Initiation and Progression of Chronic Kidney Disease
Can We Definitively Test the Chronic Hypoxia Hypothesis?

Roger G. Evans, Paul M. O’Connor

Fifteen years ago, Fine et al. first presented the chronic hypoxia hypothesis about the progression of chronic kidney disease. Subsequent refinement of this hypothesis has led to the proposition that multiple forms of chronic kidney disease are, at least partly, driven by a vicious cycle of hypoxia, renal inflammation, and fibrosis, which inexorably leads to failure of glomerular filtration (Figure). Fine et al. identified some of the critical pieces of evidence required to confirm or reject this hypothesis. The chronic hypoxia hypothesis predicts that renal tissue hypoxia can initiate signaling events that lead to renal damage and fibrosis. This part of the hypothesis has certainly been confirmed. As reviewed in detail by Mimura and Nangaku and by Fine et al., hypoxia can lead to apoptosis, epithelial-to-mesenchymal transition, inhibition of the expression of collageng and increased expression of metalloproteinase inhibitor 1, and stimulation of superoxide production via mitochondria, xanthine oxidase, and NADPH (nicotinamide adenine dinucleotide phosphate) oxidase. However, it must also be said that much of the evidence to support these statements comes from in vitro studies, often using cultured cells, rather than from in vivo studies using experimental models of chronic kidney disease. Thus, we still have some way to go to understand the molecular mechanisms linking hypoxia and the progression of chronic kidney disease.

The chronic hypoxia hypothesis also predicts that progression of chronic kidney disease should be associated with microvascular changes that limit oxygen delivery to renal tissue and mechanisms that drive dysoxia, the inefficient use of oxygen. There is now strong evidence that this is the case. It is now well established that capillary rarefaction, driven by impaired endothelial cell proliferation, plays a major role in the progression of chronic kidney disease. It is also well established that oxidative stress leads to increased renal oxygen consumption by reducing NO bioavailability, thus driving inefficient use of oxygen within renal mitochondria. The molecular mechanisms that limit endothelial cell proliferation and drive dysoxia in kidney disease represent a rich field for the development of new therapeutics. That is, if the chronic hypoxia hypothesis is correct, these mechanisms represent therapeutic targets that might allow the vicious cycle (Figure) to be broken.

Another critical prediction of the chronic hypoxia hypothesis is that decreased tissue oxygenation should be observable before the development of overt kidney disease. The best evidence for this comes from the studies by Manotham et al. They observed tissue hypoxia, as assessed by pimonidazole immunohistochemistry, in the early phases of the remnant kidney model of chronic kidney disease. However, to critically evaluate the chronic hypoxia hypothesis, the temporal relationship between renal tissue hypoxia and the progression of renal disease must be evaluated in multiple experimental models. One factor that has limited progress in this respect has been the lack of methods to allow renal tissue oxygen tension to be continuously measured in unanesthetized animals. The recent development of a telemetric method for measurement of renal tissue oxygen tension in rats may provide the impetus for further studies in this field.

Perhaps the strongest evidence for the chronic hypoxia hypothesis would come from the demonstration that renal tissue hypoxia per se, without the confounding effects of other insults, leads to nephropathy. In the current issue of Hypertension, Friederich-Persson et al. have taken an ingenious approach that has generated just such evidence. They administered the mitochondrial uncoupler 2,4-dinitrophenol to rats for a 30-day period. This treatment increased renal oxygen consumption and led to renal tissue hypoxia, but not systemic hypoxemia. Critically, 2,4-dinitrophenol treatment was associated with the development of proteinuria, increased renal vimentin expression (a marker of tubular damage), and infiltration of inflammatory cells. Remarkably, these effects were seen in the absence of hypertension, hyperglycemia, and oxidative stress or even in a statistically significant deficit in glomerular filtration rate. We think this is an important development in the field because it provides the first real evidence that renal tissue hypoxia can, in itself, initiate the development of chronic kidney disease.

The authors’ demonstration of interstitial macrophage accumulation in the kidneys of 2,4-dinitrophenol–treated animals points to hypoxia as a stimulatory event leading to inflammation. Infiltration of immune cells is a common phenotype in both human and animal models of renal disease and mounting evidence indicates that these inflammatory cells play a major role in progression of disease. Perhaps the major unresolved question in this field is what drives the infiltration of immune cells into the kidney during the development of disease?
Infiltration of immune cells might be secondary to cellular injury or tissue oxidative stress. The results of the current study do not exclude these possibilities. However, the results of in vitro studies provide evidence that hypoxia itself can activate the immune system. Given that, Friederich-Persson et al observed renal macrophage accumulation in the absence of overt injury or evidence of significant oxidative stress; the authors’ data provide perhaps the most compelling in vivo evidence that hypoxia alone is capable of initiating an immune response within the kidney.

As the authors themselves acknowledge, much still remains to be done to confirm the significance of their findings. First, they could not exclude the possibility that their findings could be explained by direct nephrotoxic effects of 2,4-dinitrophenol. One way to address this would be to examine the effects of other agents that act to increase renal oxygen consumption. The chronic hypoxia hypothesis would predict that any agent that chronically increases renal oxygen consumption, and so induces renal hypoxia, should initiate the development of chronic kidney disease. Another way in which the chronic hypoxia hypothesis could be tested would be to examine whether chronic hypoxemia, and so reduced renal oxygen delivery, exacerbates the development of chronic kidney disease. In addition, it might also be possible to examine whether chronic hypoxemia can blunt the development of chronic kidney disease. Such an approach is feasible in experimental animals because, unlike most other organs, the kidney does not mount a hyperemic response during hypoxemia or a vasoconstrictor response to hyperoxemia. Epidemiological evidence provides tantalizing support for the idea that chronic hypoxemia, as experienced by those living at altitude, can exacerbate the progression of chronic kidney disease. But controlled studies in experimental animals are warranted because such an approach may well provide insights into the mechanistic links between hypoxia and the progression of chronic kidney disease.

In conclusion, 15 years after it was first presented, the chronic hypoxia hypothesis remains to be adequately tested. However, the new studies by Friederich-Persson et al, presented in the current issue of *Hypertension*, bring us one step closer.

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**References**

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