Recent advances in renal hypoxia: insights from bench experiments and computer simulations

Anita T. Layton
Department of Mathematics, Duke University, North Carolina
Submitted 11 April 2016; accepted in final form 26 April 2016

Layton AT. Recent advances in renal hypoxia: insights from bench experiments and computer simulations. Am J Physiol Renal Physiol 311: F162–F165, 2017. First published May 4, 2016; doi:10.1152/ajprenal.00228.2016.—The availability of oxygen in renal tissue is determined by the complex interactions among a host of processes, including renal blood flow, glomerular filtration, arterial-to-venous oxygen shunting, medullary architecture, Na\textsuperscript{+} transport, and oxygen consumption. When this delicate balance is disrupted, the kidney may become susceptible to hypoxic injury. Indeed, renal hypoxia has been implicated as one of the major causes of acute kidney injury and chronic kidney diseases. This review highlights recent advances in our understanding of renal hypoxia; some of these studies were published in response to a recent Call for Papers of this journal: Renal Hypoxia.

Renal Architecture and Oxygenation

The kidney receives about 20–25% of the cardiac output, which is among the highest in the body relative to organ weight. Renal blood flow supports glomerular filtration and solute reabsorption. Despite the high renal blood flow and low O\textsubscript{2} extraction, the renal cortex is remarkably susceptible to hypoxia. This apparent paradox may be a result of diffusional shunting of O\textsubscript{2} from arteries to veins, as revealed in experimental studies in rats (23, 42, 49). Such arterial-to-venous (AV) O\textsubscript{2} shunting limits O\textsubscript{2} delivery to the renal cortex. The effects of AV shunting on O\textsubscript{2} delivery to cortical tissues were investigated in a series of modeling studies by Evans and coworkers (13, 14, 29), although a separate modeling study by Olgac and Kurtcuoglu (32) suggests that the amount of AV O\textsubscript{2} is limited. That disagreement may (or may not) be attributed to the radial geometry of the vessels (9, 33).

Compared with the cortex, blood flow to the renal medulla is relatively low. That disparity is a necessity of having an effective urine concentrating mechanism: excessive medullary blood flow may disrupt the axial osmolality gradients generated by countercurrent exchange. On the other hand, insufficient medullary blood flow may give rise to anoxia, causing tubulointerstitial injuries. Adding to the challenges of fully understanding the dynamics of renal oxygenation is the complexity of the functional anatomy of the kidney. In the rodent kidneys, nephrons and vessels have been shown to be organized in a highly structured manner. In the inner stripe of the outer medulla and in the upper inner medulla, descending vasa recta are structurally isolated within tightly packed vascular bundles, separated from the thick ascending limbs and collecting ducts (2, 19, 36, 37, 50). That structural organization likely leads to sequestration of O\textsubscript{2} within the vascular bundles and may have a key impact in the oxygenation of the renal medulla (47). A modeling study by Fry et al. (12) suggests that, in the outer medulla, the compartmentalization of medullary blood flow helps preserve oxygen supply to the inner medulla and maintain a sufficiently high oxygen tension (P\textsubscript{O2}) in that region. However, that arrangement also lowers the P\textsubscript{O2} in the interbundle regions. Consequently, the thick ascending limb cells, particularly those of superficial nephrons, operate near hypoxia (5, 12).

Renal oxygenation is known to be impaired under some pathophysiological conditions. O’Neill et al. (35) compared kidney function and oxygenation in diabetic and control Sprague-Dawley rats and reported that while arterial pressure was similar in both groups, the diabetic rats had reduced baseline P\textsubscript{O2} in both the cortex and medulla. Acute inhibition of the Na\textsuperscript{+}-glucose cotransporter-2 (SGLT2) improved cortical P\textsubscript{O2} in the diabetic kidney but reduced medullary P\textsubscript{O2} in both groups. These results, which are consistent with a study by Layton et al. (20) that used a computational model of a proximal tubule, can be explained by the shift of Na\textsuperscript{+} transport site to further downstream, less efficient nephron segments, such as the thick ascending limbs, which may be at increased risk of hypoxic injury.

Acute Kidney Injury

Acute kidney injury (AKI) is a syndrome associated with a sudden decrease in kidney function or kidney damage within a few hours or a few days. Among humans, ischemia-reperfusion (IR) injury due to sepsis or hypotension is the most common cause of AKI, resulting in acute tubular necrosis (~45% of AKI cases) (25, 27). One of the cellular protective responses to hypoxic conditions is the reduction of mitochondrial production of reactive oxygen species (ROS) by shifting glucose metabolism to glycolysis via the hypoxia-inducible factor (HIF)-1 pathway. Human mucin 1 (MUC1) is known to be induced by hypoxia and to enhance HIF-1 activity in cultured
epithelial cells (4). Pastor-Soler (39) used a mouse model of kidney IR injury to assess the role of mucin 1 (Muc1) in AKI (39). They reported that, in the absence of Muc1, renal tubules suffered more severe injuries and recovery of kidney function and morphology was impaired. Furthermore, the level of HIF-1α was Muc1 dependent during IR injury. Taken together, their data suggest that, similar to human MUC1, mouse Muc1 enhances the HIF-1 protective pathway during IR injury.

