The chronic hypoxia hypothesis: the search for the smoking gun goes on

Roger G. Evans,1 Connie P. C. Ow,1 and Peter Bie1,2

1Department of Physiology, Monash University, Melbourne, Australia; and 2Department of Cardiovascular and Renal Research, Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark

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A role for tubulointerstitial hypoxia in the initiation and progression of chronic kidney disease (CKD) was first proposed by Fiehé and colleagues (6). Since then, a considerable body of evidence has accumulated in support of this concept (14). However, it must also be acknowledged that there is currently no “smoking gun” providing direct evidence of causality (5).

At least five lines of evidence are required to assess the validity of the “chronic hypoxia hypothesis.” 1) Renal tissue hypoxia should be a common finding in animal models of CKD. This has certainly been the case in nearly all animal models studied to date (13), although recent clinical studies using blood oxygen level-dependent magnetic resonance imaging have been unable to show a strong relationship between renal hypoxia and the severity of CKD (11). 2) Renal hypoxia should activate signaling cascades that drive processes such as inflammation, fibrosis, and capillary rarefaction. There is certainly good evidence for this from in vitro studies (14). There is also good evidence of the development of inflammatory and fibrotic processes, tubular damage, and capillary rarefaction in CKD (14). However, as with any slowly evolving pathology, it has been difficult to show, in the intact animal, whether these processes are driven by hypoxia or vice versa. 3) Renal hypoxia itself should induce CKD. In support of this proposition, Friederich-Persson and colleagues have recently shown that chronic treatment with dinitrophenol (9) or triiodothyronine (8) can increase renal oxygen consumption, renal hypoxia, proteinuria, and renal inflammation in the absence of oxidative stress. 4) Hypoxia should precede the development of renal dysfunction in experimental models of CKD. This has been demonstrated in diabetic nephropathy (3) and the remnant kidney model of CKD (10). 5) It should be possible to prevent initiation and progression of CKD by preventing renal hypoxia. This final line of evidence has been the most difficult to generate, chiefly because it has proved difficult to find ways to selectively increase renal oxygenation without introducing a host of confounding factors into the experimental paradigm. However, it arguably represents the best approach for testing the chronic hypoxia hypothesis because such interventions would allow demonstration of a causal relationship between hypoxia and the progression of CKD.

One way to potentially overcome the difficulties associated with teasing out the temporal associations of hypoxia and the progression of CKD is to study models of CKD that develop after acute kidney injury (14). Such models have the advantage that the initiation of disease can be attributed to a discrete stimulus. In a recent issue of the American Journal of Physiology-Renal Physiology, Papazova and colleagues (12) present observations of renal oxygenation 2 wk after syngenic renal transplantation, used as a model of ischemia-reperfusion injury. They provide evidence for uncoupling of mitochondrial respiration in the transplanted kidney, presumably via uncoupling protein 2. Uncoupling of mitochondrial respiration was assessed in vitro, as the decrease in oxygen consumption that occurred after inhibition of uncoupling protein with guanosine diphosphate. The apparent uncoupling of mitochondrial respiration was associated with augmented renal oxygen consumption in the whole kidney and hypoxia in the renal corticomedullary border. Importantly, at this 2-wk time point there was no evidence of oxidative damage (as assessed by renal content of protein carbonyls and urinary excretion of thiobarbituric acid-reactive substances), proteinuria, or impaired function in the transplanted kidney. We believe this model provides an excellent opportunity for further testing of the chronic hypoxia hypothesis. Studies of the progression of renal dysfunction, tissue damage, and renal oxygenation in this model may allow the temporal associations between these factors to be identified, thereby providing a more definitive test of the chronic hypoxia hypothesis.

Papazova and colleagues went on to examine the effects of antioxidant treatment (mito-TEMPO), targeted to mitochondria, on mitochondrial uncoupling and renal oxygenation after renal transplantation. They found that pretreatment of the donor and the transplanted kidney with mito-TEMPO significantly blunted, but did not completely normalize, their measure of mitochondrial uncoupling. However, this treatment did not appear to greatly influence whole kidney oxygen consumption or renal tissue PO2. Their interpretation of these findings was that treatment with mito-TEMPO may have had limited efficacy, so that the kidney remained hypoxic because of the residual level of mitochondrial uncoupling. This could certainly be the case, but an alternative explanation is possible. Mitochondrial uncoupling may be one of multiple factors that contribute to the augmentation of renal oxygen consumption after renal transplantation, or other forms of ischemia-reperfusion injury. Superoxide not only activates mitochondrial uncoupling proteins but also reduces the bioavailability of nitric oxide. Reduced bioavailability of nitric oxide, in turn, can increase renal oxygen consumption by multiple mechanisms, including by reducing the efficiency of oxygen utilization within mitochondria and by enhancing tubular sodium reabsorption (4). Furthermore, ischemia-reperfusion injury can result in an array of changes to tubular cell structure and metabolism, tubular dynamics, and the intracellular localization of transport proteins, including Na+-K+-ATPase (2). The extent to which these factors persist during the subacute period after ischemia-reperfusion injury, such as the 2-wk time point studied by Papazova and colleagues (12), remains to be determined. It should also be acknowledged that mitochondrial uncoupling in the kidney can be mediated by mechanisms in.

Address for reprint requests and other correspondence: R. Evans, Dept. of Physiology, PO Box 13F, Monash Univ., Victoria 3800, Australia (e-mail: roger.evans@monash.edu).
addition to uncoupling protein 2 (e.g., the adenine nucleotide transporter), at least after expression of uncoupling protein 2 has been knocked down (7). Thus, given the complexity of the determinants of renal oxygenation in the period of transition from acute kidney injury to CKD, it appears unlikely that a single “silver bullet” treatment will reveal the smoking gun required to definitively test the chronic hypoxia hypothesis.

An additional major problem in this field is our lack of understanding of the sequence of events that drive oxidative stress and hypoxia after renal ischemia-reperfusion. Renal hypoxia occurs during ischemia, and to a variable extent during the immediate period of reperfusion (1). Reperfusion also triggers production of superoxide and other free radicals, from a variety of sources (2). Available evidence supports the hypothesis of a vicious cycle of hypoxia, oxidative stress, and tissue damage during reperfusion (Fig. 1). Central to the field is our lack of understanding of the relative importance of the various potential entry points to this vicious cycle.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS


REFERENCES


