A Model of Glucose Transport and Conversion to Lactate in the Renal Medullary Microcirculation

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Running title: Glucose and Lactate in Vasa Recta
ABSTRACT

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 cortico-medullary junction; plausible kinetic rate constant and permeability values are summarized in tabular form. Our simulations indicate that counter-current exchange of glucose from descending (DVR) to ascending vasa recta (AVR) in the outer medulla and upper inner medulla 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 $4 \times 10^{-4}$ 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 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: 541-5, 1965; Bartlett S, Espinal J, Janssens P, and Ross BD. *Biochem J* 219: 73-8, 1984).

Keywords: kidney, vasa recta, glycolysis, mathematical model
INTRODUCTION

The urinary concentrating mechanism is made possible by the steep cortico-medullary 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 hyper-osmolality in the inner medullary interstitium is built up and preserved remains unclear. A hypothesis involving an external osmolyte proposed by Niesel and Roeskenbleck (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 unspecified solute, external to the tubular fluid, that can provide an added 20-100 mOsm/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 inner medullary metabolism (37). Lactate is produced by anaerobic glycolysis, and it may later be used for gluconeogenesis in the outer medulla (OM) and cortex (37). Since 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 first developed a medullary microcirculation model to simulate lactate accumulation in IM (42), 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 inner medullary NaCl concentration gradients (and therefore the cortico-medullary 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 to 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 IMCDs, and if inner medullary 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 ~ $7\times10^{-4}$ 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, vasa recta, 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 vasa recta 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.
GLOSSARY

$C_i^0$ initial concentration of solute $i$ in plasma, that is, in DVR at corticomedullary junction

$C_i^j$ concentration of solute $i$ in compartment $j$, $j = R, P, I$

$D$ diameter of vasa recta

$f$ volume fraction of water in red cells.

$G_i^j$ overall medullary generation (or consumption) rate of component $i$ in compartment $j$, $j = R, I$

$h$ hematocrit

$J_i^j$ flux of solute $i$ through membrane $j$, $j = R, W$

$k_m$ Michaelis-Menten constant for glucose consumption rate

$L$ length of renal medulla, or position of the papillary tip when in parentheses.

$L_k^j$ hydraulic conductivity of pathway $k$ in compartment $j$, $j = R, W$

$P_i^j$ permeability of membrane $j$ to component $i$, $j = R, W, D, A$

$Q_i^j$ 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 $j$, $j = R, I$

Greek Symbols
$\Gamma$  red blood cell-to-vessel surface area ratio

$\Pi$  oncotic pressure of proteins

$\gamma_i$  activity coefficient of solute i

$\sigma_i$  reflection coefficient to solute i

$\Psi_i^j$  volumetric generation rate of component i in compartment j, j = R, I

$\Psi_{\text{max}}$  maximum volumetric glucose consumption rate in Michaelis-Menten equation

**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. Fig. 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) non-linear 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 vasa recta walls, which couple the differential and non-linear 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 inner medullary 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:

\[ \text{C}_6\text{H}_12\text{O}_6 \rightarrow 2\text{CH}_3\text{CHOHCOO}^- + 2\text{H}^+ \]  

Thus, two lactate molecules are produced for each glucose molecule that is consumed by anaerobic glycolysis.

**Anaerobic Glycolysis in 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 inner medullary abluminal cells; the latter include interstitial cells, the vascular wall cells of vasa recta, 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 since
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 inner medullary 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/g dry wt. of kidney 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 lactate generation since (1) glucose was perfused to the kidney in these
experiments and (2) lactate may also be produced in parts of the kidney other than the
inner medulla. Another estimate can be obtained by assuming that all the glucose present
in blood at the cortico-medullary junction is entirely converted to lactate: if glucose
concentration at the junction is taken as 6 mM in plasma and 3 mM in RBCs (see below),
the initial hematocrit as 0.25 (35), and blood flow rate in a single vas rectum as 9 nl/min
(35), the corresponding rate of lactate production is then estimated as \(~10\) nmol/s.
Alternatively, measurements by Bernanke and Epstein (5) indicated that in the inner
medulla of dog kidney, the oxygen consumption-to-lactate production ratio is 3 when the
medullary slice is incubated with both 100 and 5% saturated oxygen. Our recent study
suggested that IM oxygen consumption in rats is on the order of 1 nmol/s (46), yielding
an overall IM lactate production rate of about 3 nmol/s.
Other estimates of the IM interstitial lactate generation rate may be derived from the study of Bastin et al. (4), who incubated isolated rat kidneys, dissected tissue slices, and measured lactate concentration using an enzyme reagent. The investigators reported that lactate concentrations in papillary tissues increased from 22.5 to 33.3 and 57.7 mmol/kg papillary tissue dry wt. over a period of 7.5 and 120 seconds, respectively. During the first period, the lactate generation rate can therefore be estimated as \((33.3 - 22.5) / 7.5 = 1.44 \text{ mmol/kg tissue dry wt./s}\); similar calculations yield a generation rate of 0.293 mmol/kg tissue dry wt./s during the second period. In the absence of data on the density of dry papillary tissue, estimates of lactate generation rates based on unit tissue water volume can be obtained as follows. The mass fraction of water in rat papillary interstitium has been reported as 77.4% (7), i.e., the ratio of water volume-to-tissue dry weight is \(3.45 \text{ l water / kg dry wt.}\), if water density is taken as 0.993 g/ml. The lactate generation rate is thus calculated as 414 and 84 nmol/ml of tissue water/s for the 7.5- and 120-second periods, respectively. If the lactate generation rate is taken to be the same throughout the IM as that measured in papillary tissue and the tissue volume is approximated as that of the tissue water, extrapolation of the data of Bastin et al (4) using Eq. 3 below suggests that the overall lactate generation rate is on the order of 1.5-7.5 nmol/s. Since 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-second period, glucose and glycogen concentrations decrease 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/liter of tissue water, respectively. The overall consumption rate of glucose and
glycogen is thus calculated as 42 nmol/ml of tissue water/s, 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 is 3-7 times that in outer medullary and cortical tubules. Using the rates reported by these investigators (in Table 1 of their study, also cited in Table 1 in this study), as well as the numbers of collecting ducts and mTALs we previously calculated (48) based on the measurements of Mejia and colleagues (26, 27), we estimate that the overall lactate generated by the IMCDs and mTALs is about 1.4 nmol/s.

