A model of glucose transport and conversion to lactate in the renal medullary microcirculation

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Zhang, Wensheng, and Aurélie Edwards. A model of glucose transport and conversion to lactate in the renal medullary microcirculation. Am J Physiol Renal Physiol 290: F87–F102, 2006.—In this study, we modeled mathematically the transport of glucose across renal medullary vasa recta and its conversion to lactate by anaerobic glycolysis. Uncertain parameter values were determined by seeking good agreement between predictions and experimental measurements of lactate generation rates, as well as glucose and lactate concentration ratios between the papilla and the corticomedullary junction; plausible kinetic rate constant and permeability values are summarized in tabular form. Our simulations indicate that countercurrent exchange of glucose from descending (DVR) to ascending vasa recta (AVR) in the outer medulla (OM) and upper inner medulla (IM) severely limits delivery to the deep inner medulla, thereby limiting medullary lactate generation. If the permeability to glucose of OMDVR and IMDVR is taken to be the same and equal to 4 × 10^{-4} cm/s, the fraction of glucose that bypasses the IM is calculated as 54%; it is predicted as 37% if the presence of pericytes in OMDVR reduces the glucose permeability of these vessels by a factor of 2 relative to that of IMDVR. Our results also suggest that red blood cells (RBCs) act as a reservoir that reduces the bypass of glucose from DVR to AVR. The rate of lactate generation by anaerobic glycolysis of glucose supplied by blood from glomerular efferent arterioles is predicted to range from 2 to 8 nmol/s, in good agreement with lower estimates obtained from the literature (Bernanke D and Epstein FH. Am J Physiol 208: 541–545, 1965; Bartlett S, Espinal J, Janssens P, and Ross BD. Biochim J 219: 73–78, 1984).

The urinary concentrating mechanism is made possible by the steep corticomedullary osmolality concentration gradient, which is created and maintained by countercurrent exchange between the descending and ascending limbs of the loops of Henle, the collecting ducts, and the descending (DVR) and ascending vasa recta (AVR). However, the manner in which the hyperosmolality in the inner medullary interstitium is built up and preserved remains unclear. A hypothesis involving an external osmolyte proposed by Niesl and Roesskenbliek (30) and summarized by Kriz and Lever (23) has recently been examined by Jen and Stephenson (20) and Thomas and Wexler (43). These investigators showed that an unspecied solute, external to the tubular fluid, that can provide an added 20–100 mosmol/l to the interstitial osmolality throughout the inner medulla (IM), may very significantly increase water reabsorption.

Because of hypoxia in the IM, anaerobic glycolysis appears to be the dominant energy supply for IM metabolism (37). Lactate is produced by anaerobic glycolysis, and it may later be used for gluconeogenesis in the outer medulla (OM) and cortex (37). Because anaerobic glycolysis generates two lactate molecules per molecule of glucose consumed, it increases the amount of interstitial solute; lactate could thus play a significant role as an external osmolyte. Although Kriz and Lever (23) dismissed this possibility more than three decades ago, recent studies have confirmed the potential for lactate to play a role in the urinary concentration mechanism. Thomas and colleagues (42) first developed a medullary microcirculation model to simulate lactate accumulation in IM, then incorporated the microcirculatory model into a urinary concentration model (19, 42). Their predictions suggested that lactate accumulation in the interstitium could be high enough to amplify axial IM NaCl concentration gradients (and therefore the corticomedullary osmolality gradient) under a number of conditions: if the DVR permeability to lactate is as high as 10^{-3} cm/s to accumulate lactate in significant levels in IM, if that glucose is low (i.e., on the order of 10^{-5} cm/s) to prevent the significant radial diffusion of glucose from DVR to AVR, if lactate exerts its full osmotic effect across thin descending limbs (DTLs) and IM collecting ducts (IMCDs), and if IM blood flow is reduced during antidiuresis.

Vasa recta (VR) permeability to glucose and lactate has not been measured in rats. As discussed below, the glucose permeability of microvascular walls of skeletal muscle has been reported as ~10^{-5} cm/s (29), whereas extrapolation of mice permeability data (33, 36) suggests that DVR permeability to glucose is ~7 × 10^{-4} cm/s in rats. The kinetics of anaerobic glycolysis of glucose in the renal medulla have not been determined experimentally either. Given the potential importance of lactate to the urinary concentration mechanism and the scarcity of experimental data on lactate accumulation, in this study we extended our mathematical model of transport in the renal medullary microcirculation to examine the conversion of glucose to lactate. Our objective was to determine parameter values that yield good agreement between predictions and experimental measurements of glucose and lactate concentrations, as well as lactate production rates.

Glucose is supplied to the renal medulla by the medullary microcirculation, which consists of DVR and AVR and smaller capillaries. In the OM, those DVR that are destined to the IM form vascular bundles with AVR and remain separate from the peripheral capillaries, which irrigate nephron tubules (35). In the IM, VR, IMCDs, DTLs, and thin ascending limbs (ATLs) of the loops of Henle are interspersed, so that water and solutes (e.g., NaCl and urea) reabsorbed from nephron tubules and IMCDs diffuse into VR and are cleared away from the medulla (35).
While blood flows down from the cortex to the papilla in DVR, water is transported radially to AVR, thereby gradually decreasing single-vessel blood flow rates to the papillary tip and concentrating solutes in blood. At different levels between the IM-OM junction and the papilla, DVR divide into simple capillary networks that reconverge to form AVR, thereby progressively decreasing the overall blood flow to the deeper portions of the IM and papilla (35). In addition, solutes reabsorbed from nephron loops and CDs are partly trapped in the medulla through radial (i.e., transverse) exchange between DVR and AVR. Both phenomena help maintain the cortico-medullary osmolality gradient.

**Greek Symbols**

\( \Gamma \)  
Red blood cell-to-vessel surface area ratio

\( \Pi \)  
Onotic pressure of proteins

\( \gamma_i \)  
Activity coefficient of solute \( i \)

\( \sigma_i \)  
Reflection coefficient to solute \( i \)

\( \Psi_j \)  
Volumetric generation rate of component \( i \) in compartment \( j \), \( j = R, I \)

\( \Psi_{\text{max}} \)  
Maximum volumetric glucose consumption rate in Michaelis-Menten equation

\( C^0 \)  
Initial concentration of solute \( i \) in plasma, that is, in DVR at corticomedullary junction

\( C_i \)  
Concentration of solute \( i \) in compartment \( j \), \( j = R, P, \) and I

\( D \)  
Diameter of vasa recta

\( f \)  
Volume fraction of water in red blood cells

\( G_i \)  
Overall medullary generation (or consumption) rate of component \( i \) in compartment \( j \), \( j = R, I \)

\( h \)  
Hematocrit

\( J^i \)  
Flux of solute \( i \) through membrane \( j \), \( j = R, W \)

\( K_{\text{mm}} \)  
Michaelis-Menten constant for glucose consumption rate

\( L \)  
Length of renal medulla, or position of the papillary tip when shown in parentheses

\( L_k \)  
Hydraulic conductivity of pathway \( k \) in compartment \( j \), \( j = R, W \)

\( P_i \)  
Permeability of membrane \( j \) to component \( i \), \( j = R, W, D, A \)

\( Q^j \)  
Overall volume flow rate in compartment \( j \), \( j = R, P \)

\( q \)  
Volume flow rate in single vas rectum

\( r_j \)  
Ratio of lactate generation-to-glucose consumption rate in compartment \( j \), \( j = R, I \)

**Subscripts and Superscripts**

0  
Initial value (in DVR at corticomedullary junction)

A  
Ascending vasa recta

B  
Whole blood

D  
Descending vasa recta

I  
Interstitium

P  
Plasma

R  
Red blood cell

V  
Water volume

W  
Vascular wall

**Model and Parameters**

In this study, we consider the entire medulla, that is, both the OM and IM; we do not take into account the peripheral capillaries in the outer medulla, however. Three compartments are considered in this model: red blood cells (RBCs), plasma, and interstitium. Figure 1 illustrates the model geometry, and the main assumptions and equations are given in the Appendix. The model consists of 1) a set of differential mass conservation equations for water and solutes (i.e., NaCl, urea, glucose, lactate, plasma proteins and hemoglobin) in RBCs and plasma, which take into account axial convection, radial transport (that is, across RBC membranes and vascular walls), and generation or consumption; 2) nonlinear mass conservation equations for water and solutes in the interstitium, which relate fluxes from (or toward) DVR and AVR, interstitial generation or consumption rates, and reabsorption rates from nephron loops and collecting ducts; and 3) flux equations across RBC membranes and VR walls, which couple the differential and nonlinear conservation equations. The consumption of glucose and generation of lactate are accounted for in conservation equations in RBCs and interstitium. Described below are the equations and parameters related to glucose and lactate.

