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Modeling glucose metabolism and lactate production in the kidney

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ABSTRACT

The metabolism of glucose provides most of the ATP required for energy-dependent transport processes. In the inner medulla of the mammalian kidney, limited blood flow and O_2 supply yield low oxygen tension; therefore, a substantial fraction of the glucose metabolism in that region is anaerobic. Lactate is considered to be a waste product of anaerobic glycolysis, which yields two lactate molecules for each glucose molecule consumed, thereby likely leading to the production and accumulation of a significant amount of lactate in the inner medulla. To gain insights into the transport and metabolic processes in the kidney, we have developed a detailed mathematical model of the renal medulla of the rat kidney. The model represents the radial organization of the renal tubules and vessels, which centers around the vascular bundles in the outer medulla and around clusters of collecting ducts in the inner medulla. Model simulations yield significant radial gradients in interstitial fluid oxygen tension and glucose and lactate concentrations in the outer medulla and upper inner medulla. In the deep inner medulla, interstitial fluid concentrations become much more homogeneous, as the radial organization of tubules and vessels is not distinguishable. Using this model, we have identified parameters concerning glucose transport and basal metabolism, as well as lactate production via anaerobic glycolysis, that yield predicted blood glucose and lactate concentrations consistent with experimental measurements in the papillary tip. In addition, simulations indicate that the radial organization of the rat kidney may affect lactate buildup in the inner medulla.

1. Introduction

The mammalian kidneys are essentially designed to filter large amounts of plasma, reabsorb and secrete necessary substances to maintain electrolyte balance, acid-base balance, body fluid osmolality, and glucose balance, and excrete metabolic wastes and foreign chemicals. In part to achieve this goal, the human and rodent kidneys receive approximately 20–25% of the cardiac output. A portion of that blood passes through the renal filters (called the *glomeruli*) and enter long, narrow tubules (called the *nephrons*). In the human kidney, approximately 120 mL/min of this ultrafiltrate is produced, yet only 1 mL/min of urine is produced. To reabsorb more than 99% of the filtered water along the nephrons, the kidneys require a large amount of energy. Indeed, the human kidneys consume 10% of the oxygen used in cellular respiration while only occupying 0.5% of body mass.

Even though the kidneys receive a large amount of blood, blood flow in the medulla (the innermost portion of the kidney) is relatively low [20] due to shunting of blood flow in the cortex (the outermost portion of the kidney). The kidneys are susceptible to hypoxia, with oxygen tension (P_{O2}) of ~20 and ~10 mmHg in the outer medulla (OM) and inner medulla (IM), respectively [29]. The low renal P_{O2} can be attributed, in part, to the high metabolic demands of the Na^+/K^+-ATPase-mediated active reabsorption of Na^+, which requires a high rate of O_2 consumption in the kidney.

Molecules of glucose are sufficiently small to pass through the glomeruli. The filtered load of glucose is almost entirely reabsorbed along the initial segment of the nephron (called the *proximal tubule*). As a result, tubular fluid entering the renal medulla is virtually glucose-free. Glucose is supplied to the medulla via medullary blood flow and may be consumed via either aerobic or anaerobic metabolism. Aerobic metabolism requires oxygen and releases energy, via the Krebs cycle, with carbon dioxide and water as byproducts. In the OM, glucose is a fuel for respiration to support tubular transport and basal metabolism, with oxygen involved. However, the kidney also utilizes other fuels, such as fatty acids, ketone bodies, endogeneous lipids, lactate, and some amino acids [19,42]. In the IM and at the papillary tip, where the blood flow is relatively limited and the P_{O2} is sufficiently low, anaerobic glycolysis appears to be the dominant energy supply, and lactate is produced from glucose.

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Thomas [40] and Zhang and Edwards [46] investigated glucose transport and its conversion to lactate in the renal medullary circulation using simple models of vasa recta. Later, Hervy and Thomas [16] used a more detailed model to investigate the effect of medullary glucose metabolism on the urine concentrating mechanism of the rat kidney. The focus of those studies was on the accumulation of lactate in the medulla; thus, only anaerobic glycolysis was taken into account. In our previous study of glucose transport and metabolism in the kidney [5], we considered both aerobic and anaerobic glycolysis; however, we did not explicitly represent medullary lactate concentration.

All of the aforementioned models [5,16,40,46] assumed that the interstitium was well-mixed; i.e., that the distribution of nephrons and vessels was homogeneous. However, anatomic studies have revealed a substantial degree of structural organization in the renal medulla: in the OM, tubules and vessels are organized around vascular bundles [21,22,45]; in the upper IM, clusters of collecting ducts (CDs, the final segments of the nephrons) are the dominating organizing structural elements [31,33]. Modeling studies have suggested that that structural organization may result in preferential interactions among tubules and vessels, which may yield significant radial gradients in interstitial fluid osmolality, solute concentrations [23], and oxygen tension [13]. A goal of this study is to assess the effect of the medullary structural organization on the distribution of glucose and lactate.

Thus, the current study is based on our previous models of the rat kidney [12,13,23,24] which consider the radial organization of the renal tubules and vessels, centering around the vascular bundles in the OM and around clusters of CDs in the IM. These models represent oxygen utilization and predict significant radial gradients in interstitial fluid P_{O2} at different medullary levels in the rat kidney. The current model extends these to represent tubular reabsorption of Na^+, the consumption of O_2 and glucose that drives that reabsorption, as well as the generation of lactate. Whether that glucose is metabolized aerobically or anaerobically is determined based on local P_{O2} (and only *anaerobic* metabolism produces lactate). The model requires a large set of parameters, most of which were gleaned from experimental literature and were thoroughly tested in our earlier studies. However, some of the new model parameters, including the basal metabolic consumption rate of glucose, and glucose and lactate permeabilities to vasa recta, are not well characterized. Thus, another goal of this study is to identify a set of model parameters that yield model predictions in good agreement with experimental measurements of tissue glucose and lactate concentrations at the papillary tip. In addition, we will address the effect of medullary structural organization on glucose and lactate concentration.