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

In order to account for the dependence of the volumetric glucose consumption rate (Ψ_glu, in nmol/cm^3/s) upon glucose concentration (C_glu), especially at low C_glu values, a Michaelis-Menten equation is used for Ψ_glu, following the approach of Thomas (42):

$$\Psi_{\text{glu}} = \frac{Ψ_{\text{max}} C_{\text{glu}}}{k_m + C_{\text{glu}}} \quad (2)$$
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 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 in order to relate the overall interstitial lactate production rate ($G_{\text{lac}}^i$) to $\Psi_{\text{glu}}$:

$$\frac{G_{\text{lac}}^i}{r_1} = A_{\text{im}}^0 L_{\text{im}} \int_0^y (0.25y + 0.05) \Psi_{\text{glu}} \, dy$$  \hspace{1cm} (3)

where $A_{\text{im}}^0$ is the medullary cross-sectional area at the IM-OM junction (estimated as 17.5 mm$^2$ from Eq. A20), and $L_{\text{im}}$ 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 $G_{\text{lac}}^i$ taken as 3 nmol/s (see above), $\Psi_{\text{max}}$ is then calculated as 83 nmol/cm$^3$/s using Eq. 3. The latter value corresponds to the baseline case in this study. As described below, towards the papillary tip, our results suggest that glucose concentrations become small enough that the dependence of $\Psi_{\text{glu}}$ on $C_{\text{glu}}$ turns out to be significant; consequently, if $\Psi_{\text{max}}$ is maintained at 83 nmol/cm$^3$/s, the overall lactate generation rate calculated using our model, $G_{\text{lac}}^i$, is lower than 3 nmol/s.

The glycolytic rate in red blood cells is estimated as follows. Messana et al. (28) reported that the rate of glucose consumption and lactate production in human erythrocytes vary with pH but remain independent of oxygenation. They measured the glucose consumption rate as ~15-60 nmol/ml RBCs/min (i.e., 0.9-3.6 mmol/l RBCs/h)
and the ratio of lactate production to glucose consumption ($r_R$) as close to 1.

Ataullakhanov et al. (1) reported that glucose consumption rates in human erythrocytes range from 0.24 to 2.6 mmol/l RBCs/h, while $r_R$ 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/l RBCs/h (22). The baseline values for $\Psi_{max}$ and $r_R$ in rat erythrocytes are therefore chosen as 5.6 mmol/l RBCs/h (that is, 1.56 nmol/cm$^3$ RBCs/s) and 1.5, respectively. Simulation results (not shown) suggest that variations in these two RBC parameters have negligible effects, since the overall lactate production rate is about $10^2$ to $10^3$ lower in RBCs than in the IM interstitium.

**Initial Concentrations**

Lactate concentration has been reported as ~0.92 mM in plasma from the femoral artery of mongrel dogs (14), ~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 two-fold variations in these two parameter values have a negligible effect on lactate generation rates, as well as glucose and lactate concentrations in the inner medulla (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 RBC; the
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 is 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 (29), Michel and Curry reported that the glucose permeability of the microvascular wall in skeletal muscle, which is dominated by that across paracellular
pathways, is about $10^{-5}$ cm/s. According to these investigators, the permeability across transcellular pathways is at least 3 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, 4 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 for skeletal muscle microvascular walls (29). 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 vasa recta 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 $1.89 \times 10^{-5}$ cm$^2$/s, and the molecular radii of those solutes as 0.35, 0.31 and 0.27 nm, respectively, using the on-line property calculator SPARC (http://ibmlc2.chem.uga.edu/sparc). The resulting permeabilities and reflection coefficients to glucose and lactate are shown in Table 1.
Since estimates of the permeability of vasa recta walls to glucose range from $10^{-5}$ 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 below). 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 AQP-1 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 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 vasa recta 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) in order 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-Guinazu 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 2-5 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 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) suggest that that glucose concentration in rat kidney decreases from 5.9 to 2.3 mmoles/liter of interstitial tissue water over a 2-minute period following dissection and under full ischemia, while lactate concentration increases from 6.5 to 16.6 mmoles/liter 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, since 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 upon their data.

**Baseline Results**

We first performed simulations with baseline parameters. Shown in Figs. 2A and 2B are predicted glucose and lactate concentration profiles along the cortico-medullary 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 while 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 inner medulla; this latter fact suggests that RBCs may act as a reservoir for glucose, as discussed below. The initial, rapid rise of \(C_{glu}^R\) results from our assumption, based on literature measurements, that glucose concentration at the cortico-medullary 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. Since our model did not account for such a mechanism in the renal medulla, the initial rise of \(C_{glu}^R\) 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-Guinazu 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 (\(C_{\text{lac}}^1\)) is predicted to be about 4 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 cortico-medullary 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. Since the fraction of lactate generated in RBCs is less than 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 cortico-medullary axis. Throughout most of the medulla, plasma and interstitial concentrations of sodium and urea are calculated to be 10 to 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) therefore blood flow to the deep medulla. Hence, NaCl and urea have an indirect effect on glucose supply to the IM and on 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 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 vasa recta uptake of water and sodium in the OM affects the counter-current exchange of glucose, as discussed further below.

Illustrated in Fig. 2D are the predicted overall and single vessel plasma volume flow rates along the cortico-medullary 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 \( r_{l} \).

