISF and examined whether such a mechanism functions in a countercurrent system when parameters take physiological values. We have also tested the sensitivity and limits of the system when these parameters are changed.

The values of the parameters are given in Table 1. They are based on data reported in the literature and on measurements made in our own laboratory (11).

Table 1 also shows the range of reported values for each parameter and relevant references. Where there are no reported values for a parameter (e.g., \( P_{p1} \) and \( P_{p2} \)), the criteria for choosing a particular value are given. Values for Na⁺ are used as typical values for...
small solutes and those for albumin for plasma proteins. The use of Na⁺ may be questioned on the ground that, although the permeability of the AVR to Na⁺ and urea is very similar, the permeability of the outer medullary DVR to urea greatly exceeds that to Na⁺ (25). As we did not wish to overcomplicate the present model with this feature, we did not incorporate it. In some calculations, we have deliberately chosen a wide range of values for certain parameters, e.g., flow velocity, reflection coefficient, and hydraulic permeability, to examine their effects on the protein distribution in the system.

In all results, normalization is carried out by using the value of that variable at the entrance of the DVR, i.e., $U_0$ for velocity, $C_p^0$ for protein concentration, $C_s^0$ for small solute concentration, and $U_0\pi r_1^2$ for volume flux. Length $x$ is normalized by using $L$, which is 7 mm in the model.

In Fig. 3A, concentration of small solutes in the DVR lags behind that in the ISF. It follows a very similar linear increase with distance, $x$, as in the ISF. In the AVR, small solute concentration overtakes that in the ISF almost immediately after the turn at the tip of papilla and decreases linearly toward the base of the capillary loop. The concentration difference between the ISF and vasa recta is bigger in the DVR than that in the AVR because of higher solute permeability and bigger surface area of the AVR. It is also noticed that the concentration difference between the AVR and ISF increases in the direction of flow, i.e., from $x = 1$ to $x = 0$. The ratio of the product of solute permeability ($P$) and surface area ($A$) to flow rate ($F$), $(P \times A)/F$, determines the equilibration of small solutes between microvessels and their surrounding ISF (28). As water is reabsorbed from the ISF to AVR, the flow rate in the AVR increases, decreasing $(P \times A)/F$ and hence the degree of equilibration between the AVR and the ISF.

In Fig. 3B, we find a steady increase in the plasma protein concentration in the DVR from the base to the tip of papilla. This is mainly due to water filtration from the DVR to ISF, combined with the high protein reflection coefficient of the DVR. From the base to the tip of the capillary loop, there is an ~27% increase in the protein concentration. Although there are no measurements of protein concentrations in the plasma entering the DVR, it is reasonable to take this as being 1.25 times greater than the concentration in systemic arterial plasma as a result of glomerular filtration. The further increase in protein concentration as the blood flows through the DVR would mean that in the papilla (from $x = 0.8$ to $x = 1$), it would be 1.5–1.6 times greater than that in systemic arterial plasma. This degree of concentration is consistent with experimental measurements (26, 29), where the protein concentration in the DVR is 1.4–1.7 times that in the arterial plasma. In the AVR, protein concentration decreases in the direction of flow as water is reabsorbed from the ISF. Near the tip of the capillary loop, $x = 1$, we observe a rapid decrease in protein concentration. Measurements of plasma proteins in the AVR of the papilla suggest the fall in concentration is on the order of 20–25% rather than the 50–60% that our model predicts. The discrepancy is not unexpected, because, in our model, there is not only a sudden change in the properties of the vessels as plasma enters the AVR and direction of flow reverses but also a sudden fall in the hydrostatic pressure. In reality, these changes occur much more gradually, with a less rapid fall in AVR