2. Model description

Our model representation accounts for the 3D architecture of the renal medulla of the rat kidney using the "region-based" approach (described further below) developed by Layton and Layton [26]. The current model is extended from previously applied models of the urine concentrating mechanism and oxygen transport and metabolism in the medulla of a rat kidney in an antidiuretic (i.e., water deprived) state [12,13,23,24], to include glucose transport and metabolism and lactate production. A schematic diagram of the model medulla is shown in Fig. 1A. Represented in the model are the descending limbs and ascending limbs, CDs, and vasa recta, which are represented by rigid tubes that extend from the cortico-medullary boundary ($x = 0$) to the papillary tip ($x = L$):

- Two-thirds of the loops of Henle are assumed to turn at the boundary of the OM and IM (marked by a dashed line in Fig. 1A), whereas the remaining one-third of the loops turn at all depths of the IM.

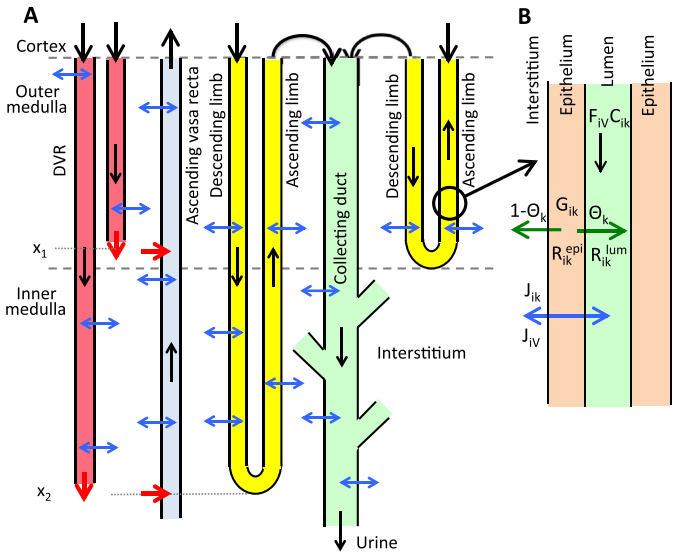

Fig. 1. A, schematic diagram of overall structure of model medulla. **B**, schematic diagram showing key processes involved in the conservation of fluid and solutes in the luminal flow of a tubule i (Eqs. (2) and (3)). Panel **A** depicts a short loop, which consists of a descending limb and a contiguous ascending limb and which turns at the OM-IM boundary, and a long loop that turns within the IM (at x_2). Although only one long loop is shown, the model represents one long loop that turns at every spatial point in the IM. Similarly, only two representative DVR are shown (with one terminating at x_1 and one at x_2), whereas the model represents one DVR that terminates at every spatial point. A representative CD is shown. The black arrows at the cortico-medullary boundary represent boundary flows. The outflow of the ascending limbs determines the inflow of the CD. The red arrows at the DVR outlets denote capillary sources at x_1 and x_2. The net fluid and solute accumulations at those medullary levels are taken up by the ascending vasa recta, as indicated by the red arrows pointing into the ascending vasa recta. The blue arrows represent transmural water and solute fluxes. CD outflow becomes urine. In panel **B**, lumen is surrounded by a layer of epithelial cells. Within the lumen, F_{iV} denotes water flow and C_{ik} denotes the concentration of solute k. Flow direction is indicated by the black arrow. The product $F_{iV}C_{ik}$ gives solute flow rate. The net volumetric consumption rate of a reactive solute is denoted by R_{ik}^{lum} within the lumen and by R_{ik}^{epi} in the epithelia. The epithelial volumetric generation rate of the solute is denoted by G_{ik}. A fraction θ_k of the net generation (or consumption) of the solute by the cells is directed into (or taken out of) the lumen, and indicated by the green arrow; the remainder $(1-\theta_k)$ is directed into (or taken out of) the interstitium. Transmural water and solute fluxes are denoted by J_{iV} and J_{ik}, respectively, and by the blue arrow. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

- The CDs undergo successive coalescences within the IM, illustrated by the "branches" along the IMCD in Fig. 1A.
- Descending vasa recta (DVR) terminate at all depths of the medulla, and are assumed to peel off to supply the capillary plexus.
- Given the extremely important role of red blood cells (RBC) in oxygen transport and metabolism, the model explicitly represents RBC by dividing blood flow in the vasa recta into two compartments: plasma and RBC. The RBC compartment is contained within the plasma compartment. RBCs within vasa recta are represented by rigid tubes and interact with nearby plasma.
- Tubules and vessels interact via the interstitium, extending from the corticomedullary boundary to the papillary tip.
- The model includes only the medulla, thus does not represent the proximal convoluted tubule, where neoglucogenesis occurs. While neoglucogenesis can occur in the proximal straight tubule, which is represented in the model, under certain conditions, for simplicity, glucose production is ignored.

As previously noted, blood flow in the vasa recta is separated into the plasma compartment and the RBC compartment. DVR, which supply the capillary plexus, terminate at all depths of the medulla. The shortest DVR terminates just below the cortico-