The Michaelis-Menten equation was used since 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, \( \Psi_{\text{glu}} = \Psi_{\text{max}} \), while at low \( C_{\text{glu}} \) values (<0.1 mM), \( \Psi_{\text{glu}} \) is proportional to \( C_{\text{glu}} \). Shown in Fig. 3A and 3B are the predicted interstitial glucose concentration distribution, overall lactate generation rate, and interstitial lactate concentration at the papillary tip as a function of \( k_{m} \). A ten-fold increase in \( k_{m} \) significantly raises predicted papillary \( C_{\text{glu}}^{i} \) to ~1 mM and lowers the corticomedullary junction-to-papillary tip glucose concentration ratio to 7, whereas a ten-fold decrease in \( k_{m} \) slightly lowers \( C_{\text{glu}}^{i} \). Conversely, the overall lactate generation rate, \( G_{\text{lac}}^{i} \), and the concentration of lactate at the papillary tip, \( C_{\text{lac}}^{i} \) (L), 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 interstitial glucose concentration 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., \( \Psi_{\text{max}} \) is less than half the baseline value,
taken as 83 nmol/cm³/s), \( C^l_{\text{glu}} \) is much higher than \( k_m \), so that throughout most of the IM, the volumetric lactate production rate remains constant, with \( \Psi_{\text{lac}} = -r_l \Psi_{\text{glu}} = -r_l \Psi_{\text{max}} \). \( G^l_{\text{lac}} \) is then proportional to \( \Psi_{\text{max}} \). Conversely, when the glucose conversion rate is high (i.e., \( \Psi_{\text{max}} \) 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 \( C^l_{\text{glu}} \) and close to zero in the deep inner medulla; the actual volumetric consumption of 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 \( G^l_{\text{lac}} \) slightly. According to our simulations, multiplying the baseline value of \( \Psi_{\text{max}} \) by a factor ten would raise \( G^l_{\text{lac}} \) by only 52%. Increasing the value of \( \Psi_{\text{max}} \) significantly beyond its baseline value thus would have a limited effect on \( G^l_{\text{lac}} \) 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 \( k_m \) 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 \( k_m \) 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 below).

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 \( G^l_{\text{lac}} \) and \( C^l_{\text{lac}}(L) \) by a factor 2.
Vasa Recta Permeability to Glucose

The permeability of vasa recta 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 ($P_{\text{glu}}^{D}$) 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 varied permeability values over a wide range. Since glucose appear to permeate across microvascular walls mainly through paracellular pathways (29), it seemed reasonable to assume a fixed AVR-to-DVR permeability ratio.

Shown in Fig. 5A are predicted interstitial glucose concentration 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 $P_{\text{glu}}^{D}$. We used a logarithmic scale for the abscissa in order to clearly show trends for low permeability values. A decrease in $P_{\text{glu}}^{D}$ diminishes the radial diffusion of glucose from DVR to AVR, thereby reducing glucose bypass from DVR to AVR in the outer medulla and preserving delivery of glucose to IMDVR; hence the predicted increase in glucose concentration in the inner medullary interstitium (Fig. 5A) and in the overall lactate generation rate (Fig. 5B).
However, if $P_{\text{glu}}^D$ 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 $C_{\text{glu}}^I$ (hence $G_{\text{lac}}^I$) decreases with decreasing $P_{\text{glu}}^D$. Under these conditions, glucose is transported to the interstitium not only from DVR but also from AVR in order to satisfy metabolic demands, as reflected by the fact that $C_{\text{glu}}^I$ is then lower than both $C_{\text{glu}}^D$ and $C_{\text{glu}}^A$ (not shown). The overall lactate generation rate appears to reach a maximum for $P_{\text{glu}}^D$ values on the order of $5 \times 10^{-5}$ cm/s.

It is also interesting to note that $C_{\text{glu}}^I$ may increase towards the papillary tip when the vasa recta permeability to glucose is low enough. This phenomenon stems from countercurrent exchange, the finite permeability of vasa recta, 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.

Since the pericytes that surround outer medullary DVR 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 $P_{\text{glu}}^D$ 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, $C_{\text{glu}}^R$ rapidly increases in the OM to surpass $C_{\text{glu}}^D$, whereas in AVR $C_{\text{glu}}^R$ rapidly decreases near the papillary tip to become lower than $C_{\text{glu}}^A$. Thus, in DVR glucose is transported from RBCs to plasma throughout the inner medulla, and in AVR, glucose is initially transported from RBCs to plasma near the papillary tip and then in the reverse direction. These effects result from counter-current exchange and the high interstitial glucose consumption rate. The baseline model predicts that at the papillary tip, glucose concentrations in RBC, plasma and interstitium are 0.8, 0.1 and 0.07 mM, respectively, and the hematocrit (that is, the ratio of RBC-to-whole blood flow rate) is 0.16. The amount of glucose is thus calculated to be 1.1 times higher in RBCs than in plasma at the papillary tip.

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, allow 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 glucose concentration gradient increases significantly as $P_{\text{glu}}^R$ decreases (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 significant 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 henceforth to the interstitium. Our model thus suggests that RBCs in AVR act as storage of glucose rather than a sink, 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, $G_{\text{lac}}^I$ is calculated to rise from 1.3 to 1.7 nmol/s, a 31% increase. Further decreases in $P_{\text{glu}}^R$ below $5 \times 10^{-6}$ cm/s will reduce $G_{\text{lac}}^I$ since a low RBC permeability to glucose helps to preserve it within the microcirculation, but it also limits glucose transport to the interstitium where it is needed for metabolic purposes.

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

The initial concentration of glucose in plasma also remains uncertain, as described above. We therefore varied the initial $C_{\text{glu}}^0$ from 1 to 18 mM; the initial $C_{\text{glu}}^0 / C_{\text{glu}}^R$ 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 $C^0_{\text{glu}}$ and $G^1_{\text{lac}}$, as illustrated in Fig. 7A and 7B, respectively. As $C^0_{\text{glu}}$ increases beyond 10 mM, the lactate generation rate is found to reach an asymptote corresponding to $G^1_{\text{lac}} = 3 \text{ nmol/s}$, the overall generation rate value that we used to estimate $\Psi_{\text{max}}$. Indeed, glucose is then so plentiful in the IM that the volumetric glucose consumption rate is equal to its maximum value everywhere in the inner medulla.

**Lactate Permeability**

To the best of our knowledge, there are no reported measurements of vasa recta wall permeability to lactate ($P^\text{D}_{\text{lac}}$ and $P^\text{A}_{\text{lac}}$, 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 $P^\text{D}_{\text{lac}}$ and $P^\text{A}_{\text{lac}}$ based on pore theory. We then investigated the effect of varying both permeabilities while maintaining $P^\text{A}_{\text{lac}} / P^\text{D}_{\text{lac}} = 1.6$, as in the baseline case.