### Table 1. Values for parameters of the model

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Chosen Value</th>
<th>Range of Values in Literature</th>
<th>Reference No(s).</th>
</tr>
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<tbody>
<tr>
<td>$r_1$</td>
<td>7.8 μm</td>
<td>6–10 μm</td>
<td>14, 22</td>
</tr>
<tr>
<td>$r_2$</td>
<td>10.5 μm</td>
<td>6–15 μm</td>
<td>14</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>1.7</td>
<td>1.7–2.3</td>
<td>22</td>
</tr>
<tr>
<td>$G$</td>
<td>$4^+$</td>
<td>$0.85–1.0$</td>
<td>19, 32</td>
</tr>
<tr>
<td>$\sigma_{p1}$</td>
<td>0.9*</td>
<td>$0.59–0.78$</td>
<td>11, 19</td>
</tr>
<tr>
<td>$\sigma_{p2}$</td>
<td>0.6*</td>
<td>$0.017–0.05$</td>
<td>16, 23</td>
</tr>
<tr>
<td>$\sigma_{s1}$</td>
<td>0.01*</td>
<td>$0.004–0.008$</td>
<td>24, 32</td>
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<tr>
<td>$L_{p1}$</td>
<td>$10^4$ cm$^{-1}$ s$^{-1}$ cmH$_2$O$^{-1}$</td>
<td>$1–2 \times 10^6$ cm$^{-1}$ s$^{-1}$ cmH$_2$O$^{-1}$</td>
<td>1, 22</td>
</tr>
<tr>
<td>$L_{p2}$</td>
<td>$9 \times 10^7$ cm$^{-1}$ s$^{-1}$ cmH$_2$O$^{-1}$</td>
<td>$3–20 \times 10^{–6}$ cm$^{-1}$ cmH$_2$O$^{-1}$</td>
<td>11, 17</td>
</tr>
<tr>
<td>$p_1$</td>
<td>10 cmH$_2$O</td>
<td>$8.9–12.5$ cmH$_2$O</td>
<td>22</td>
</tr>
<tr>
<td>$p_2$</td>
<td>6 cmH$_2$O</td>
<td>$5–12$ cmH$_2$O</td>
<td>11, 10, 22</td>
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<tr>
<td>$p_0$</td>
<td>4 cmH$_2$O</td>
<td>$2–8$ cmH$_2$O</td>
<td>3</td>
</tr>
<tr>
<td>$P_{p1}$</td>
<td>$2 \times 10^{–6}$ cm/s$^2$</td>
<td>Estimate for microvessels with continuous endothelium</td>
<td>15</td>
</tr>
<tr>
<td>$P_{p2}$</td>
<td>$2 \times 10^{–7}$ cm/s$^2$</td>
<td>Estimate for microvessels with fenestrated endothelium</td>
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<td>$P_{s1}$</td>
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<td>$P_{s2}$</td>
<td>$55 \times 10^{–4}$ cm/s</td>
<td>$6–20 \times 10^{–4}$ cm/s</td>
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<tr>
<td>$C_p^0$</td>
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<td>Estimate on basis of values of the systemic arterial plasma</td>
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<tr>
<td>$C_s^0$</td>
<td>5.0 g/dl</td>
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<tr>
<td>$U_0$</td>
<td>500–1,000 μm/s</td>
<td></td>
<td>22</td>
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</table>

$r_1$ and $r_2$, Radii of the descending (DVR) and ascending vasa recta (AVR), respectively; $\lambda$, ratio of nos. of AVR to DVR; $G$, concentration gradient of small solute in the interstitial fluid (ISF); $\sigma_{p1}$, $\sigma_{p2}$, $\sigma_{s1}$, and $\sigma_{s2}$: reflection coefficients of vessel to plasma proteins and small solutes; $L_{p1}$ and $L_{p2}$, hydraulic permeability of the DVR and AVR, respectively; $p_1$, $p_2$, and $p_0$: hydrostatic pressure of DVR, AVR, and ISF, respectively; $P_{p1}$, $P_{p2}$, $P_{s1}$, and $P_{s2}$: permeability of DVR and AVR, respectively, to proteins and small solutes; $C_p^0$ and $C_s^0$: value of concentration of small solute ($C_s^0$) and protein ($C_p^0$) at $x = 0$; $U_0$: flow velocity at entrance to DVR. *Value allowed to vary over a range in the model. †Probably a serious underestimate; see Ref. 14.
plasma protein concentration. The concentration of protein leaving the AVR ($x = 0$ in Fig. 3B) may appear to be low, but this is dictated by mass balance, i.e., by the volume of fluid that is recovered from the medulla under steady-state conditions and medullary blood flow. At present, there are no measurements against which we can compare these predictions.