Medullary hypoxia is a consequence of decreased blood flow in the papilla, the bypass of oxygen from DVR to AVR by radial diffusion, and the high energy requirement of active NaCl transport in the medullary thick descending limbs (mTALs) (6). Despite some controversy (9), the main source of ATP for IM cell metabolism is thought to be anaerobic glycolysis (37). As described below, we consider anaerobic glycolysis in erythrocytes and in the abluminal cells of the inner medullary interstitium. The conversion of glucose to lactate is simplified as

\[
C_6H_{12}O_6 \rightarrow 2CH_2CHOHCOO^- + 2H^+ \quad (1)
\]

Thus two lactate molecules are produced for each glucose molecule that is consumed by anaerobic glycolysis.
Anaerobic Glycolysis in the Medulla

Glucose metabolism in the renal medulla involves glucose synthesis by gluconeogenesis and glucose consumption by oxidation, glycolysis, and the pentose phosphate shunt. The contribution of this last pathway appears to be small (37). Glucose oxidation has been shown to occur in the glomerulus, the OM, and the distal convoluted tubules (37). It is thought to play a critical role in providing energy for the urine concentrating mechanism (5). The main site of glycolysis in the kidney appears to be the IM and the papilla, as indicated by the mapping of glycolytic enzymes (37). Finally, glucose synthesis has been found to occur in the superficial and deep cortex and in the OM (17); Roxe et al. (38), however, observed that the rate of renal gluconeogenesis in the dog is extremely low. As reviewed by Laris (24), glucose that is added to plasma can be entirely recovered, indicating that there is no consumption of glucose in plasma. Taken together, these observations suggest that in the kidney, the production of lactate by anaerobic glycolysis occurs mainly in RBCs throughout the medulla, and in the IM abluminal cells; the latter include interstitial cells, the vascular wall cells of VR, and the epithelial cells of nephron tubules. Given the scarcity of experimental data related to reaction rates in these different types of cells (see below), and because tubular walls are impermeable to glucose and lactate (42), the term “interstitial lactate generation rate” in this study denotes the combined rate of lactate production by all three cell types.

Estimates of the rate of anaerobic glycolysis in the IM interstitium vary by about one order of magnitude. Bartlett et al. (3) measured the medullary lactate production rate in rat kidneys perfused by solutions with biological concentrations of glucose (5 mM) and lactate (2 mM) as 176 \(\mu\)mol h\(^{-1}\) g kidney dry wt\(^{-1}\) for male Wistar rats with a body weight of 280–350 g. If the weight of the kidney is taken as 0.36% that of the body (32), and the kidney wet-to-dry weight ratio as 4 (31), the overall lactate production rate in the kidney is calculated to be 12–15 nmol/s. This value represents an upper limit for IM overall lactate production rate in the kidney is calculated to be 11.5–15 nmol/s. This value represents an upper limit for IM overall lactate production rate in the kidney is calculated to be 11.5–15 nmol/s. Because these measurements were obtained in vitro, in the absence of blood flow and reabsorption from nephrons, and given the simplifying assumptions made in converting these data, these estimates remain highly uncertain. Bastin et al. (4) also observed that over the 120-s period, glucose and glycogen concentrations decreased from 20.4 and 18.7 to 8.1 and 14.0 mmol/kg dry wt, that is, from 5.9 and 5.4 to 2.3 and 4.0 mmol/l of tissue water, respectively. The overall consumption rate of glucose and glycogen is thus calculated as 42 mmol/ml tissue water\(^{-1}\) s\(^{-1}\), exactly half of lactate generation rate, as would be expected under ischemic conditions (see below).

As described above, in this study the contribution of the tubular system to lactate generation and transport is implicitly taken into account in the interstitial glycolytic rate. Bagnasco et al. (2) measured the anaerobic glycolytic rate of dissected rat nephron segments incubated with glucose with and without antimycin A, an inhibitor of oxidative metabolism. They found that all distal tubules produce lactate; among them, the rate in IMCDs and mTALs is \(1.4\) nmol/s. The overall lactate generation rate is thus calculated as 414 and 84 mmol/kg dry wt, that is, from 5.9 and 5.4 to 2.3 and 4.0 mmol/l of tissue water, respectively. The overall consumption rate of glucose and glycogen is thus calculated as 42 mmol/ml tissue water\(^{-1}\) s\(^{-1}\), exactly half of lactate generation rate, as would be expected under ischemic conditions (see below).

As shown in Eq. 1, two lactate molecules are produced for each glucose molecule that is consumed by anaerobic glycolysis. Because glucose molecules may also be oxidized, the ratio of lactate production-to-glucose consumption in the interstitium (\(r_I\)) may differ from 2. Nevertheless, in the IM interstitium where oxygen is scarce, we assume a ratio of 2 as the baseline value of \(r_I\).

To account for the dependence of the volumetric glucose consumption rate (\(\Psi_{\text{glu}}\)) on glucose concentration (\(C_{\text{glu}}\)), especially at low glucose concentration values, a Michaelis-Menten equation is used for \(\Psi_{\text{glu}}\), following the approach of Thomas (42)

\[
\Psi_{\text{glu}} = \frac{\Psi_{\text{max}}C_{\text{glu}}}{K_m + C_{\text{glu}}}
\]

where \(K_m\) is the Michaelis-Menten constant and \(\Psi_{\text{max}}\) is the maximum volumetric glycolysis rate. A value of 0.1 mM is
Table 1. Baseline values of parameters related to glucose and lactate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Literature Value</th>
<th>Reference</th>
<th>Baseline Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial plasma lactate concentration, C_{lac}^0, mM</td>
<td>1.7</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Initial RBC lactate concentration, mM</td>
<td>2.6</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Initial plasma glucose concentration, C_glu^0, mM</td>
<td>5.8</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>Initial RBC glucose concentration, mM</td>
<td>0.67–3.7</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Permeability of RBC to lactate, cm/s</td>
<td>1 × 10^{-4}</td>
<td>13</td>
<td>1 × 10^{-4}</td>
</tr>
<tr>
<td>Permeability of RBC to glucose, cm/s</td>
<td>2 × 10^{-4}</td>
<td>21</td>
<td>1 × 10^{-5}</td>
</tr>
<tr>
<td>Permeability of DVR wall to lactate, cm/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permeability of AVR wall to lactate, cm/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permeability of DVR wall to glucose, cm/s</td>
<td>2.8 × 10^{-3} (mice)</td>
<td>33</td>
<td>4 × 10^{-4} (see text)</td>
</tr>
<tr>
<td>Permeability of AVR wall to glucose, cm/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflection coefficient of DVR wall to lactate</td>
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<td></td>
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<tr>
<td>Reflection coefficient of DVR wall to lactate</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Reflection coefficient of AVR wall to glucose</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Reflection coefficient of AVR wall to glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medullary lactate generation rate, nmol/s</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>RBC glucose consumption rate, mmol·l^{-1}·h^{-1}</td>
<td>12–15</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Ratio of lactate production to glucose consumption in RBCs</td>
<td>5.6</td>
<td>22</td>
<td>5.6</td>
</tr>
<tr>
<td>Ratio of lactate production to glucose consumption in interstitium</td>
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<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Maximum volumetric rate of glucose consumption in IM interstitium, ω_{max}, mmol·cm^{-3}·s^{-1}</td>
<td>1.5–2.7</td>
<td>2 (see text)</td>
<td></td>
</tr>
<tr>
<td>Maximum volumetric rate of glucose consumption in RBC, mmol·cm^{-3}·s^{-1}</td>
<td>83 (see text)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michaelis-Menten rate constant K_{m}, mM</td>
<td>0.1</td>
<td>42</td>
<td>0.1</td>
</tr>
<tr>
<td>Lactate generation rate from IMCD, pmol·min^{-1}·mm^{-1}</td>
<td>2.8</td>
<td>2</td>
<td></td>
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<tr>
<td>Lactate generation rate from OMCD, pmol·min^{-1}·mm^{-1}</td>
<td>0.87</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lactate generation rate from mTAL, pmol·min^{-1}·mm^{-1}</td>
<td>0.36</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

RBC, red blood cell; DVR and AVR, descending and ascending vasa recta, respectively; IMCD and OMCD, inner medullary and outer medullary collecting duct, respectively; mTAL, medullary thick ascending limb of Henle’s loop.

chosen for $K_m$ (42). As shown by Edwards et al. (15), the overall medullary interstitial solute generation rate is obtained by integrating the product of the local generation rate and the interstitial cross-sectional area, adjusted for the number of vessels. We apply their final result (Eq. A12 in their study) to the production of lactate to relate the overall interstitial lactate production rate ($G_{\text{lac}}^0$) to $\Psi_{\text{glu}}$.

\[
\frac{G_{\text{lac}}^0}{r_1} = A_{\text{med}} \int_0^t (0.25y + 0.05)\Psi_{\text{glu}} dy
\]

where $A_{\text{med}}$ is the medullary cross-sectional area at the IM-OM junction (estimated as 17.5 mm² from Eq. A20), and $L_{\text{eq}}$ is the axial length of inner medulla of the rat kidney, taken as 5.9 mm (34). When glucose concentrations are high enough, $\Psi_{\text{glu}} \approx \Psi_{\text{max}}$, according to Eq. 2; with $G_{\text{lac}}^0$ taken as 3 mmol/s (see above), $\Psi_{\text{max}}$ is then calculated as 83 nmol·cm⁻³·s⁻¹ using Eq. 3. The latter value corresponds to the baseline case in this study. As described below, toward the papillary tip, our results suggest that glucose concentrations become small enough that the dependence of $\Psi_{\text{glu}}$ on glucose concentration turns out to be significant; consequently, if $\Psi_{\text{max}}$ is maintained at 83 nmol·cm⁻³·s⁻¹, the overall lactate generation rate calculated using our model, $G_{\text{lac}}$, is lower than 3 mmol/s.