Our model suggests that changes in $P^\text{D}_{\text{lac}}$ and $P^\text{A}_{\text{lac}}$ 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, $C^1_{\text{lac}}(L)/C^1_{\text{lac}}(0)$ is predicted to be between 2 and 5, that is, within the range of reported experimental values (11, 39, 41), if $P^\text{D}_{\text{lac}}$ remains between $5 \times 10^{-5}$ and $6 \times 10^{-4}$ cm/s. As $P^\text{D}_{\text{lac}}$ increases from $5 \times 10^{-5}$ to $6 \times 10^{-4}$ cm/s, $C^1_{\text{lac}}(L)$
increases from 5 to 15 mM. The strong dependence of \( C_{\text{lac}}^i \) on vasa recta 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 (\( P_{\text{lac}}^R \)) were found to have a negligible effect on glucose concentration and lactate generation rate. A 10-fold increase in \( P_{\text{lac}}^R \) from the baseline value raised \( C_{\text{lac}}^i \) 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 ~5 to 14 nl/min/vasa rectum in the antidiurectic kidney (35). The baseline blood flow rate was taken as 9 nl/min/vasa rectum (35). The effects of increasing the initial blood flow rate in a single DVR (\( q_B^0 \)) 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 \( q_B^0 \) (Fig. 9A). Predicted lactate concentration at the papillary tip, however, reaches its maximum when \( q_B^0 = 10-11 \) nl/min, even though \( G_{\text{lac}}^i \) increases proportionally with \( q_B^0 \) (Fig. 9B). Indeed, an increase in \( q_B^0 \) 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 $q_B^0 < 10 \text{ nl/min}$, the former effect dominates; when $q_B^0 > 11 \text{ nl/min}$, 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 appendix), and in the simulations above, the overall reabsorption rate of water ($G_T^I$) was kept constant. Since 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 $G_T^I$ 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 $\mu$l/s (15). As shown in Fig. 10B, our model suggests that increasing $G_T^I$ dilutes interstitial solute concentrations - hence the reduction in $C_{\text{lac}}^I$ at the papillary tip - but has little effect on the lactate generation rate. Variations in $C_{\text{glu}}^I$ 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 $G_T^I$ would result in more significant variations in $C_{\text{glu}}^I$ 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 $G_i^1$ fourfold would lower $C_{\text{glu}}^1 (L)$ 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 $G_i^1$ fourfold would lower $C_{\text{glu}}^1 (L)$ 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, while the reabsorption rate of sodium was taken as a constant throughout the entire medulla (in the baseline case, it is zero at the OM-IM junction and increases linearly towards 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 vasa recta, due to the simultaneous reabsorption of water and sodium in the vascular bundles; variations in the fractional amount of glucose that bypasses the inner medulla were then found to be insignificant.

In the second case, we increased the rate of volumetric sodium reabsorption throughout the medulla by a factor two and kept the baseline water and urea interstitial generation rates (that is, the latter were taken as zero in the OM vascular bundles), in order to generate a significant axial sodium concentration gradient in the outer medulla.
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 cortico-medullary 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 less than 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. Since diffusion appears to be the predominant mode of transport across vasa recta for small solutes (see Peclet 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 inner medulla 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 plasma compartment, allowing us to investigate the specific role of erythrocytes in glucose transport along vasa recta. 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., aquaporin-1 water channels and UTB urea transporters) pathways, whereas Thomas (42) assumed that the 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; (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-Guinazu 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 of lactate is 2 to 5 times greater. To the best of our knowledge, there have been no direct measurements of lactate generation rate in the renal medulla of rats. As described in the Model and Parameters section, 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 interstitial glucose concentration ($C_{\text{glu}}^I$) is strongly dependent on the values of $\Psi_{\text{max}}$, the Michaelis-Menten constant ($k_m$), the vascular wall permeability to glucose ($P_{\text{glu}}^D$ and $P_{\text{glu}}^A$), and the initial glucose concentration ($C_{\text{glu}}^0$). The overall lactate generation rate ($G_{\text{lac}}^I$) was found to be significantly affected by the values of $P_{\text{glu}}^D$ and $P_{\text{glu}}^A$, $C_{\text{glu}}^0$, and the inflowing blood flow rate ($q_{\text{in}}^0$). Finally, the interstitial lactate concentration ($C_{\text{lac}}^I$) was found to be mostly a function of vascular permeability to lactate and glucose, of $C_{\text{glu}}^0$, and of the rate of water uptake from the nephrons and collecting ducts ($G_{\text{vG}}^I$). With baseline parameter values, the papillary tip-to-corticomedullary junction glucose concentration ratio was predicted to be less than 0.1, far below experimental determinations. Our sensitivity analysis thus indicated that the baseline values of $k_m$ and $C_{\text{glu}}^0$ were underestimated, and/or those of $P_{\text{glu}}^D$ and $P_{\text{glu}}^A$ were
overestimated. The papillary tip-to-corticomedullary junction lactate concentration ratio and \( G_{\text{lac}} \) were calculated as 3.8 and 1.6 nmol/s, respectively, that is, within experimental range.

As described above, the DVR permeability to glucose is highly uncertain; estimates based on the literature range from \( 10^{-5} \) to \( 7\times10^{-4} \) 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 \( P_{\text{glu}}^A / P_{\text{glu}}^D \) ratio constant as we varied permeabilities. Our simulations indicate that a decrease in permeability reduces the bypass of glucose from OMDVR to OMAVR through radial diffusion, thereby increasing glucose supply in the IM and lactate generation. However, as the permeability of DVR to glucose is lowered below \( 5\times10^{-5} \) cm/s (and that of AVR below \( 7.5\times10^{-5} \) 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 (a) the low glucose permeability value (i.e., \( 10^{-5} \) cm/s) given by Michel and Curry (29) is for skeletal muscle microvessels, (b) the ultrastructure of DVR and AVR walls is relatively simple (35), (c) extrapolation of glucose permeability measurements from mice (33, 36) suggests that \( P_{\text{glu}}^D \) is on the order of \( 7\times10^{-4} \) cm/s in rats, (d) 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).