The values predicted for the concentration of plasma proteins in the interstitium are very low. Near the base of the medulla, ISF protein concentration is $<10\%$ of that in the plasma of the DVR. Protein concentration declines slowly toward the tip of the papilla, the gradient being $\sim 0.1$. In contrast to this small gradient, the protein concentration difference between the plasma in the vasa recta and the surrounding ISF is between 0.2 and 1.2 over a radial distance of $10–15$ $\mu$m ($\sim 1/50$ of $L$). Thus the average protein concentration gradient in the radial direction is 100–600 times greater than that in the axial direction. This is consistent with our earlier assumption that, in the ISF, the protein gradient in the axial direction is much smaller than that in the radial direction. The concentration of protein in the ISF that is predicted by the model, however, is very much lower than experimental estimates. Thus Pallone (20) reported protein concentrations that were 60–70$\%$ of those in the plasma of neighboring AVR, and MacPhee and Michel (11) estimated interstitium albumin concentrations that were 25$\%$ of those in systemic arterial plasma. The distribution of protein in the ISF and plasma of the vasa recta that is predicted by the model depends on the values of the parameters used in the calculation. The consequences of varying these values are considered later in this discussion. Here we note that if we start with a set of parameters in the physiological range, the countercurrent exchange system reduces an initially high concentration of plasma proteins (value used as initial condition for the calculation) to a steady-state protein level in the interstitium fluid that is very low, despite the lack of drainage of the ISF by lymphatics.

Velocities of flow in the DVR and AVR are shown in Fig. 3C. The values have been normalized by the flow velocity at the entrance of the DVR, $U_0$. Following the direction of flow, we observe a steady decrease in velocity in the DVR as fluid is filtered from it, and a more rapid increase in velocity in the AVR as fluid is reabsorbed. Direct observations of red cell velocity in the papilla report that velocity in AVR is well below that in DVR (4), which is consistent with our model prediction.
regarding velocity near the tip of the capillary loop (i.e., between $x = 0.5$ and $x = 1.0$). The discontinuity in velocity at $x = 1$ is caused by the sudden changes in the number and size of the ascending vasa recta. In reality, changes will be more gradual. If we examine the velocity in the DVR carefully, we find a very small increase near the entrance, $x = 0$. Similarly, there is a very small decrease in the plasma protein concentration of the DVR close to its entrance (Fig. 3B), where, near $x = 0$, concentration of proteins in ISF approaches zero. These are artifacts caused by the boundary condition at $x = 0$, where the same concentrations of small solutes in the DVR and the ISF are assumed. Different conditions could be used that would eliminate these artifacts. However, we are satisfied with the simplest one used here, which has negligible effect on solute distribution away from this boundary.

Figure 4 summarizes how the mean ISF concentration of proteins is influenced by the values of some of the different parameters of the model. In Fig. 4A, the mean concentration of plasma proteins in the ISF, $C_{p0}$, is presented for different values of small solute concentration gradient, $G$, at two values of $U_p$. At $U_0 = 500 \ \mu\text{m/s}$ and $G = 4$, which are the values we used in previous calculation, $C_{p0}$ is below 3% of the concentration of plasma proteins at the entrance of the DVR. When $G$ increases, we find an increase in $C_{p0}$, which peaks at $-G = 6$ and is then followed by a decrease. This is caused by changes in water filtration and reabsorption in the DVR and AVR. As $G$ increases, the small solute concentration difference between the vasa recta and ISF increases, as a steeper gradient of solute in the ISF makes it harder for the values in the vasa recta to catch up. When $G < 6$, increases in $G$ promote more filtration of fluid from the DVR, carrying more plasma proteins into the interstitium. When $G > 6$, the balance between the transport of proteins by filtration and reabsorption tilts toward reabsorption into AVR.