The glycolytic rate in red blood cells is estimated as follows. Messana et al. (28) reported that the rates of glucose consumption and lactate production in human erythrocytes vary with pH but remain independent of oxygenation. They measured the glucose consumption rate as $\sim 15–60$ nmol·ml RBCs⁻¹·min⁻¹ (i.e., 0.9–3.6 nmol·liter RBCs⁻¹·h⁻¹) and the ratio of lactate production to glucose consumption ($r_R$) as close to 1. Ataullahanov et al. (1) reported that glucose consumption rates in human erythrocytes range from 0.24 to 2.6 mmol·liter RBCs⁻¹·h⁻¹, whereas $r_R$ varies between 1.5 and 2.7 depending on arsenate and orthophosphate concentrations. In rats, the RBC glucose consumption rate has been reported as 5.6 mmol·liter RBCs⁻¹·h⁻¹ (22). The baseline values for $\Psi_{\text{max}}$ and $r_R$ in rat erythrocytes are therefore chosen as 5.6 mmol·liter RBCs⁻¹·h⁻¹ (that is, 1.56 nmol·cm⁻³·s⁻¹) and 1.5, respectively. Simulation results (not shown) suggest that variations in these two RBC parameters have negligible effects, because the overall lactate production rate is $\sim 10^{-2}$⁻¹·h⁻¹ lower in RBCs than in the IM interstitium.

Initial Concentrations

Lactate concentration has been reported as $\sim 0.92$ mM in plasma from the femoral artery of mongrel dogs (14), $\sim 1.7$ mM in the OM of dogs (11), and 2.6 mM in the serum of rat medullary blood (41). In the absence of more specific data, we assume an initial (i.e., at the corticomedullary junction in DVR plasma) lactate concentration of 2 mM. As reviewed by Kaneko (22), lactate concentration in RBCs has been reported as 0.078 mM in humans. Lacking experimental data for rats, we assume an initial lactate concentration of 2 mM in RBCs as well as in plasma. Our simulations indicate that twofold variations in these two parameter values have a negligible effect on lactate generation rates, as well as glucose and lactate concentrations in the IM (results not shown).
Glucose concentration in human whole blood has been reported as 5.6 mM (45). As reviewed by Kaneko (22), RBC glucose concentration ranges between 0.67 and 3.7 mM in mammals. Glucose concentrations in rat arterial blood have been measured by Laris (24) as 114 mg/100 ml water in plasma and 78 mg/100 ml water in RBCs; the investigator also determined the average water fraction in plasma and RBCs as 92 and 65%, respectively. Based on these experimental values, we estimate glucose concentration in renal arterial blood as 5.8 mM in the plasma phase and 2.8 mM in the RBCs. Roe et al. (38) also reported that glucose concentration in the renal arteriole of dog ranges from 3.2 to 7.7 mM and averages 5.8 mM. In the absence of more specific data in the glomerular efferent arterioles, the initial (i.e., at the corticomedullary junction in DVR) glucose concentration is taken as 6 mM in plasma and 3 mM in RBCs. The effects of varying these parameter values on concentration profiles are described below.

Permeability

Lactate and glucose transport across the erythrocyte membrane is mediated by carriers (8, 12, 21), making it difficult to measure the permeability of the RBC membrane to these two solutes. Experimental values are spread over a wide range, depending on the methodologies and solute concentrations used (8).

Deuticke et al. (13) estimated the human erythrocyte permeability to lactic acid at 30°C as $3.7 \times 10^{-5}$ cm/s, and the activation enthalpy as 24 kcal/mol. Using these data and the Arrhenius equation, we calculate the RBC permeability to lactate at 37°C as $\sim 10^{-4}$ cm/s.

According to the review of Jung (21), the permeability of the human RBC membrane to glucose ranges from $2 \times 10^{-6}$ to $4 \times 10^{-4}$ cm/s. In the absence of rat data, we use $10^{-5}$ cm/s as our baseline value.

In their review, Michel and Curry (29) reported that the glucose permeability of the microvascular wall in skeletal muscle, which is dominated by that across paracellular pathways, is $\sim 10^{-5}$ cm/s. According to these investigators, the permeability across transcellular pathways is at least three orders of magnitude lower and can be neglected. Pallone et al. (33) measured mice OMDVR permeabilities to sodium and glucose as $3 \times 10^{-3}$ and $2.8 \times 10^{-3}$ cm/s, respectively, which suggests that DVR permeability to glucose is comparable to that to sodium. In rats, the DVR permeability to sodium was measured as $0.75 \times 10^{-3}$ cm/s (36), that is, four times lower than that in mice. Assuming that the glucose-to-sodium permeability ratio is the same in these two species, we estimate the DVR permeability to glucose in rats as $7 \times 10^{-4}$ cm/s, that is, 70 times higher than the value given by Michel and Curry (29) for skeletal muscle microvascular walls. This may not be unreasonable given the simple structure of DVR walls, which in OM are composed of a single layer of endothelial cells surrounded by a discontinuous layer of smooth muscle cell-like pericytes; the latter gradually disappear in the IM (35).

As an alternative approach, pore theory can be used to estimate the permeability and reflection coefficients of the VR paracellular pathway to glucose and lactate, assuming that this route consists of homogeneous slit pores in parallel. This approach is described in Zhang and Edwards (47) and can be summarized as follows. Using the measured DVR and AVR reflection coefficients to albumin, the half-width of the slit pore in DVR and AVR walls is estimated as 3.8 and 4.4 nm, respectively (47). The Stokes-Einstein diffusivities of glucose, lactate, and urea are calculated as 1.16, 1.44, and $1.89 \times 10^{-5}$ cm²/s, and the molecular radii of those solutes as 0.35, 0.31, and 0.27 nm, respectively, using the online property calculator SPARC (http://ibmlc2.chem.uga.edu/sparc). The resulting permeabilities and reflection coefficients to glucose and lactate are shown in Table 1.

Because estimates of the permeability of VR walls to glucose range from $10^{-3}$ to $\sim 7 \times 10^{-4}$ cm/s, and given that permeability is a determinant factor, a wide range of values is considered in this study (see RESULTS). We predict that the reflection coefficients of DVR and AVR paracellular pathways to both solutes are very small, on the order of 0.01. These estimates are much lower than the value of 0.5 used by Thomas (42), because our model distinguishes between transport across aquaporin 1 (AQP1) water channels, which are impermeable to solutes, and that across paracellular pathways, which are shared by water and solutes. Simulations in which we increased and decreased reflection coefficients by a factor of 10 suggest that these parameters have an insignificant effect on glucose and lactate concentration distributions, as well as on water fluxes (results not shown). These predictions agree with those of Thomas (42), who also found that lactate concentration profiles are essentially independent of the reflection coefficient of VR to lactate.

RESULTS

In this study, we examined the conversion of glucose to lactate in the medulla, assuming that blood from the glomerular efferent arterioles is the only source of glucose consumed by anaerobic glycolysis in the IM interstitium. Predicted glucose and lactate concentration ratios were compared with experimental measurements (see immediately below) to estimate uncertain parameter values and to assess the determinant factors in lactate generation.

To the best of our knowledge, there have been no direct measurements of glucose and lactate concentrations in the renal medulla of rats. As discussed by Thomas (42), Ruiz-Guinauz et al. (39) found that glucose and lactate concentrations at the papillary tip of the golden hamster kidney are one-third and twice those in aortic blood, respectively. It should be noted that concentrations may be slightly higher in DVR at the corticomedullary junction than in the arteriole due to glomerular filtration. Scaglione et al. (41) reported that lactate concentration in rats is about two to five times greater at the papillary tip than that at the corticomedullary boundary, in good agreement with measurements in dogs performed by Dell and Winter (11). Glucose concentration has been reported to average 5.8 mM in the renal arteriole of the dog (38) and is expected to be lower in the renal medullary interstitium. As described in MODEL AND PARAMETERS, extrapolation of measurements by Bastin et al. (4) suggests that that glucose concentration in rat kidney decreases from 5.9 to 2.3 mmol/l of interstitial tissue water over a 2-min period following dissection and under full ischemia, whereas lactate concentration increases from 6.5 to 16.6 mmol/l of interstitial tissue water over the same period. The molar concentration of
glucose and lactate (i.e., per unit volume of tissue) should be lower than these values, because water is only a fraction of interstitial tissue volume. Given the in vitro conditions of the study of Bastin et al. (4) as well as the numerous assumptions needed to extrapolate their results, we do not believe that accurate estimates of glucose and lactate medullary concentration can be obtained based on their data.

**Baseline Results**

We first performed simulations with baseline parameters. Shown in Fig. 2, A and B, are predicted glucose and lactate concentration profiles along the corticomedullary axis. As illustrated in Fig. 2A, glucose diffuses from DVR to the interstitium down its concentration gradient. In the IM, part of the glucose is converted to lactate by anaerobic glycolysis, whereas the rest diffuses back into AVR; as described by Eq. 2, the conversion rate depends on the local glucose concentration in interstitium ($C_{glu}^I$). It is noticeable that in DVR, the predicted concentration of glucose in RBCs ($C_{glu}^R$) rapidly increases in the outer medulla and remains significantly higher than that in plasma ($C_{glu}^P$) throughout the IM; this latter fact suggests that RBCs may act as a reservoir for glucose, as discussed below. The initial, rapid rise in $C_{glu}^R$ results from our assumption, based on literature measurements, that glucose concentration at the corticomedullary junction is much lower in RBCs than in plasma; this would suggest the existence of a mechanism that maintains this concentration difference in the general circulation. Because our model did not account for such a mechanism in the renal medulla, the initial rise in $C_{glu}^R$ represents equilibration with the higher external glucose concentration, that is, $C_{glu}^P$. With baseline values, the predicted ratio of glucose concentration at the corticomedullary junction to that at the papillary tip is $>10$, that is, much higher than expected from the data of Ruiz-Guiñazu et al. (39), indicating a need to adjust some of the uncertain parameter values.