In order to obtain the best agreement between our predictions and experimental data, we sought to find parameter values that generate \( C_{\text{glu}}^1 \) and \( C_{\text{lac}}^1 \) papillary tip-to-
corticomedullary junction ratios of about 1/3 and comprised between 2 and 5, respectively. To obtain high enough values of $C_{gla}^l$, we fixed $k_m$ at 1 mM (see Results).

The initial blood concentration of glucose, $C_{gla}^0$, was set at either 6 or 10 mM, and $P_{gla}^D$ at either $10^{-4}$ or $5 \times 10^{-5}$ cm/s, while the ratio $P_{gla}^A / P_{gla}^D$ was kept equal to 1.5. For each set of $(C_{gla}^0, P_{gla}^D)$ values, we determined the values of $\Psi_{max}$ and $P_{lac}^D$ which yield $C_{gla}^l (L)/C_{gla}^0 \approx 0.33$ and $C_{lac}^l (L)/ C_{lac}^l (0) \approx 4$. The lactate permeability ratio was also kept constant, such that $P_{lac}^A / P_{lac}^D = 1.6$. Results are shown in Table 3. Among the parameters $C_{gla}^0$, $P_{gla}^D$ (hence $P_{gla}^A$), and $\Psi_{max}$, the latter is the one that has the most significant effect on corticomedullary glucose concentration gradients. On the other hand, corticomedullary lactate concentration gradients depend mostly on $P_{lac}^D$ (hence $P_{lac}^A$); the value of $P_{lac}^D$ which yields $C_{lac}^l (L)/ C_{lac}^l (0) \approx 4$ 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 in order to increase lactate generation rate ($G_{lac}^l$), it is necessary that both the glucose content in the blood that enters the medulla (i.e., $C_{gla}^0$) be high, and that glucose bypass in the outer medulla be limited (that is, lower values of $P_{gla}^D$ and $P_{gla}^A$ 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 outer medullary glucose bypass was reduced from 54% (baseline case) to 0.5%; the glucose conversion rate then increased from 18% to 28%, and the lactate generation rate from 1.6 to 2.4 mmol/s; glucose concentration at the papillary tip increased nearly 4-fold, to about 0.3 mM.
Our model indicates that RBCs act partly as a glucose reservoir. A 4-fold increase in the initial concentration of glucose in RBCs from 1 to 4 mM, which corresponds to a 16% increase in the glucose content of blood entering the medulla, is sufficient to raise the predicted $G_{\text{lac}}^1$ by 31%, whereas a 400% increase in glucose content obtained by simultaneously increasing the initial values $C_{\text{glu}}^D$ and $C_{\text{glu}}^R$ raises the predicted $G_{\text{lac}}^1$ by 233%. Because the permeability to glucose of erythrocytes is about one order of magnitude lower than that of DVR (which more than compensates for the higher surface area of RBCs, about twice that of the vessel walls in the baseline case), the glucose present in RBCs is carried deeper into the inner medulla; however, the low RBC permeability also limits glucose transport to the interstitium for glycolytic consumption, as shown in Fig. 6. It is also worth remarking that the reservoir role of RBCs is made possible by the low glucose consumption rate in RBC; the rate of glycolysis in RBCs is less than 1% that in the IM interstitium in the baseline case.

Although the overall production of lactate in the renal medulla is perhaps as high as 15 nmol/s, as described above, our model predicts that the amount of lactate generated in IM by the consumption of glucose from the glomerular efferent arterioles remains significantly below this value, even when parameter values are selected so as to increase glucose supply to the medulla and decrease glucose bypass in the OM and upper IM, as illustrated in Table 3. As described below, there are other sources of glucose in the kidney, but their contribution to anaerobic glycolysis is most likely negligible.
As described by Thorens (44), the filtered glucose is completely reabsorbed in the proximal tubule, and the cells of the S3 segment, which are glycolytic, may use part of the reabsorbed glucose as an energy source thanks to the high-affinity glucose transporter GLUT-1. In the cortex and in the outer 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 outer medullary microcirculation. Given the ultrastructure of the OM, this fraction of glucose is more likely to be carried away from the medulla, up to the venal rein, 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 glucogenesis to blood glucose has been estimated to be 5 to 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) in dogs suggested 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 glycolysis in the inner medullary 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 vasa recta permeability to glucose and lactate, and of the kinetics of glycolysis in the IM would be useful in confirming the trends predicted by our model.
ACKNOWLEDGEMENTS

This work was supported by National Institutes of Health Grant DK 53775.
APPENDIX

Mathematical Model

Our model of the countercurrent exchange in the renal medullary microcirculation consists of a series of conservation equations in plasma, red blood cells, and interstitium, together with flux equations. The solutes being considered in this study include NaCl, urea, glucose, lactate, plasma proteins and hemoglobin; since 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 vasa recta 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:

$$\frac{dQ^p}{dx} = \pm (J_v^w - \Gamma J_v^r)N\pi D + \left(\frac{Q^p}{N}\right)\frac{dN}{dx}$$  \hspace{1cm} (A1)

$$\frac{dQ^r}{dx} = \pm \Gamma J_v^r N\pi D + \left(\frac{Q^r}{N}\right)\frac{dN}{dx}$$  \hspace{1cm} (A2)

where $Q^p$ and $Q^r$ are the plasma and RBC flow rates along the vessels, respectively, and $J_v^w$ and $J_v^r$ are the volume fluxes (per unit membrane area) across vasa recta walls.
(positive if directed from vasa recta to interstitium) and RBC membranes (positive if directed from RBC to plasma), respectively. The parameter $\Gamma$ represents RBC-to-vessel surface area ratio, $N$ denotes the number of vasa recta and $D$ their diameter, and “+” and “-“ apply to AVR and DVR, respectively. The second term on the right-hand side of Eqs. A1-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:

$$\frac{d(Q^PC_i^P)}{dx} = \pm\left[J_i^W - \Gamma J_i^R\right] N \pi D + \left(\frac{Q^PC_i^P}{N}\right) \frac{dN}{dx}$$

(A3)

$$\frac{d(fQ^RC_i^R)}{dx} = \pm J_i^R \pi N \pi D \pm h \frac{\pi}{4} D^2 \Psi_i^R + \left(\frac{fQ^RC_i^R}{N}\right) \frac{dN}{dx}$$