The fall in $C_{p0}$ at higher levels of $G$ is dependent on $\sigma_{s2} > 0$. The initial value 0.01, which we chose for $\sigma_{s2}$, is probably unreasonably high, and a figure of 0.004–0.006 would be consistent (on pore theory) with $\sigma_{s2} = 0.6$–0.7 if both small and large solutes share the same pathway through the walls of the AVR as water (i.e., no aquaporin channels here). Furthermore, our initial value of $U_0 = 500 \ \mu\text{m/s}$ is also probably on the low side. Measurements for red cell velocity in papillary DVR are in the range of 500–1,100 \ \mu\text{m/s} (22). According to Fig. 3C, velocity in the vessels might be expected to be 40–50% of $U_0$. Thus it seems reasonable to consider values of $U_0$ higher than 500 \ \mu\text{m/s}. We have therefore examined the effects of varying $U_0$ on $C_{p0}$ with $\sigma_{s2}$ at 0.01 and 0.005 and $G$ remaining constant at 4. The results of these calculations are summarized in Fig. 4B. It is seen here that with $U_0$ in the range of 1.5–2.0 \ mm/s (consistent with papillary velocity of 0.6–0.8 \ mm/s) and $\sigma_{s2} = 0.005$, $C_{p0}$ rises to 15% of the $C_p$ (i.e., $\sim 19\%$ of the concentration in the arterial plasma. Although this is still considerably less than the estimates by Pallone (20), it is only slightly less than the values reported by MacPhee and Michel (11). Further decreases in $\sigma_{s2}$ bring $C_{p0}$ well into the range of values reported by the latter authors.

The reflection coefficients of the DVR and AVR to plasma proteins also have significant effects on the mean concentration of plasma proteins in the ISF. In Fig. 5, we present changes in $C_{p0}$ with different values of $\sigma_{p1}$ and $\sigma_{p2}$. At a given value of $\sigma_{p1}$, increases in $\sigma_{p2}$ result in a smaller proportion of proteins being carried into the AVR with reabsorption; therefore, there are more plasma proteins accumulating in the interstitium. It is seen that $C_{p0}$ increases more rapidly at higher values of $\sigma_{p2}$. In all cases, when $\sigma_{p2}$ rises toward $\sigma_{p1}$, the system ceases to function and the concentration of plasma proteins in the ISF increases rapidly to infinity. On the other hand, increases in the reflection coefficient of the DVR, $\sigma_{p1}$, result in decreases in $C_{p0}$.
due to less plasma protein leakage into the ISF. At greater values of $\sigma_{p1}$, i.e., $\sigma_{p1} = 0.95$, the countercurrent exchange system can have steady-state solutions over a wider range of $\sigma_{p2}$, i.e., up to values of $\sigma_{p2 \text{ max}}$ approaching 0.84. For protein to be cleared from the ISF and for steady-state concentrations to be maintained, $\sigma_{p1}$ must be significantly greater than $\sigma_{p2}$. From this it seems that if $\sigma_{p2}$ is as high as 0.78 (19), then $\sigma_{p1}$ is probably 0.95 or more.

Hydraulic permeability of the vasa recta is one of the key parameters that determine the transcapillary water flux. We expect changes in $L_{p1}$ and $L_{p2}$ to have a significant effect on the drainage of plasma proteins from the ISF. In Fig. 6, it is seen that as $L_{p2}$ increases, $C_{p0}$ falls. The increased permeability of the AVR promotes the uptake of fluid into these vessels, and more protein is cleared from the ISF. For the values of parameters used in the calculation, the system no longer functions (i.e., does not converge to a steady state) when $L_{p2}$ is $<7 \times 10^{-6}$ cm $\cdot$ s$^{-1}$ $\cdot$ cmH$_2$O$^{-1}$. In those cases, rapid accumulation of plasma proteins in the interstitium occurs. When $L_{p2}$ decreases from 1.0 to $0.5 \times 10^{-6}$ cm $\cdot$ s$^{-1}$ $\cdot$ cmH$_2$O$^{-1}$, protein concentration in ISF decreases because of less leakage of proteins from the DVR.

The DVR are much less permeable to plasma proteins than the AVR, given their lower solute and hydraulic permeabilities and high protein reflection coefficients. Changes in their protein concentration reflect fluid filtration from the DVR. In Fig. 7, distribution of $C_{p1}$ with depth, $x$, is plotted for different values of $G$. From $Eq. \ 1$, the difference in small solute concentration between the ISF and the DVR is the driving force for water filtration. This works against the osmotic pressure imposed by differences in protein concentration between the DVR and ISF. Larger values of $G$, as explained earlier, increase the small solute concentration differences between the DVR and ISF and cause a higher water filtration from the DVR. They result in increases in plasma protein concentration inside the DVR. In Fig. 7, it is seen that when $G$ increases from 4 to 8, for example, the rise in protein concentration from the base to the tip of the capillary loop increases from <30 to >60%. Most of the increase in $C_{p1}$, particularly when $G$ is >6, occurs between 0 < $x$ < 0.6. Although there are no experimental data making direct comparisons between the concentration of plasma proteins in the DVR as these vessels enter the medulla and their