The lactate that is produced in the interstitium diffuses down its concentration gradient to DVR and is carried down to the papillary tip; as blood flows back up along AVR, lactate diffuses back to the interstitium (Fig. 2B). In the baseline case, the concentration of lactate in the interstitium ($C_{lac}^I$) is predicted to be about four times greater at the papillary tip than at the corticomedullary boundary, in good agreement with experimental data (11, 41).

At steady state, the net amount of solute generated (or reabsorbed) is equal to the AVR-to-DVR solute mass flow difference at the corticomedullary boundary. For baseline parameter values, the net amount of lactate generated by anaerobic glycolysis in the IM is predicted to be 1.6 nmol/s. Because the fraction of lactate generated in RBCs is $<1\%$, the overall and interstitial glycolytic rates are not distinguished in the remainder of this study, unless stated otherwise.

Shown in Fig. 2C are predicted interstitial sodium and urea concentrations along the corticomedullary axis. Throughout most of the medulla, plasma and interstitial concentrations of sodium and urea are calculated to be 10–100 times larger than those of glucose and lactate. As opposed to the latter solutes, NaCl and urea significantly affect transversal water transport (see Eq. A10) and, therefore, blood flow to the deep medulla.
Hence, NaCl and urea have an indirect effect on glucose supply to the IM and on the lactate generation rate. Lactate may, in turn, affect interstitial sodium and urea reabsorption rates, a phenomenon that is beyond the scope of this study; these rates were maintained constant in our simulations.

The flatness of the predicted sodium concentration profile in the OM interstitium within a vascular bundle (Fig. 2C) contradicts experimental results obtained by Gottschalk and Mylle (18). Indeed, the measurements of these investigators were performed in a portion of the OM interstitium interspersed with nephrons, whereas our model applies only to those DVR that traverse the vascular bundles, which we assumed are completely isolated from nephrons (see the APPENDIX). This is obviously an oversimplification, but we do not believe there are enough experimental data at present to allow us to obtain an accurate estimate of the amount of water and small solutes taken up by those DVR that form part of vascular bundles, versus those that irrigate the capillary plexus. Moreover, interstitial solute concentrations in these two separate regions are expected to be different. Nevertheless, it is likely that VR uptake of water and sodium in the OM affects the countercurrent exchange of glucose, as discussed further below.

Illustrated in Fig. 2D are the predicted overall and single-vessel plasma volume flow rates along the corticomedullary axis. Water reabsorbed from tubules is driven into AVR and carried away to the general circulation. As opposed to the overall flow rate, the single-vessel flow rate is lower in AVR than in DVR; this is because the number of AVR is more than twice that of DVR.

**Glycolytic Rate**

As described above, several parameters related to the anaerobic glycolysis rate remain difficult to evaluate precisely. In the absence of experimental data, the maximum volumetric rate \( \Psi_{\text{max}} \) was taken as a constant in the IM interstitium; the actual rate depends on the local \( C_{\text{glu}}^I \) as described by Eq. 2. We first explored the effect of variations in the three parameters related to the glycolytic rate, \( K_m, \Psi_{\text{max}}, \) and \( r_I \).

The Michaelis-Menten equation was used because glucose concentration may be too low to maintain a constant local glycolytic rate. Following the approach of Thomas (42), the baseline value of \( K_m \) was taken as 0.1 mM, meaning that if glucose concentration is much higher than 0.1 mM \( \Psi_{\text{glu}} = \Psi_{\text{max}}, \) whereas at low glucose concentration values \((<0.1 \text{ mM})\) \( \Psi_{\text{glu}} \) is proportional to glucose concentration. Shown in Fig. 3, A and B, are the predicted interstitial glucose concentration \( C_{\text{glu}}^I \) distribution, overall lactate generation rate, and interstitial lactate concentration at papillary tip \( C_{\text{lac}}^I \) as a function of \( K_m \). A 10-fold increase in \( K_m \) significantly raises predicted papillary \( C_{\text{glu}}^I \) to \( ~1 \text{ mM} \) and lowers the corticomedullary junction-to-papillary tip glucose concentration ratio to 7, whereas a 10-fold decrease in \( K_m \) slightly lowers \( C_{\text{glu}}^I \). Conversely, \( C_{\text{lac}}^I \) and the concentration of lactate at the papillary tip, \( C_{\text{lac}}^I \), are found to be inversely proportional to \( K_m \). Indeed, increasing \( K_m \) raises the glucose concentration threshold beyond which \( \Psi_{\text{glu}} \) remains constant and equal to the maximum volumetric rate \( \Psi_{\text{max}} \).

Shown in Fig. 4 are the predicted overall lactate generation rate and \( C_{\text{glu}}^I \) at the papillary tip as a function of \( \Psi_{\text{max}} \) with \( K_m \) fixed at 0.1 mM. When the glucose conversion rate is small \((i.e., \Psi_{\text{max}} \text{ is less than half the baseline value, taken as } 83 \text{ mmol/cm}^3\text{s}^{-1})\), \( C_{\text{glu}}^I \) is much higher than \( K_m \), so that throughout most of the IM, the volumetric lactate production rate remains constant, with \( \Psi_{\text{lac}} = -r_I \Psi_{\text{glu}} = -r_I \Psi_{\text{max}} \). \( C_{\text{lac}}^I \) is then proportional to \( \Psi_{\text{max}} \). Conversely, when the glucose conversion rate is high \((i.e., \Psi_{\text{max}} \text{ is greater than the baseline value})\), predicted glucose concentrations are very low near the papillary tip, so that \( \Psi_{\text{glu}} \) and \( \Psi_{\text{lac}} \) are proportional to \( C_{\text{glu}}^I \) and close to 0 in the deep IM; the actual volumetric consumption of glucose and lactate in vasa recta
glucose is then calculated to be significantly lower than $\Psi_{\text{max}}$, particularly near the papillary tip. Hence, further increases in $\Psi_{\text{max}}$ would only raise $G_{\text{luc}}$ slightly. According to our simulations, multiplying the baseline value of $\Psi_{\text{max}}$ by a factor of 10 would raise $G_{\text{luc}}$ by only 52%. Increasing the value of $\Psi_{\text{max}}$ significantly beyond its baseline value would have a limited effect on $G_{\text{luc}}$ and lactate accumulation in the medulla but would deplete glucose near the papillary tip.

Analysis of the combined effect of changes in both $\Psi_{\text{max}}$ and $K_{\text{in}}$ shows that even if $\Psi_{\text{max}}$ is elevated, the predicted glucose concentration can be maintained at high levels in the IM interstitium provided that $K_{\text{in}}$ is large enough. Our model suggests that in that case, further increases in $\Psi_{\text{max}}$ will have a more significant effect on the overall generation rate of lactate (see Table 3).

As expected, reducing the lactate production-to-glucose consumption ratio ($r_l$) from 2 to 1 does not change the predicted glucose concentration distribution in the medulla, but decreases both $G_{\text{luc}}$ and $C_{\text{luc}}(L)$ by a factor of 2.

**VR Permeability to Glucose**

The permeability of VR to glucose has not been determined experimentally. As described above, baseline permeabilities to glucose were estimated as $4 \times 10^{-4}$ and $6 \times 10^{-4}$ cm/s for DVR and AVR, respectively, based on pore theory. From the measured DVR permeability to glucose and sodium in mice (33) and that to sodium in rats (36), the permeability of DVR to glucose ($P_{\text{D},\text{glu}}$) in rats was calculated as $7 \times 10^{-4}$ cm/s. However, Michel and Curry (29) reported in their review that skeletal muscle microvessel permeability to glucose is on the order of $10^{-5}$ cm/s, the value used by Thomas in his model of lactate transport in the medulla (19, 42). Given these uncertainties, we used permeability values over a wide range. Because glucose appears to permeate across microvascular walls mainly through paracellular pathways (29), it seemed reasonable to assume a fixed AVR-to-DVR permeability ratio.

As shown in Fig. 5A, predicted $C_{\text{glu}}$ profiles for different values of the DVR permeability to glucose: $7 \times 10^{-4}$, $1 \times 10^{-4}$, $5 \times 10^{-5}$, and $1 \times 10^{-5}$ cm/s. The AVR-to-DVR permeability ratio was maintained at 1.5, as in the baseline case. Illustrated in Fig. 5B is the predicted overall lactate generation rate as a function of $P_{\text{D},\text{glu}}$. We used a logarithmic scale for the abscissa to clearly show trends for low permeability values. A decrease in $P_{\text{D},\text{glu}}$ diminishes the radial diffusion of glucose from DVR to AVR, thereby reducing glucose bypass from DVR to AVR in the OM and preserving delivery of glucose to IMDVR; hence the predicted increase in glucose concentration in the IM interstitium (Fig. 5A) and in the overall lactate generation rate (Fig. 5B).