(A4)

where $C_i^P$ denotes the plasma concentration of solute i, $C_i^R$ denotes the RBC concentration of solute i based upon erythrocyte water, $f$ is the volume fraction of water in red cells, taken as 0.717 (10, 40), and $J_i^W$ and $J_i^R$ are the molar fluxes of solute through vasa recta walls and RBC membranes, respectively. As above, “+” and “-“ apply to AVR and DVR, respectively; $h$ is the hematocrit (defined as $h = Q^R / (Q^R+Q^P)$), taken as 0.25 in blood entering DVR (35); and $\Psi_i^R$ is the volumetric solute generation rate in RBCs (in mmol/cm$^3$ RBC/s), 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. Since we only consider those DVR that are destined to the inner medulla, 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 zero in the outer medulla. Moreover, since anaerobic
glycolysis is assumed to occur in the IM interstitium only, glucose consumption and lactate production rates are also taken to be zero 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:

\[
\left[ J_i^W(x)N(x)\pi D \right]_{DVR} + \left[ J_i^W(x)N(x)\pi D \right]_{AVR} + A_{int}\Psi_i = 0 \quad (A5)
\]

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

\[
A_{int}(x_{im}) = A_{im}(0.25x_{im} + 0.05) \quad (A6)
\]

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

\[
\Psi_v(x_{im}) = 1.9 \times 10^{-2}(1 - x_{im}) \quad (A7)
\]

\[
\Psi_{Na}(x_{im}) = 1.75 \times 10^{-3}x_{im} \quad (A8)
\]

\[
\Psi_u(x_{im}) = 5.88 \times 10^{-3} \exp[\delta(x_{im} - 1)] \quad (A9)
\]

where \( x_{im} \) is the dimensionless axial length based on the length of the inner medulla.

**Flux Equations**

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

\[
J_v^W = L_P^W \left( \Delta P - \sigma_{pr} \Delta \Pi_{pr} - RT \sum \sigma_i \gamma_i \left( C_i^P - C_i^I \right) \right) + L_A^D \left( \Delta P - \Delta \Pi_{pr} - RT \sum \gamma_i \left( C_i^P - C_i^I \right) \right)
\]

(A10)
where \( L_P^W \) and \( L_A^P \) 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 zero in AVR. \( \Delta P \) is the transcapillary hydraulic pressure difference, \( \Delta \Pi_{pr} \) 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, \( i = \text{NaCl, urea, glucose, and lactate} \)). The interstitial concentration and the activity coefficient of solute \( i \) are denoted by \( C_i^I \) and \( \gamma_i \), respectively.

If \( L_R \) represents the overall hydraulic conductivity of the RBC membrane, the volume flux across the RBC membrane may be expressed as:

\[
J_R^V = L_R \left( \Pi_{pr} - \Pi_{Hb} - RT \sum_i \gamma_i \left( C_i^R - C_i^P \right) \right) \tag{A11}
\]

where \( \Pi_{pr} \) and \( \Pi_{Hb} \) 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 vasa recta walls can be written as:

\[
J_i^W (para) = J_i^W (para) \times (1 - \sigma_i) \left[ \frac{C_i^P - C_i^I \exp(-P \epsilon)}{1 - \exp(-P \epsilon)} \right] \tag{A12}
\]

\[
P \epsilon = \frac{J_i^W (para) \times (1 - \sigma_i)}{P_i^W} \tag{A13}
\]

where \( P_i^W \) is the permeability of the vasa recta wall to solute \( i \), and the Peclet number, \( P \epsilon \), is a measure of the importance of convection relative to diffusion. In the baseline case, the Peclet number for small solutes (sodium, urea, glucose, and lactate) is
consistently less than 0.02, indicating that transport of small solutes across vessel walls is dominated by diffusion. For solutes other than urea, \( J_i^W = J_i^W \) (para), since 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:

\[
J_{uc}^D = P_{uc}^D (C_{u}^D - C_{u}^1)
\]

where \( P_{uc}^D \) denotes the urea permeability of UTB urea transporters in DVR walls. The flux of small solutes across the RBC membrane is given by:

\[
J_i^R = P_i^R (C_i^R - C_i^P)
\]

where \( P_i^R \) denotes the permeability of the RBC membrane to solute \( i \).

**Parameters**

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

\[
\Gamma_{DVR} = \left( \frac{129 D_{DVR}}{4 \times 61} \right) \left( \frac{Q^R}{Q^P + Q^R} \right) \left( \frac{Q_0^R N_{DVR}}{Q^R N_0} \right)^{0.5}
\]

\[
\Gamma_{AVR} = \left( \frac{129 D_{AVR}}{4 \times 61} \right) \left( \frac{Q^R}{Q^P + Q^R} \right) \left( \frac{Q_0^R N_{AVR}}{2.25 Q^R N_0} \right)^{0.5}
\]

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 \( x_{im} = 0 \) 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 ($A_{\text{im}}, \text{cm}^2$) as follows (16):

\[
N_{DVR}(x_{\text{im}}) = \frac{0.3A_{\text{im}}}{(D_{\text{DVR}}^2 + 2.25D_{\text{AVR}}^2)\pi/4} \quad \text{(A18)}
\]

\[
N_{AVR} = 2.25N_{DVR} \quad \text{(A19)}
\]

\[
A_{\text{im}}(x_{\text{im}}) = 0.175 - 0.3883x_{\text{im}} + 0.2606x_{\text{im}}^2 - 0.04193x_{\text{im}}^3 \quad \text{(A20)}
\]

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.
REFERENCES


Figure Legends

Figure 1:
Geometric model of one unit of microcirculatory countercurrent exchange in the rat medulla. AVR and DVR, ascending and descending vasa recta, respectively. RBC, red blood cell. There are about 6000 DVR destined to the IM at the corticomedullary junction, and 200 DVR at the papillary tip. On average, one DVR gives rise to about 2.24 AVR. In the inner medulla, water and solutes (sodium and urea) are reabsorbed from nephron loops and collecting ducts and carried away by AVR blood flow to the general circulation.