![Graph showing the distribution of plasma proteins in the DVR at different values of $G$.](http://ajprenal.physiology.org/)

![Graph showing the effects of $L_{p1}$ and $L_{p2}$ on $C_{p0}$.](http://ajprenal.physiology.org/)
concentration at subsequent points along the vessels within the medulla, there are several comparisons of plasma protein concentrations in the papillary DVR and AVR with those in the systemic arterial blood. Values in the range of 1.5 (1.38–1.76) have been reported from DVR plasma at the base of the papilla (x = 6.8 cm). If the protein concentration of the plasma entering the DVR is raised 1.25 times above that in systemic arterial blood as a result of glomerular filtration, at the base of the papilla it is raised a further 20%. Figure 7 shows that such an increase would be achieved if G = 4, justifying our selection of this value in the model.

In nephrons, urea and other end products of body metabolism are concentrated before they are discharged. There is a net protein free flux of fluid from the nephron segments to the ISF. In the steady state, this volume flux has to be reabsorbed by the circulation through fluid reabsorption. A model of the countercurrent exchange system has been built with basic equations governing the transcapillary exchange of solutes and water. The focus of the study is on the function of the system when parameters take values from experimental measurements. We have also investigated whether the steady-state distribution of solute and water. The counter-current exchange system has been found to reach a steady state when employing physiological data for its parameters, which confirms that the leakage of plasma proteins from the DVR into the ISF can be balanced by their clearance into the AVR. Indeed, with our initial choice of parameters, the model reduced the ISF protein concentration to values that were very much lower than those that have been estimated experimentally.

Although our model is greatly simplified (e.g., assumption of uniform gradient of small solutes; omission of anastomoses and capillary beds between DVR and AVR), the rise in protein concentration that it predicts in the plasma flowing in the DVR agrees well with experimental estimates. By contrast, the predicted rapid fall in plasma protein concentration at the beginning of the AVR (i.e., between x = 1 and x = 0.8) is much greater than experimental measurements indicate. We have already noted that this is a consequence of the sudden change in the permeability properties of vessels as they change from being DVR to AVR, together with the (unrealistic) step change in intravascular pressure. In addition, our model has assumed a step change in the number of vessels at the turn of the

Table 2, we present the effects of $P_{p1}$ and $P_{p2}$ on the mean concentration of proteins in the ISF. The bold value of $C_{p0}$ in Table 2 corresponds to the values of $P_{p1}$ and $P_{p2}$ used in the previous calculation. It is seen that the protein diffusive permeability has negligible effects on the transport of plasma proteins. When $P_{p1}$ increases 10 times from 2 to $20 \times 10^{-6}$ cm/s, there is $<5.4\%$ increase in the mean concentration of the plasma proteins in the interstitium. Similarly, when we increase $P_{p2}$ by an order of magnitude, there is a $<6\%$ increase in $C_{p0}$. This is consistent with our assumption that transcapillary exchange of plasma proteins in the renal medulla is largely by convection.

### Conclusions

In this study, we have investigated the hypothesis that, in the absence of lymphatics in the renal medulla, plasma proteins in the interstitium are cleared by the ascending vasa recta through fluid reabsorption. A model of the countercurrent exchange system of the DVR, AVR, and ISF has been built with basic equations governing the transcapillary exchange of solutes and water. The focus of the study is on the function of the system when parameters take values from experimental measurements. We have also investigated whether the steady-state distribution of solute and flow velocity predicted by the model agree with available data measured in the renal medulla. The counter-current exchange system has been found to reach a steady state when employing physiological data for its parameters, which confirms that the leakage of plasma proteins from the DVR into the ISF can be balanced by their clearance into the AVR. Indeed, with our initial choice of parameters, the model reduced the ISF protein concentration to values that were very much lower than those that have been estimated experimentally.