However, if $P_{\text{D},\text{glu}}$ is further reduced below $5 \times 10^{-5}$ cm/s, our model suggests that the transport of glucose across the vessel walls becomes severely limited, and $C_{\text{glu}}$ decreases with decreasing $P_{\text{D},\text{glu}}$. Under these conditions, glucose is transported to the interstitium not only through DVR but also from AVR to satisfy metabolic demands, as reflected by the fact that $C_{\text{glu}}$ is then lower than both $C_{\text{glu}}$ and $C_{\text{glu}}$ (not shown). The overall lactate generation rate appears to reach a maximum for $P_{\text{D},\text{glu}}$ values on the order of $5 \times 10^{-5}$ cm/s.

It is also interesting to note that $C_{\text{glu}}$ may increase toward the papillary tip when the VR permeability to glucose is low enough. This phenomenon stems from countercurrent exchange, the finite permeability of VR, and the resulting lag in concentration equilibration between DVR, AVR, and the interstitium. The papilla-to-corticomедullary junction glucose concentration ratio is therefore not necessarily a well-defined measure of axial glucose concentration gradients.

Because the pericytes that surround OMDVR gradually disappear in the IM (35), it is possible that the glucose permeability of OMDVR is lower than that of IMDVR. To examine this assumption, we lowered the parameter $P_{\text{D},\text{glu}}$ in the OM to half its baseline value without changing IM permeability values. As a consequence of the OM permeability reduction, the fraction of glucose that bypasses the IM was predicted to decrease from 54 to 37%, the glucose conversion ratio to increase from 18 to 21%, and the glucose concentration at the papillary tip to increase from 0.07 to 0.10 mM.

**Reservoir Effect of RBCs**

As shown in Fig. 2A, with the baseline RBC permeability to glucose (i.e., $10^{-5}$ cm/s), our model predicts that in DVR, $C_{\text{glu}}$ rapidly increases in the OM to surpass $C_{\text{glu}}$, whereas in AVR $C_{\text{glu}}$ rapidly decreases near the papillary tip to become lower than $C_{\text{glu}}$. Thus in DVR glucose is transported from RBCs to plasma throughout the inner medulla, and in AVR, glucose is
Glucose concentration profiles are plotted for two values of to preserve glucose in blood, as shown in Fig. 6. Predicted which is close to 2 throughout the medulla, allows erythrocytes 
interstitium, where it is needed for metabolic purposes. As expected, the RBC-to-plasma glu-
low RBC permeability to glucose helps to preserve it within the 
to rise from 1.3 to 1.7 nmol/s, a 31% increase. Further de-
thereby raising the overall generation rate of lactate. As 
RBCs in AVR act as storage of glucose rather than a sink, 
and then in the reverse direction. These effects result from 
countercurrent exchange and the high interstitial glucose con-
amount of glucose is thus calculated to be 1.1 times higher in 
that is, the ratio of RBC-to-whole blood flow rate) is 0.16. The 
overall amount of glucose supplied to the renal medulla 
baseline values by a factor of 4 is predicted to raise Glac 
the overall generation rate value that we used to estimate \( \Psi_{\text{max}} \). Indeed, glucose is then so plentiful in the IM that the volumet-
C\(_{\text{glu}}\) values at the corticomedullary junction is kept equal to 2. As in the baseline case. As 
expected, the higher the \( C_{\text{glu}} \), the higher the predicted values of \( C_{\text{glu}} \) and \( G_{\text{lac}} \), as illustrated in Fig. 7, A and B, respectively. 
C\(_{\text{glu}}\) increases beyond 10 mM, the lactate generation rate is 
found to reach an asymptote corresponding to \( G_{\text{lac}}^0 = 3 \) nmol/s, the 
the overall glucose consumption rate is equal to its maximum value everywhere in the IM.

We also examined the effect of varying the initial (i.e., at the 
corticomedullary junction in DVR) RBC concentration of 
glucose between 1 and 4 mM, that is, within the range of 
reported values (22). The initial plasma glucose concentration, 
\( C_{\text{glu}}^p \), was kept fixed at 6 mM. Our model suggests that \( G_{\text{lac}} \) increases linearly with the increase in initial \( C_{\text{glu}}^0 \) (results not 
shown). As the initial \( C_{\text{glu}} \) increases from 1 to 4 mM, the 
overall amount of glucose supplied to the renal medulla 
increases by 16% (the initial hematocrit is taken as 0.25), yet \( G_{\text{lac}} \) is predicted to rise from 1.3 to 1.7 nmol/s, a 31% increase. 
For comparison (see below), a fourfold (i.e., 400%) increase in 
the overall amount of glucose supplied to the renal medulla 
obtained by simultaneously increasing the initial \( C_{\text{glu}}^p \) and \( C_{\text{glu}} \) 
baseline values by a factor of 4 is predicted to raise \( G_{\text{lac}} \) from 
0.48 to 1.6 nmol/s, a 233% increase. RBCs therefore appear to 
play a significant role in storing glucose for metabolic pur-
poses.

The \( C_{\text{glu}}^0 \) also remains uncertain, as described above. We 
therefore varied the initial \( C_{\text{glu}}^0 \) from 1 to 18 mM; the initial 
\( C_{\text{glu}}^p/C_{\text{glu}}^0 \) ratio was kept fixed at 2, as in the baseline case. As 
expected, the higher the \( C_{\text{glu}}^0 \), the higher the predicted values of 
\( C_{\text{glu}}^p \) and \( G_{\text{lac}} \), as shown in Fig. 6, A and B, respectively.

The \( C_{\text{glu}}^0 \) increases by 16% (the initial hematocrit is taken as 0.25), yet 
\( G_{\text{lac}}^0 \) is predicted to rise from 1.3 to 1.7 nmol/s, a 31% increase. 
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expected, the higher the \( C_{\text{glu}}^0 \), the higher the predicted values of 
\( C_{\text{glu}}^p \) and \( G_{\text{lac}} \), as shown in Fig. 6, A and B, respectively.

The \( C_{\text{glu}}^0 \) increases by 16% (the initial hematocrit is taken as 0.25), yet 
\( G_{\text{lac}}^0 \) is predicted to rise from 1.3 to 1.7 nmol/s, a 31% increase. RBCs therefore appear to 
play a significant role in storing glucose for metabolic pur-
poses.

Fig. 6. Effect of RBC permeability to glucose on medullary glucose concen-
tration. A: \( P_{\text{glu}}^R = 2 \times 10^{-6} \) cm/s; B: \( P_{\text{glu}}^R = 4 \times 10^{-4} \) cm/s. The curves 
corresponding to plasma and RBC in both DVR and AVR can hardly be 
distinguished.

The low permeability to glucose of the RBC membrane 
\( P_{\text{glu}}^R \), as well as the moderate cell-to-wall surface area ratio, 
which is close to 2 throughout the medulla, allows erythrocytes 
to preserve glucose in blood, as shown in Fig. 6. Predicted 
glucose concentration profiles are plotted for two values of 
\( P_{\text{glu}}^R \): \( 2 \times 10^{-6} \) and \( 4 \times 10^{-4} \) cm/s, the two limiting values 
reported by Jung (21). As expected, the RBC-to-plasma glu-
cose concentration gradient increases significantly as \( P_{\text{glu}}^R \) de-
creases (Fig. 6A) and decreases as \( P_{\text{glu}}^R \) increases (Fig. 6B). However, predicted glucose concentrations in plasma and in 
interstitium remain unaffected. \( P_{\text{glu}}^R \), nevertheless, has a signif-
icient effect on lactate generation: when \( P_{\text{glu}}^R \) is low, the high 
\( C_{\text{glu}}^R \) values at the papillary tip mean that throughout most of the 
IM, glucose is transported from AVR RBCs to plasma, and 
thereby raising the overall generation rate of lactate. As 
\( P_{\text{glu}}^R \) decreases from \( 4 \times 10^{-4} \) to \( 5 \times 10^{-6} \) cm/s, \( G_{\text{lac}}^R \) is calculated 
to rise from 1.3 to 1.7 nmol/s, a 31% increase. Further de-
creases in \( P_{\text{glu}}^R \) below \( 5 \times 10^{-6} \) cm/s will reduce \( G_{\text{lac}}^R \) because a 
low RBC permeability to glucose helps to preserve it within the 
interstitium, where it is needed for metabolic purposes.

Fig. 7. A: effect of initial plasma glucose concentration (\( C_{\text{glu}}^0 \)) on interstitial 
glucose concentration (\( C_{\text{glu}}^I \)). Numbers above curves indicate values of \( C_{\text{glu}}^I \) in 
mM. B: overall IM lactate generation rate (\( G_{\text{lac}}^I \)). The plasma-to-RBC glucose 
concentration ratio in DVR at the corticomedullary junction is kept equal to 2.
The strong dependence of Clac kept fixed, so that ity, and we estimated mainly through paracellular pathways, given its water solubil-we assumed that lactate permeates across DVR and AVR walls transport through lactate transporters in the microvascular wall, respectively) in rats. In the absence of evidence of significant increase in P
on VR permeability to lactate (P
lac to lactate, (P
lac and P
lac, respectively) in rats. In the absence of evidence of significant transport through lactate transporters in the microvascular wall, we assumed that lactate permeates across DVR and AVR walls mainly through paracellular pathways, given its water solubility, and we estimated P
lac and P
lac based on pore theory. We then investigated the effect of varying both permeabilities while maintaining P
lac/P
lac = 1.6, as in the baseline case.

