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1 Correspondence to Dr. A.C. Schoolwerth, Division of Nephrology, Box 160 MCV Station, Richmond, VA 23298-0160.

Remnant Kidney Oxygen Consumption: Hypermetabolism or Hyperbole?1

R. Michael Culpepper and Anton C. Schoolwerth2

R.M. Culpepper, A.C. Schoolwerth, Division of Nephrology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA


ABSTRACT

On the basis of observations in surgically created remnant kidneys of rat and dog, a novel hypothesis for progressive injury in the setting of reduced renal mass has been put forth. Both rat and dog remnant kidneys exhibit significant hypertrophy that is accompanied by an increased rate of oxygen consumption (QO2) per remaining nephron but not per gram of tissue. This putative "hypermetabolism" is seen in the face of progressive scarring of the tubulointerstitial compartment of the remnant kidney, and interventions that reduce QO2 in these models have been associated with reduced tissue injury in previous studies. The proposed pathway by which an increase in QO2 leads to cellular damage is via the production of oxygen-reactive species or free radicals. In this article, the available data upon which this "hypermetabolism" hypothesis is based are reviewed and the constructs within which these data have been analyzed are examined. From these considerations, a set of questions not yet answered that may serve to direct more fruitful query into this intriguing problem is posed.

Key Words: Oxygen radicals, oxidative stress, kidney hypertrophy, interstitial nephritis, nephron loss

In recent years, the view that progressive nephron destruction results from a limited number of common pathways that are independent of the underlying disease process has become increasingly accepted (1). Considerable experimental activity has been devoted to an elucidation of these pathways and their respective mechanisms of injury (2). Of special inter-

est are the functional adaptations that result from the loss of renal mass because these may be maladaptive in the sense that they contribute further to renal injury. The remnant kidney model, in which both morphologic and functional alterations occur, has been used extensively in these investigations. These changes include compensatory renal growth and adjustments in renal hemodynamics, tubular transport, and metabolic activity. Recently, it has been suggested that marked increases in oxidative metabolism occur in the residual renal tissue and that this "hypermetabolism" may be deleterious, providing a pathway for tubular damage and disease progression (3,4). In this editorial review, we review the data upon which the "hypermetabolism hypothesis" is based and comment on its possible role in promoting renal injury. These issues are considered in the context of changes known to occur with compensatory renal growth.

COMPENSATORY RENAL GROWTH

With the removal of significant renal tissue, such as with unilateral nephrectomy or creation of the remnant kidney (usually % nephrectomy), substantial compensatory renal growth occurs in both adult and young animals. As described in a recent comprehensive review (5), all component parts of the nephron are enlarged in compensatory growth with proximal tubular mass increasing out of proportion to that of other nephron segments. Increases in tubular length, diameter, and volume are noted. Cell surface area also increases, with marked increases occurring particularly in the basolateral membrane. The enlargements in cell diameter and volume reflect an increase in cell size, i.e., hypertrophy. Biochemical measures of hypertrophy include increases in protein content per cell, protein content per unit DNA, or RNA content per unit DNA. Normalization to unit DNA is based on the assumption that the amount of DNA in each nucleus remains constant (5).

With the above measurements, some 80% of kidney growth in adult rats after % nephrectomy can be ascribed to hypertrophy, predominantly in proximal tubules (5,6). A small, but consistent, increase in total DNA content (15 to 20%) reflects an increase in cell number, i.e., hyperplasia. After unilateral nephrectomy, RNA and protein content per unit DNA, as well as kidney weight, increase within 12 h: the RNA/DNA ratio increases by 20 to 30% within 48 h.
This hypertrophic response is exaggerated in animals placed on high-protein diets; in fact, the latter induces renal growth without the stimulus of a decrease in renal mass. Other changes have also been observed to accompany compensatory renal growth. These include an increase in the ratio of mitochondria to nuclei, an enhanced activity of Na,K-ATPase in cortex and outer medulla, and increased activity of other enzymes including choline kinase, an enzyme necessary for membrane phospholipid synthesis (5).

**BASIS OF RENAL “HYPERMETABOLISM HYPOTHESIS”**

The “hypermetabolism hypothesis” evolved from a series of observations made in the remnant rat kidney (3,4). Data from this model had consistently demonstrated the development of glomerulosclerosis, hypertension, and progressive renal failure. These responses have been related to unfavorable adaptive changes in renal hemodynamics, especially the elevation in glomerular capillary hydraulic pressure, which drives an increased GFR in the remnant kidney. Further, the rate of nephron destruction was shown to be ameliorated by the feeding of a low-protein diet, a maneuver that substantially reverses these glomerular hemodynamic changes (7). Subsequent data were interpreted to indicate that primary tubular and/or interstitial injury might contribute significantly to progressive nephron destruction in this same model of reduced renal mass. Nath and coworkers (8) demonstrated that ammonia activated the alternate complement pathway in the remnant kidney, leading to tubulointerstitial damage. Those workers showed that bicarbonate feeding prevented the adaptive increase in ammonium production in residual renal tissue and led to an amelioration in tissue damage. Previous studies had shown that the enhanced ammoniagenesis in this model was significantly reduced by dietary protein restriction (9). Recently, Harris and colleagues (3) demonstrated that both a low-phosphate diet, separate from dietary protein content, and the calcium channel antagonist verapamil exerted protective effects on the residual nephrons in the rat remnant kidney model (10,11).