Although our model is greatly simplified (e.g., assumption of linear gradient of small solutes; omission of anastomoses and capillary beds between DVR and AVR), the rise in protein concentration that it predicts in the plasma flowing in the DVR agrees well with experimental estimates. By contrast, the predicted rapid fall in plasma protein concentration at the beginning of the AVR (i.e., between $x = 1$ and $x = 0.8$) is much greater than experimental measurements indicate. We have already noted that this is a consequence of the sudden change in the permeability properties of vessels as they change from being DVR to AVR, together with the (unrealistic) step change in intravascular pressure. In addition, our model has assumed a step change in the number of vessels at the turn of the

### Table 2. $C_{p0}$ for different values of $P_{p1}$ and $P_{p2}$

<table>
<thead>
<tr>
<th>$P_{p1} \times 10^{-6}$ cm/s</th>
<th>20</th>
<th>100</th>
<th>200</th>
<th>400</th>
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</thead>
<tbody>
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<td>0.0378</td>
<td>0.0378</td>
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<td>0.0378</td>
<td>0.0378</td>
<td>0.0423</td>
</tr>
</tbody>
</table>

$C_{p0}$, mean concentration of plasma proteins in the ISF. Bold value, values of $P_{p1}$ and $P_{p2}$ used in previous calculation.
The presence of large numbers of anastomosing capillaries between the DVR and AVR that we have omitted from our model, together with more realistic pressure gradients in the vessels, should lead to a more gradual reversal of fluid filtration into fluid uptake as blood flows from the DVR to the AVR. These should give rise to a much slower fall in \(C_{p2}\) with the depth over the initial part of the AVR. To incorporate these features into our model, however, would require developing a multiunit system that would have taken us beyond the aims of the present investigation. Nevertheless, it should be noted that when mean \(C_{p2}\) is estimated over the initial segment of the AVR (i.e., between \(x = 1\) and \(x = 0.8\)), its value is not much less than those in published data for protein concentration in AVR plasma. The very low steady-state values of ISF protein that the model predicted by using the initial set of parameters were a surprise. It appears that a major reason for this was the value of \(\sigma_{p2}\) that we initially selected. If its real value is \(<0.005\), then higher values of \(C_{p0}\) will be predicted, and these should fall well into the range of measured values.

A further omission from our model is the consideration of a radial gradient of protein concentration in the ISF. Edwards and Pallone (2) have pointed out that influx of fluid into the AVR may lead to unstirred layers of protein around these vessels. These gradients will reduce the oncotic pressure difference across the walls of the AVR, limiting fluid uptake. Edwards and Pallone draw attention to the apparent “safety mechanism” for fluid uptake in such circumstances. A reduction in fluid uptake into the AVR, in the face of steady influx of fluid into the medullary ISF from the nephrons, will lead to an increase in ISF hydrostatic pressure. This may rise above that in the AVR without the AVR collapsing (10). A rise in ISF pressure of only \(1\)–\(2\) cmH\(_2\)O above the AVR pressure should ensure adequate fluid clearance by the vasculature. As noted previously (11), such conditions would greatly favor the clearance of protein from the ISF into the AVR. The predictions of the present model, however, suggest that this method of protein clearance may occur only occasionally.

It is possible that in this paper we may have overestimated the convective influx of protein into the ISF from the DVR. The movement of water from the DVR into the ISF occurs largely through aquaporin channels (21). Although this efflux of water will concentrate the protein in the DVR, it will not be coupled to a protein efflux. It will, nevertheless, steepen the protein concentration gradients across the walls of the DVR and should promote the transport of proteins from these vessels into the ISF by other pathways. Furthermore, protein is likely to be lost from the intervening capillaries, particularly if these vessels are in regions where the efflux of fluid from the circulating plasma is gradually reduced and reversed into influx from the ISF.

Despite its shortcomings, the model does indicate that the clearance of plasma proteins from the medullary ISF into the AVR plasma can occur efficiently by a convection mechanism. This mechanism is possible only because of the different permeabilities of the DVR and AVR (most critically that \(\sigma_{p1} > \sigma_{p2}\) and \(L_{p2} > L_{p1}\)) and is facilitated by the continual addition of protein-free fluid to the ISF as a result of reabsorption by the nephrons.

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REFERENCES