Our model suggests that changes in P
lac and P
lac have a negligible effect on glucose concentration and lactate generation rate but significantly affect lactate concentration and axial concentration gradients. As shown in Fig. 8, predicted lactate concentration at the papillary tip and the papillary tip-to-corticomedullary junction lactate concentration ratio both increase roughly exponentially with permeability. With other parameters equal to their baseline values, C
lac(L) is predicted to be between 2 and 5, that is, within the range of reported experimental values (11, 39, 41), if P
lac remains between $5 \times 10^{-5}$ and $6 \times 10^{-4}$ cm/s. As P
lac increases from $5 \times 10^{-5}$ to $6 \times 10^{-4}$ cm/s, C
lac(L) increases from 5 to 15 mM. The strong dependence of C
lac on VR permeability to lactate, already predicted by previous investigators (42), further demonstrates that the accumulation of lactate in IM depends not only on the amount of lactate that is generated but also on the rate at which it is exchanged across medullary countercurrent systems.

Similarly, changes in the permeability of the RBC membrane to lactate (P
lac) were found to have a negligible effect on glucose concentration and lactate generation rate. A 10-fold increase in P
lac from the baseline value raised C
lac at the papillary tip slightly, whereas a 10-fold decrease lowered it from 11.7 to 10.0 mM.

**Blood Flow Rate**

Measured blood flow rates in a single DVR mostly range from $\sim 5$ to 14 nl·min$^{-1}$·vas rectum$^{-1}$ in the antidiuretic kidney (35). The baseline blood flow rate was taken as 9 nl·min$^{-1}$·VR$^{-1}$ (35). The effects of increasing the initial blood flow rate in a single DVR (q
0) from 5 to 14 nl/min on interstitial glucose and lactate concentrations, as well as the lactate generation rate, are shown in Fig. 9. Predicted glucose concentration at the papillary tip increases moderately with increasing q
0 (Fig. 9A). Predicted lactate concentration at the papillary tip, however, reaches its maximum when q
0 = 10–11 nl/min, even though $G_{lac}$ increases proportionally with q
0 (Fig. 9B). Indeed, an increase in q
0 results in opposite effects: it raises the net amount of glucose supplied by the microcirculation, thereby increasing the generation rate of lactate and corticomedullary lactate concentration gradients; but it also dilutes blood (i.e., solute washout), thereby reducing axial solute concentration gradients. When q
0 is <10 nl/min, the former effect dominates; when q
0 is >11 nl/min, the reverse is true.

**Effect of Reabsorption Rates**

Several investigators (3, 14, 41) have reported that the relationship between lactate generation and water and solute reabsorption is complicated, in that solute diuresis, but not water diuresis, affects lactate generation in a significant way. The diuretic state affects the amount of water and solute reabsorbed from nephron loops and collecting ducts. In this study, reabsorption into the interstitium was taken into account by means of interstitial generation rates (see the Appendix), and in the simulations above, the overall reabsorption rate of water (G
in) was kept constant. Because the relationship between the reabsorption rate of water and the accumulation of lactate in the medulla cannot be explicitly determined in this model, the effects of isolated changes in G
in on glucose metabolism were
investigated as illustrated in Fig. 10. The water reabsorption rate was decreased or increased by a factor 4 relative to its baseline value, 0.13 μl/s (15). As shown in Fig. 10B, our model suggests that increasing $G^I_\text{v}$ dilutes interstitial solute concentrations, hence the reduction in $C_{\text{l}}$ at the papillary tip, but has little effect on the lactate generation rate. Variations in $C_{\text{glu}}$ are also significant, except near the papillary tip (Fig. 10A); indeed, the low glucose concentration at the papillary tip is controlled by the high $\Psi_{\text{max}}$ value and/or the low $K_m$ value. If we either decreased $\Psi_{\text{max}}$ or increased $K_m$, similar changes in $G^I_\text{v}$ would result in more significant variations in $C_{\text{glu}}$ at $x = L$. If $\Psi_{\text{max}}$ were lowered by a factor 3 and $K_m$ were kept at its baseline value (0.1 mM), increasing $G^I_\text{v}$ fourfold would lower $C_{\text{glu}}(L)$ from 1.5 to 0.4 mM; if $K_m$ were increased by a factor 10 and $\Psi_{\text{max}}$ were kept at its baseline value, increasing $G^I_\text{v}$ fourfold would lower $C_{\text{glu}}(L)$ from 0.6 to 0.4 mM.

In the above simulations, the interstitial generation (i.e., reabsorption) rates of water, sodium, and urea were taken to be zero in the OM vascular bundles, hence the absence of an axial sodium gradient in OM, as discussed above and illustrated in Fig. 2C. Given that the amount of water and sodium reabsorbed within the vascular bundles may not be negligible and yet remains difficult to estimate accurately, we performed limiting-case simulations. First, we assumed constant volumetric reabsorption rates of water, sodium, and urea in the OM; the OM generation rates of water and urea were taken to be equal to their baseline values at the OM-IM junction, whereas the reabsorption rate of sodium was taken as a constant throughout the entire medulla (in the baseline case, it is 0 at the OM-IM junction and increases linearly toward the papillary tip, as expressed in Eq. A8), so that the total amount of sodium reabsorbed in the renal medulla was 1.1 times that in the baseline case. With those assumptions, the predicted sodium concentration profile remained flat in the OM VR, due to the simultaneous reabsorption of water and sodium in the vascular bundles; variations in the fractional amount of glucose that bypasses the IM were then found to be insignificant.

In the second case, we increased the rate of volumetric sodium reabsorption throughout the medulla by a factor of 2 and kept the baseline water and urea interstitial generation rates (that is, the latter were taken as 0 in the OM vascular bundles), to generate a significant axial sodium concentration gradient in the OM. The calculated amount of reabsorbed sodium was then 2.2 times greater than in the baseline case. The concentration of sodium was then predicted to increase from 164 mM at the corticomedullary junction to 251 mM at the OM-IM junction, and the fraction of glucose that is transported from DVR to AVR in the OM (i.e., that bypasses the IM) was predicted to increase by <1%. Indeed, increased OM interstitial sodium concentrations result in higher osmotic pressure differences across OMDVR walls, hence greater water efflux from DVR lumen to interstitium through both AQP-1 water channels and paracellular pathways, which raises the amount of glucose carried by convection across OMDVR walls. Because diffusion appears to be the predominant mode of transport across VR for small solutes (see Pécel number calculations below), the convection-induced increase in the fraction of glucose that bypasses the IM remains small.

**DISCUSSION**

Given the potential importance of lactate to the urinary concentrating mechanism, in this study we sought to better characterize the conversion of glucose to lactate in the medullary microcirculation by finding parameter values that yield good agreement between predictions and experimental measurements of glucose and lactate concentrations.

Our study is different from that of Thomas (42) in several respects, as summarized in Table 2. We considered the entire medulla, not just the IM, so that the effect of the partial bypass of glucose from DVR to AVR in the OM could be examined. Because we took into account all the DVR that are destined to the IM as well as the returning AVR, as opposed to the single-unit approach used by Thomas (42), we were able to predict an overall lactate generation rate, instead of specifying the glucose conversion ratio. In our model, AVR were modeled separately from the interstitium, a more accurate representation than that of Thomas (42). Our model also distinguished between RBCs and the plasma compartment, allowing us to investigate the specific role of erythrocytes in glucose transport along VR. In addition, we calculated radial water fluxes at every depth along the corticomedullary axis, by evaluating Starling forces and distinguishing between paracellular and transcellular (i.e., AQP-1 water channels and UTB urea transporters) pathways, whereas Thomas (42) assumed that the
edge, there have been no direct measurements of lactate generation rate in the renal medulla of rats. As described in Model and parameters, indirect estimates of the overall lactate generation rate vary between 1.5 and 15 nmol/s and are most likely on the lower end of that interval.

Our simulations suggest that the profile of $C^L_{glu}$ is strongly affected by the values of $\Psi_{max}$, $K_m$, the vascular wall permeability to glucose ($P^D_{glu}$ and $P^I_{glu}$, and $C^L_{glu}$, $G^L_{lac}$ was found to be significantly affected by the values of $P^D_{glu}$ and $P^I_{glu}$, $C^L_{glu}$, and the initial blood flow rate (q$_b$). Finally, $C^I_{lac}$ was found to be mostly a function of vascular permeability to lactate and glucose, of $C^L_{glu}$, and of the rate of water uptake from the nephrons and collecting ducts ($G^L_i$). With baseline parameter values, the papillary tip-to-cortical medullary junction glucose concentration ratio was predicted to be <0.1, far below experimental determinations. Our sensitivity analysis thus indicated that the baseline values of $K_m$ and $C^L_{glu}$ were underestimated, and/or those of $P^D_{glu}$ and $P^I_{glu}$ were overestimated. The papillary tip-to-cortical medullary junction lactate concentration ratio and $C^I_{lac}$ were calculated as 3.8 and 1.6 mmol/s, respectively, that is, within the experimental range.