Figure 2:
(A) medullary concentration of glucose in plasma, RBC and interstitium
(B) medullary concentration of lactate in plasma, RBC and interstitium. The curves corresponding to plasma and RBC in AVR can hardly be distinguished.
(C) interstitial concentration of sodium ($C_{Na}^I$) and urea ($C_{u}^I$)
(D) overall ($Q^P$) and single vessel ($q^P$) plasma volume flow rate relative to overall and single vessel volume flow rate of blood entering DVR, respectively. Initial hematocrit is equal to 0.25.
Position along the cortico-medullary axis is denoted by x, and L represents the total length of the medulla.

Figure 3:
(A) Interstitial glucose concentration distribution as a function of the Michaelis-Menten constant \( k_m \). Numbers adjacent to curves indicate values of \( k_m \) in mM.

(B) Overall IM lactate generation rate (\( G_{\text{lac}}^I \)) and interstitial lactate concentration at papillary tip (\( C_{\text{lac}}^I (L) \)), as a function of \( k_m \) (in mM). The baseline value of \( k_m \) is 0.1 mM.

**Figure 4:**
Effect of maximum volumetric glycolytic rate in the IM interstitium (\( \Psi_{\text{max}} \)) on the overall lactate generation rate (\( G_{\text{lac}} \)) and the interstitial glucose concentration at the papillary tip (\( C_{\text{glu}}^I (L) \)). When \( \Psi_{\text{max}} = 0 \), \( G_{\text{lac}} = G_{\text{lac}}^R \).

**Figure 5:**
(A) Interstitial glucose concentration distribution as a function of permeability to glucose. Numbers beside curves indicate value of DVR permeability (\( P_{\text{glu}}^D \)) in cm/s.

(B) Overall IM lactate generation rate (\( G_{\text{lac}}^I \)) as a function of permeability to glucose.

As discussed in text, the AVR-to-DVR permeability ratio is kept fixed, so that \( P_{\text{glu}}^A / P_{\text{glu}}^D = 1.5 \) in all cases.

Decreases in permeability reduce glucose bypass in the OM and upper IM, thereby increasing available glucose for glycolysis. However, very low permeability values limit transversal transport of glucose from blood to interstitium, thereby decreasing available glucose.
Figure 6:

Effect of RBC permeability to glucose ($P_{glu}^R$) on medullary glucose concentration:

(A) $P_{glu}^R = 2 \times 10^{-6}$ cm/s.

(B) $P_{glu}^R = 4 \times 10^{-4}$ cm/s. The curves corresponding to plasma and RBC in both DVR and AVR can hardly be distinguished.

Figure 7:

Effect of initial plasma glucose concentration ($C_{glu}^0$) on:

(A) interstitial glucose concentration. Numbers above curves indicate values of $C_{glu}^0$ in mM.

(B) overall IM lactate generation rate ($G_{lac}^I$)

The plasma-to-RBC glucose concentration ratio in DVR at the corticomedullary junction is kept equal to 2.

Figure 8:

Effect of DVR and AVR permeability to lactate ($P_{lac}^D$ and $P_{lac}^A$) on interstitial lactate concentration at papillary tip ($C_{lac}^i(L)$) and papillary tip-to-corticomedullary junction concentration ratio ($C_{lac}^i(L)/C_{lac}^i(0)$). As discussed in text, the AVR-to-DVR permeability ratio is kept fixed, so that $P_{lac}^A/P_{lac}^D = 1.6$ in all cases.

Figure 9:
Effects of initial single vessel blood flow rate ($q_{B}^{0}$) on

(A) interstitial glucose concentration at papillary tip ($C_{glu}^{i} (L)$) relative to $C_{glu}^{0}$

(B) overall IM lactate generation rate ($G_{lac}^{i}$) and interstitial lactate concentration at the papillary tip ($C_{lac}^{i} (L)$).

**Figure 10:**

Effects of overall water reabsorption rate from nephron loops and collecting ducts into interstitium ($G_{v}^{1}$) on:

(A) interstitial glucose concentration distribution along axis. Numbers above curves indicate values of $G_{v}^{1}$ in µl/s.

(B) overall IM lactate generation rate ($G_{lac}^{i}$) and interstitial lactate concentration at the papillary tip ($C_{lac}^{i} (L)$).

$G_{v}^{1}$ is varied between one-fourth and four times the baseline value, 0.13 µl/s. The rate of water reabsorption per unit interstitial volume is assumed to increase linearly from OM-IM junction to papillary tip (15).
**Table 1**