Protein kinase C (PKC) is a family of serine- and threonine-specific protein kinases that can be activated by calcium and the second messenger diacylglycerol. Members of the PKC family regulate a number of processes that contribute to tissue damage and recovery. The effects of PKC-ε depend on cell type and injury. For instance, the activation of PKC-ε has been associated with protection from ischemic injury in the heart (3), artery (45), and intestine (48), whereas PKC-ε-deficient septic mice exhibit less inflammation (44). In the kidney, activation of PKC-ε appears to have detrimental effects, including the initiation of mitochondrial dysfunction and fragmentation in the proximal tubule (30, 31). Rong et al. (41) investigated the role of PKC-ε in AKI and IR injury using a mouse kidney transplantation model. Their data suggest that local renal PKC-ε expression mediates proinflammatory signaling and that inhibition of PKC-ε may be used to prevent hypoxia-induced kidney injury.

There appears to be contradictory evidence as to whether AKI can occur in the absence of widespread renal tissue hypoxia. Renal tissue hypoxia has been observed during the acute phase of reperfusion after ischemia induced by blockage of the aorta that supplies the kidney (21, 22, 43). On the other hand, some clinical studies have revealed relatively well-preserved oxygenation in the nonfunctional transplanted kidney (34, 40). To resolve this controversy, Abdelkader et al. (1) measured renal O₂ delivery, O₂ consumption (QO₂), and tissue Po₂ in the cortex and inner medulla of the rat kidney during reperfusion after a period of ischemia. They failed to detect hypoxia using Clark electrodes but were able to detect cellular hypoxia with pimonidazole adduct histochemistry. Their findings suggest that hypoxia may well be present even if it cannot be detected electrochemically.

Despite the substantial progress that has been made in the understanding of the pathophysiology of AKI, clinical outcome of AKI remains poor and more effective therapeutic strategies are needed. One such strategy is ischemic preconditioning. While somewhat counterintuitive, ischemic preconditioning has been shown to reduce susceptibility to IR injury (28). In a recent review, Kapitsinou and Hasse (18) discuss the roles of HIF and prolyl-4-hydroxylase domain (PHD) proteins in mediating ischemic preconditioning through the coordinated activation of renoprotective signaling pathways. These findings suggest that HIF-activating compounds may be used to induce preischemic activation of these signaling pathways to mimic normal hypoxia response, which would protect the kidney from ischemia and promote renal tissue repair.

**Chronic Kidney Diseases**

The transition from AKI to chronic kidney diseases (CKD) has yet to be completely understood (46), and the extent to which treatment of AKI may suppress CKD progress remains controversial, with supportive evidence found in some studies (17, 26), and not others. In a recent study, Gobe et al. (15) assessed the degree to which recombinant human erythropoietin (rhEPO) treatment may retard the progression from AKI to CKD. Their study was motivated by the observation that treatment of IR injury with rhEPO reduces AKI and improves kidney function. In their rat IR injury model, they found that administration of rhEPO at the time of reperfusion yielded function and morphological improvements of the kidney 4 days post-IR. Unfortunately, after 28 days, rhEPO treatment led to elevated tubulointerstitial fibrosis (15).

It is generally believed that hypoxia plays a key role in the initiation and progression of CKD (10). However, despite considerable efforts, direct evidence of casualty remains lacking. To assess the validity of the “chronic hypoxia hypothesis,” one may study models of CKD that develop after AKI. Papatsova et al. (38) used as an AKI model Lewis rat after syngenic renal transplantation. They assessed mitochondrial function, in vivo kidney function, oxygen metabolism, renal oxidative damage, and tubulointerstitial injury 2 wk after IR injury. They reported uncoupling of mitochondrial respiration in the transplanted kidney. Their results indicate that increased mitochondrial uncoupling and the associated increase in renal QO₂, lead to renal hypoxia early after IR injury, and this event precedes damage.

Increased QO₂ was also observed in the early subtotal nephrectomy (STN) model of CKD in rats (8, 16), despite a substantial reduction in glomerular filtration rate. By lowering tubular QO₂, kidney function may be improved (7, 8). To better understand the possible underlying cellular mechanisms for improving renal QO₂ and kidney function, Li et al. (24) focused on HIF-1 and AMP-activated protein kinase (AMPK) and on the mechanisms by which they may facilitate cellular adaptation to hypoxia. They found that in the STN model of CKD, activation of HIF-1α may improve cell survival by limiting protein synthesis and inhibiting apoptosis. Furthermore, HIF-1α restores AMPK activation in the STN kidney. The conclusion of that study is that HIF-1α and AMPK, the actions of which appear to be linked at a molecular level, may be key components of a coordinated cellular response to hypoxia.

**Conclusion**

CKD is a growing public health and economic burden. In the United States, 1 in 10 adults, or more than 20 million, have some levels of CKD. In 2011, patients with CKD incurred $45.5 billion in Medicare expenditures. As previously noted, a strong correlation has been demonstrated between AKI episodes and subsequent development of CKD (6). Other major risk factors for developing CKD include chronic diseases such as diabetes and hypertension (11). Further research is needed to provide better insights into the mechanisms that underlie the pathways for developing CKD. Once this critical barrier is overcome, more effective therapies may be developed.

**GRANTS**

This work was supported in part by National Institute of Diabetes and Digestive and Kidney Diseases Grants DK-089066 and R01-DK-106102.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).
REFERENCES