As described above, the DVR permeability to glucose is highly uncertain; estimates based on the literature range from $10^{-5}$ to $7 \times 10^{-4}$ cm/s (29, 33, 36). As reviewed by Michel and Curry (29), glucose transport across the microvascular wall is mainly through paracellular pathways; we therefore maintained the $P^D_{glu}/P^I_{glu}$ ratio constant as we varied permeabilities. Our simulations indicate that a decrease in permeability reduces the bypass of glucose from OM DVR to OM AVR through radial diffusion, thereby increasing glucose supply in the IM and lactate generation. However, as the permeability of DVR to glucose is lowered below $5 \times 10^{-5}$ cm/s (and that of AVR below $7.5 \times 10^{-5}$ cm/s), glucose transport from the vascular lumen to the interstitium is predicted to become rate limiting, leading to a decrease in the glycolytic reaction rate. Given that $J$) the low glucose permeability value (i.e., $10^{-5}$ cm/s) given by Michel and Curry (29) is for skeletal muscle microvessels; 2) the ultrastructure of DVR and AVR walls is relatively simple (35); 3) extrapolation of glucose permeability measurements from mice (33, 36) suggests that $P^D_{glu}$ is on the order of $7 \times 10^{-4}$ cm/s in rats; and 4) lactate and glucose are of similar size so that vascular wall permeabilities to these two molecules are expected to be of similar magnitude in the absence of transporters, it is unlikely that the DVR permeability to glucose is as low as $10^{-5}$ cm/s and that to lactate as high as $10^{-3}$ cm/s, as assumed by Thomas and colleagues (19, 42).

To obtain the best agreement between our predictions and experimental data, we sought to find parameter values that generate $C^L_{glu}$ and $C^I_{lac}$ papillary tip-to-cortical medullary junction ratios of about one-third and comprised between 2 and 5, respectively. To obtain high enough values of $C^L_{glu}$ we fixed $K_m$ at 1 mM (see results). The initial blood concentration of glucose, $C^0_{glu}$, was set at either 6 or 10 mM, and $P^D_{glu}$ at either $10^{-4}$ or $5 \times 10^{-5}$ cm/s, whereas the $P^D_{glu}/P^I_{glu}$ ratio was kept equal to 1.5. For each set of ($C^L_{glu}$, $P^D_{glu}$) values, we determined the values of $\Psi_{max}$ and $P^I_{lac}$ that yield $C^L_{glu}(L)/C^I_{lac}(0) = 0.33$ and $C^L_{lac}(L)/C^I_{lac}(0) = 4$. The lactate permeability ratio was also kept constant, such that $P^I_{lac}/P^D_{lac} = 1.6$. Results are shown in Table 3. Among the parameters $C^L_{glu}$, $C^I_{glu}$ (hence $P^D_{glu}$), and $\Psi_{max}$, the latter is the one that has the most significant effect on corticomedullary glucose concentration gradi-

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Table 2. Comparison with prior work of Thomas (42)

<table>
<thead>
<tr>
<th>Study</th>
<th>Thomas (42)</th>
<th>Present Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model range</td>
<td>IM</td>
<td>IM + OM</td>
</tr>
<tr>
<td>Number of vasa recta</td>
<td>1 DVR extending to papillary tip</td>
<td>All DVR destined to IM</td>
</tr>
<tr>
<td>Interstitium</td>
<td>Lumped with AVR</td>
<td>Separate from AVR</td>
</tr>
<tr>
<td>RBCs</td>
<td>Lumped with plasma</td>
<td>Separate from plasma</td>
</tr>
<tr>
<td>Water radial flux</td>
<td>Fixed fraction of axial flow</td>
<td>Evaluated by Starling forces</td>
</tr>
<tr>
<td>Glycolytic rate</td>
<td>Fixed glucose conversion ratio</td>
<td>Fixed maximum volumetric rate</td>
</tr>
<tr>
<td>$P^D_{glu}$, cm/s</td>
<td>$4 \times 10^{-5}$</td>
<td>$4 \times 10^{-4}$</td>
</tr>
<tr>
<td>$P^I_{glu}$, cm/s</td>
<td>NA</td>
<td>$2 \times 10^{-4}$</td>
</tr>
<tr>
<td>$P^D_{lac}$, cm/s</td>
<td>$10^{-3}$</td>
<td>$5 \times 10^{-4}$</td>
</tr>
<tr>
<td>$P^I_{lac}$, cm/s</td>
<td>NA</td>
<td>$8 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

**Predicted values**: NA, not applicable; AQP1, aquaporin-1. See the GLOSSARY for an explanation of all other abbreviations. *Values at the inner medulla-outer medulla (IM-OM) junction. Because the model of Thomas (42) applied to the IM only, whereas the present one is based on the entire medulla, the parameter values corresponding to our study and given in this table were extrapolated to the OM-IM junction when necessary. †Predicted values based on case 1 in Table 3 below.

radial flux is a fixed fraction of the axial flow. Finally, parameters such as initial glucose concentrations and vascular wall permeabilities varied considerably between the two studies. Consequently, 1) we predicted generally lower glucose concentrations at the papillary tip; 2) we could examine the effect of glucose bypass in the OM and the role of RBCs; and 3) we were able to estimate the overall rate of lactate generation and compare it with experimental data.

Reported measurements of glucose and lactate concentrations in the renal medulla appear to be scarce. As described above, the experimental data of Ruiz-Guinauz et al. (39), Scaglione et al. (41), and Dell and Winter (11) suggest that the interstitial concentration of glucose is about one-third lower at the papilla than at the corticomedullary junction, and that lactate is two to five times greater. To the best of our knowl-
sorbed glucose as an energy source thanks to the high-affinity
transporters. On the other hand, corticomedullary lactate concentration
gradients depend mostly on $P_{\text{DIC}}^{\text{in}}$ (hence $P_{\text{DIC}}^{\text{in}}$); the value of $P_{\text{DIC}}^{\text{in}}$
that yields $C_{\text{DIC}}(L)/C_{\text{DIC}}(0) \approx 4$ was consistently found to be
$\sim 2 \times 10^{-4}$ cm/s in all the cases examined.

The results shown in Table 3 also suggest that to increase
glucose concentration of blood entering the medulla, it is necessary that both the glucose content in the blood that enters the medulla (i.e., $C_{\text{DIC}}$) be high, and that glucose bypass in the outer medulla be limited (that is, lower values of $P_{\text{DIC}}^{\text{in}}$ and $P_{\text{DIC}}^{\text{out}}$ are more favorable). To further illustrate the relative importance of these two factors, we performed a simulation in which OM glucose permeability was greatly decreased so that OM glucose bypass was reduced from 32 (baseline case) to 0.5%, the glucose conversion rate then increased from 18 to 28%, and the lactate generation rate from 54 (baseline case) to 0.5%; the glucose conversion rate in RBC; the rate of glycolysis in RBCs is
increased by 10.220.33.4 on September 30, 2017 http://ajprenal.physiology.org/ Downloaded from
highly unlikely that the contribution of gluconeogenesis to blood glucose has
been estimated to be 5–25% under normal conditions, it is very
likely that these figures are overestimated due to a number of
technical difficulties. Conversely, the study of Roxe et al. (38)
did suggest that the amount of glucose generated by
renal gluconeogenesis is negligible. If a significant amount of
and lactate, and of the kinetics of glycolysis in the IM
medulla, glucose is a fuel for respiration, but other potential
fuels (such as fatty acids, endogenous lipids, lactate, and
succinate) appear to be preferred (37). It is therefore possible
that a fraction of glucose reabsorbed from the medullary S3
segment diffuses radially into the OM microcirculation. Given
the ultrastructure of the OM, this fraction of glucose is more
likely to be carried away from the medulla, up to the renal vein,
by AVR arising in the interbundle region, than to enter the
vascular bundles and flow down the IM along DVR. The
contribution of reabsorbed glucose to lactate production should
therefore remain insignificant.

Another possible source of glucose is that generated by
gluconeogenesis, which in the kidney can only occur in the
proximal tubule (37). As reviewed by Ross et al. (37), although
the contribution of renal gluconeogenesis to blood glucose has
been estimated to be 5–25% under normal conditions, it is very
likely that these figures are overestimated due to a number of
technical difficulties. Conversely, the study of Roxe et al. (38)
did suggest that the amount of glucose generated by
renal gluconeogenesis is negligible. If a significant amount of
glucose is indeed generated in the proximal tubules (37), part
of it could also diffuse into the outer medullary microcirculation.
However, for the same reasons as those stated above, it is
highly unlikely that the contribution of gluconeogenesis to
lactate production is significant.

In summary, this study provides plausible intervals (i.e.,
yielding predictions that are consistent with existing experimental
data) for unknown parameters related to anaerobic
glycologysis in the IM interstitium and lactate transport in the
renal medulla. Our estimates of permeability to glucose are
generally higher than those used previously in the literature,
and our predictions of the overall lactate generation rate are on
the lower side of estimates indirectly derived from experimental
data. Measurements of glucose and lactate concentration at
different depths of the renal medulla, of VR permeability to
lactate and glucose, and of the kinetics of glycologysis in the IM
would be useful in confirming the trends predicted by our
model.

APPENDIX

Mathematical Model

Our model of the countercurrent exchange in the renal medullary
microcirculation is a series of conservation equations in
plasma, RBC, and interstitium, together with flux equations. The
solutes being considered in this study include NaCl, urea, glucose,
lactate, plasma proteins, and hemoglobin; because there is no transport
of NaCl, plasma proteins, and hemoglobin across the RBC
membrane, the permeability of the latter to those three solutes is taken
as zero. The effect of plasma protein concentration polarization on water and protein transport can be neglected (47) and is not considered here. Solutes in plasma permeate across VR walls through paracellular pathways shared with water. We also account for two additional, transcellular pathways across DVR walls: AQP-1 water channels and UTB urea transporters. Reactions involving glucose and lactate are considered in RBCs and IM interstitium.