Baseline Values of Parameters Related to Glucose and Lactate

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Literature Values</th>
<th>Reference</th>
<th>Baseline values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial plasma lactate concentration, ( C_{\text{lac}}^0 ) (mM)</td>
<td>1.7</td>
<td>(11)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2.6</td>
<td>(41)</td>
<td></td>
</tr>
<tr>
<td>Initial RBC lactate concentration (mM)</td>
<td></td>
<td></td>
<td>2 (see text)</td>
</tr>
<tr>
<td>Initial plasma glucose concentration, ( C_{\text{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></td>
<td>2.8</td>
<td>(24)</td>
<td></td>
</tr>
<tr>
<td>Permeability of RBC to lactate (cm/s)</td>
<td>( 1 \times 10^{-4} )</td>
<td>(13)</td>
<td>( 1 \times 10^{-4} )</td>
</tr>
<tr>
<td>Permeability of RBC to glucose (cm/s)</td>
<td>( 2 \times 10^{-6} - 4 \times 10^{-4} )</td>
<td>(21)</td>
<td>( 1 \times 10^{-5} )</td>
</tr>
<tr>
<td>Permeability of DVR wall to lactate (cm/s)</td>
<td></td>
<td></td>
<td>( 5 \times 10^{-4} ) (see text)</td>
</tr>
<tr>
<td>Permeability of AVR wall to lactate (cm/s)</td>
<td></td>
<td></td>
<td>( 8 \times 10^{-4} ) (see text)</td>
</tr>
<tr>
<td>Permeability of DVR wall to glucose (cm/s)</td>
<td>( 2.8 \times 10^{-3} ) (mice)</td>
<td>(33)</td>
<td>( 4 \times 10^{-4} ) (see text)</td>
</tr>
<tr>
<td></td>
<td>( 1 \times 10^{-5} ) (skeletal muscle microvessels)</td>
<td>(29)</td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permeability of AVR wall to glucose (cm/s)</td>
<td>$6 \times 10^{-4}$ (see text)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflection coefficient of DVR wall to lactate</td>
<td>0.010 (see text)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflection coefficient of AVR wall to lactate</td>
<td>0.007 (see text)</td>
<td></td>
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<tr>
<td>Reflection coefficient of DVR wall to glucose</td>
<td>0.013 (see text)</td>
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<tr>
<td>Reflection coefficient of AVR wall to glucose</td>
<td>0.009 (see text)</td>
<td></td>
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<tr>
<td>Medullary lactate generation rate (nmol/s)</td>
<td>3 (5) 12-15 (3) 1.5-7.5 (4) 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC glucose consumption rate (mmol/l/h)</td>
<td>5.6 (22) 5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of lactate production to glucose consumption in RBCs</td>
<td>1 (28) 1.5-2.7 (1) 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio of lactate production to glucose consumption in interstitium</td>
<td>2 (see text)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum volumetric rate of glucose consumption in IM interstitum, $\Psi_{max}$ (nmol/cm$^3$/s)</td>
<td>83 (see text)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum volumetric rate of glucose</td>
<td>1.56 (see text)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consumption in RBC (nmol/cm²/s)</td>
<td>Michaelis-Menten rate constant $k_m$, (mM)</td>
<td>0.1</td>
<td>(42)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------------------</td>
<td>-----</td>
<td>------</td>
</tr>
<tr>
<td>Lactate generation rate from IMCD (pmol/min/mm)</td>
<td>2.8</td>
<td>(2)</td>
<td></td>
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<tr>
<td>Lactate generation rate from OMCD (pmol/min/mm)</td>
<td>0.87</td>
<td>(2)</td>
<td></td>
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<tr>
<td>Lactate generation rate from mTAL (pmol/min/mm)</td>
<td>0.36</td>
<td>(2)</td>
<td></td>
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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>
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<tbody>
<tr>
<td><strong>Model</strong></td>
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<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; paracellular pathways and AQP-1 are distinguished</td>
</tr>
<tr>
<td>Glycolytic rate</td>
<td>Fixed glucose conversion ratio</td>
<td>Fixed maximum volumetric rate</td>
</tr>
<tr>
<td>Initial blood flow rate (nl/min/vessel)</td>
<td>3.75</td>
<td>6.5 (plasma), 2.1 (RBCs)</td>
</tr>
<tr>
<td>Initial $C_{\text{glu}}$ (mM)</td>
<td>10</td>
<td>2.5 (plasma), 3.6 (RBCs)</td>
</tr>
<tr>
<td>Initial $C_{\text{lac}}$ (mM)</td>
<td>2</td>
<td>5.1 (plasma), 4.7 (RBCs)</td>
</tr>
<tr>
<td>Overall initial amount of glucose (mol/min/vessel)</td>
<td>$37.5 \times 10^{-12}$</td>
<td>$21.7 \times 10^{-12}$</td>
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</table>
### Baseline Parameters*

| Parameter | Subscript | Baseline | Predicted
<table>
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<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>( P^D_{\text{glu}} ) (cm/s)</td>
<td>( \text{D} )</td>
<td>( 4 \times 10^{-5} )</td>
<td>( 4 \times 10^{-4} )</td>
</tr>
<tr>
<td>( P^A_{\text{glu}} ) (cm/s)</td>
<td>( \text{A} )</td>
<td>NA</td>
<td>( 6 \times 10^{-4} )</td>
</tr>
<tr>
<td>( P^D_{\text{lac}} ) (cm/s)</td>
<td>( \text{D} )</td>
<td>( 10^{-3} )</td>
<td>( 5 \times 10^{-4} )</td>
</tr>
<tr>
<td>( P^A_{\text{lac}} ) (cm/s)</td>
<td>( \text{A} )</td>
<td>NA</td>
<td>( 8 \times 10^{-4} )</td>
</tr>
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</table>

### Predicted Values†

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P^D_{\text{glu}} ) (cm/s)</td>
<td>( 10^{-3} )</td>
</tr>
<tr>
<td>( P^D_{\text{lac}} ) (cm/s)</td>
<td>( 10^{-3} )</td>
</tr>
<tr>
<td>( k_m ) (mM)</td>
<td>0.1</td>
</tr>
<tr>
<td>( C_{\text{glu}} ) (L) (mM)</td>
<td>Mostly 4-9</td>
</tr>
<tr>
<td>( C_{\text{lac}} ) (L) (mM)</td>
<td>Mostly &lt; 30</td>
</tr>
<tr>
<td>Glucose conversion ratio</td>
<td>20-25% (assumed)</td>
</tr>
<tr>
<td>Glucose shunt in OM</td>
<td>(not estimated)</td>
</tr>
<tr>
<td>( G_{\text{lac}} ) (nmol/s)</td>
<td>(not estimated)</td>
</tr>
<tr>
<td>RBC effect</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Values at the IM-OM junction. Since the model of Thomas (42) applied to 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.
Table 3

Optimized parameters*

<table>
<thead>
<tr>
<th>Fixed Parameters</th>
<th>Variable Parameters</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{glu}}^0$ (mM)</td>
<td>$P_{\text{glu}}^D / P_{\text{glu}}^A$ (cm/s)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>$1 \times 10^{-4} / 1.5 \times 10^{-4}$</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>$5 \times 10^{-5} / 7.5 \times 10^{-5}$</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>$1 \times 10^{-4} / 1.5 \times 10^{-4}$</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>$5 \times 10^{-5} / 7.5 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

$k_m = 1$ mM.

*The AVR-to-DVR permeability ratio was kept fixed, at 1.5 for glucose and 1.6 for lactate (see text).

Note that the baseline value of $\Psi_{\text{max}}$ is 83 nmol/cm³/s.
Fig. 2
Fig. 3
Fig. 4
Fig. 5
Fig. 6
Fig. 7
Fig. 8
Fig. 9
Fig. 10