Conservation Equations

If x is the axial coordinate along the cortico-medullary axis, conservation of volume in plasma and RBCs can be expressed as

\[
\frac{dQ}{dx} = \frac{dA}{dx} \frac{dV}{dx} + \left( \frac{Q^p}{N} \right) \frac{dN}{dx} + \frac{Q^r}{N} \frac{dN}{dx} \tag{A1}
\]

where \(Q^p\) and \(Q^r\) are the plasma and RBC flow rates along the vessels, respectively, and \(J^r_{nv}\) and \(J^r_w\) are the volume fluxes (per unit membrane area) across VR walls (positive if directed from VR to interstitium) and RBC membranes (positive if directed from RBC to plasma), respectively. The parameter \(J^r_{nv}\) represents RBC-to-vessel surface area ratio, \(N\) denotes the number of VR, \(D\) their diameter, and \(\pm\) and \(-\) apply to AVR and DVR, respectively. The second term on the right-hand side of Eqs. A1 and A2 accounts for the fact that at various depths in the medulla, DVR break up to form a capillary plexus, from which AVR are formed and ascend.

Conservation of solutes in plasma and RBCs can be expressed as

\[
\frac{d(Q^p C^p_i)}{dx} = \frac{dA}{dx} \frac{dV}{dx} + \left( \frac{Q^p C^p_i}{N} \right) \frac{dN}{dx} + \frac{Q^r C^r_i}{N} \frac{dN}{dx} \tag{A3}
\]

\[
\frac{d(Q^r C^r_i)}{dx} = \frac{dA}{dx} \frac{dV}{dx} + \frac{Q^r C^r_i}{N} \frac{dN}{dx} \tag{A4}
\]

where \(C^p_i\) denotes the plasma concentration of solute \(i\), \(C^r_i\) the RBC concentration of solute \(i\) based on erythrocyte water, \(f\) is the volume fraction of water in red cells, taken as 0.717 (10, 40), and \(J^r_{nv}\) and \(J^r_w\) are the molar fluxes of solute \(i\) based on VR and RBC membranes, respectively. As above, + and − apply to AVR and DVR, respectively; \(h\) is the hematocrit [defined as \(h = Q^r/(Q^p + Q^r)\)], taken as 0.25 in blood entering DVR (35); and \(\Psi^r_i\) is the volumetric solute generation rate in RBCs (in mmol·cm⁻³·RBC·s⁻¹), which is negative if the solute is consumed.

Reabsorption of water, NaCl, and urea from the loops of Henle and collecting ducts is accounted for by interstitial generation rates. Because we only consider those DVR that are destined to the IM, that is, those that form part of OM vascular bundles, from which nephron loops are excluded, interstitial generation rates for water, sodium, and urea are taken to be 0 in the outer medulla. Moreover, because anaerobic glycolysis is assumed to occur in the IM interstitium only, glucose consumption and lactate production rates are also taken to be 0 in the OM. Because axial transport is limited by the orientation and density of lipid-laden interstitial cells (25), at a given depth in the medulla, reabsorption, generation, or consumption is balanced by transport into the microcirculation at steady state (15), so that:

\[
[J^p_{nv}(x)N(x)\pi D]_{DVR} + [J^p_{av}(x)N(x)\pi D]_{AVR} + A_{nv}\Psi^r_i = 0 \tag{A5}
\]

where \(A_{nv}\) denotes the cross-sectional area of the interstitium and is expressed as a function of cross-sectional area of inner medulla \(A_{nv}; \) see Eq. A20 (15)

\[
A_{nv}(x_m) = A_{nv}(0.25x_m + 0.05) \tag{A6}
\]

and \(\Psi^r_i\) is the volumetric generation rate in the interstitium (in mmol·cm⁻³·s⁻¹). As described previously (15), for water, sodium, and urea, respectively, we assume that:

\[
\Psi^w(x_m) = 1.9 \times 10^{-7}(1 - x_m) \tag{A7}
\]

\[
\Psi^s(x_m) = 1.75 \times 10^{-3}x_m \tag{A8}
\]

\[
\Psi^u(x_m) = 5.88 \times 10^{-5} \exp[6(x_m - 1)] \tag{A9}
\]

where \(x_m\) is the dimensionless axial length based on the length of the IM.

Flux Equations

The volume flux across the capillary wall, \(J^w_v\), is the sum of volume fluxes across paracellular pathways and AQP-1 water channels, written as

\[
J^w_v = L^w_P(\Delta P - \sigma_P \Delta \Pi_P) + RT \sum_i \gamma_i (C^p_i - C^r_i) \tag{A10}
\]

where \(L^w_P\) and \(L^r_P\) represent the hydraulic conductivities of the paracellular pathway and AQP-1, respectively. The superscript \(D\) signifies that AQP-1 is expressed in DVR only, so that the second term on the right-hand side is taken to be 0 in AVR. \(\Delta P\) is the transcapillary hydraulic pressure difference, \(\Delta \Pi_P\) is the transcapillary oncotic pressure difference due to plasma proteins, and \(\sigma_i\) is the reflection coefficient of the paracellular pathway to solute \(i\). The subscript \(i\) refers to small solutes present in plasma and interstitium (that is, \(i = NaCl\), urea, glucose, and lactate). The interstitial concentration and the activity coefficient of solute \(i\) are denoted by \(C^i\) and \(\gamma_i\), respectively. If \(L^w_P\) represents the overall hydraulic conductivity of the RBC membrane, the volume flux across the RBC membrane may be expressed as

\[
J^w_r = L^w_P(\Pi_{im} - \Pi_{ih} - RT \sum_i \gamma_i (C^p_i - C^r_i)) \tag{A11}
\]

where \(\Pi_{im}\) and \(\Pi_{ih}\) are the oncotic pressures due to proteins in plasma and to hemoglobin in RBCs, respectively, and \(i\) denotes the small solutes present in plasma and/or erythrocytes.

The paracellular flux of solute \(i\) across VR walls can be written as

\[
J^w_i(\text{para}) = J^w_i(\text{para}) \times (1 - \sigma_i) \left( C^p_i - C^l \exp(-Pe) \right) \tag{A12}
\]

\[
Pe = \frac{J^w_i(\text{para}) \times (1 - \sigma_i)}{P^w_i} \tag{A13}
\]

where \(P^w_i\) is the permeability of the VR wall to solute \(i\), and the Pécel number, \(Pe\), is a measure of the importance of convection relative to diffusion. In the baseline case, the Pécel number for small solutes (sodium, urea, glucose, and lactate) is consistently <0.02, indicating that transport of small solutes across vessel walls is dominated by diffusion. For solutes other than urea, \(J^w_i = J^w_i(\text{para})\) because they only pass through paracellular routes. For urea, besides the flux across paracellular pathways, we also consider that across UTB urea transporters within DVR walls, which can be expressed as

\[
J^w_i = P^u_i(C^p_i - C^r_i) \tag{A14}
\]

where \(P^u_i\) denotes the urea permeability of UTB urea transporters in DVR walls. The flux of small solutes across the RBC membrane is given by

\[
J^w_i = P^r_i(C^p_i - C^r_i) \tag{A15}
\]

where \(P^r_i\) denotes the permeability of the RBC membrane to solute \(i\).
Parameters

The RBC-to-wall surface area ratio is given by (46)

\[ \Gamma_{DVR} = \frac{129D_{DVR}}{4 \times 61} \left( \frac{Q^R}{Q^P + Q^R} \right)^{0.5} \]

\[ \Gamma_{AVR} = \frac{129D_{AVR}}{4 \times 61} \left( \frac{Q^R}{Q^P + Q^R} \right)^{0.5} \times \frac{Q^N_{DVR}}{2.25Q^N_{AVR}} \]  

(A16)

where \( D_{DVR} \) and \( D_{AVR} \) are the DVR and AVR vascular diameters (in \( \mu \text{m} \)), and the subscript 0 signifies that the quantity is evaluated in DVR at the corticomedullary junction. The calculated \( \Gamma_{DVR} \) and \( \Gamma_{AVR} \) remain close to 2 throughout the medulla. The number of DVR destined to the medulla is constant in OM and can be obtained by setting \( s_{im} = 0 \) in Eq. A18 below, with \( D_{DVR} = 15.6 \mu \text{m} \) and \( D_{AVR} = 20.0 \mu \text{m} \). In the IM, the number of DVR is assumed to decrease with the cross-sectional area of the inner medulla (\( A_{im}, \text{cm}^2 \)) as follows (16)

\[ N_{DVR}(x_{im}) = \frac{0.3A_{im}}{(D_{DVR} + 2.25D_{AVR})/4} \]

\[ N_{AVR} = 2.25N_{DVR} \]  

(A18)

\[ A_{im}(x_{im}) = 0.175 - 0.383x_{im} + 0.2606x_{im}^2 - 0.04193x_{im}^3 \]  

(A19)

Baseline parameter values and boundary conditions can be found in a previous study (46). Parameter values involving glucose and lactate are discussed above and listed in Table 1.

GRANTS

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REFERENCES