Using the isolated perfused rat remnant kidney, Harris et al. (3) found that oxygen consumption (QO2) per remaining nephron was increased almost threefold compared with that in normal kidneys. The remnant kidney, representing only one sixth of the original renal mass, had achieved 80% of normal kidney weight and exhibited a GFR and tubular reabsorption of sodium that were 51 and 40%, respectively, of normal. However, when factored per gram kidney weight, QO2 was identical in remnant and normal kidneys. Of great interest was the demonstration that basal QO2 consumption, defined as QO2 unassociated with tubular sodium transport and presumably related to basic cell maintenance, was also not different in remnant and normal kidneys when expressed per gram kidney weight. A remarkable three quarters of total QO2 was unassociated with the “work” of sodium reabsorption in this preparation. In the same study (3), both verapamil and dietary phosphate restriction decreased the QO2 of the remnant kidney, an effect that appeared to be independent of sodium transport. More recent work from the same laboratory (7) showed that QO2 per gram tissue, measured both in vivo and in the perfused kidney in vitro, was significantly higher in remnant kidneys from rats fed diets containing 50% compared with 4% protein.

Nath and coworkers (12) have also measured QO2 in vivo in the remnant rat kidney. Compared with that in normal rat kidneys, the QO2 per remnant kidney was not significantly different. However, because of the reduced nephron number in the remnant, QO2 per nephron was more than two-fold greater than that in normal kidneys. In an attempt to identify the consequences of this putative hypermetabolism, two indices of “oxidant stress” were measured (12). Tissue malondialdehyde (MDA), a conventional marker of oxidant stress related to membrane lipid peroxidation, was not different in remnant compared with normal kidneys when expressed as nanomoles of MDA per milligram of protein. In fact, the MDA content was reduced in remnant kidneys. A late increase in remnant kidney MDA content was found only in rats fed 30% compared with 6% protein diets. An increase in remnant kidney urinary excretion of products of lipid peroxidation was seen, providing a partial explanation for the failure to detect significant tissue levels of MDA (12). Kidney glutathione and glutathione redox ratios were also different in remnant compared with normal control kidneys.

Altogether, these studies indicate that the increase in QO2 that occurs in the remnant rat kidney compared with control kidneys is proportional to the degree of tissue hypertrophy, so that QO2 per gram kidney weight remains unchanged. Because the compensatory growth occurring in residual nephrons of the remnant kidney is due to hypertrophy and not hyperplasia, these findings indicate a substantial increase in QO2 per renal tubular cell in the remnant kidney. However, it appears that this increase in QO2 is appropriately proportioned to the increase in cell (and protein) mass. The remnant kidney is created by a drastic reduction in nephron number. Because no new nephrons are formed in the adult remnant kidney model, there is an obligatory twofold to threefold increase in QO2 relative to each residual nephron.

In contrast to these data in the rat, Fine demonstrated a different response of the remnant dog kidney (13). Impressive renal growth was observed in
the dog. Despite % nephrectomy, the remnant kidney weight actually exceeded that of a normal dog kidney. Interestingly, $Q_O_2$ per kidney and per gram kidney was significantly less in the remnant dog kidney compared with that in control kidneys. An increase in $Q_O_2$ in these remnant kidneys compared with control kidneys could be demonstrated only when $Q_O_2$ was normalized to GFR. The latter function was chosen as an index of oxygen-consuming renal work on the basis of sodium delivery to the tubule. Although nephron counts were not performed in this study, the $Q_O_2$ per nephron would be augmented in remnant compared with control kidneys on the basis of the argument given above. Overall, the increase in $Q_O_2$ was substantially less than that observed in the rat.

Moreover, because $Q_O_2$ per gram kidney was significantly less in remnant compared with control dog kidney, the quantitative relations between cell function and $Q_O_2$ per cell are far from clear in the dog. The author speculated that a possible relationship existed between these findings and previous observations that the dog remnant kidney infrequently develops glomerulosclerosis and progressive nephron destruction compared with the rat remnant kidney (14, 15).

Overall, the data from the rat model demonstrate a consistent response with respect to $Q_O_2$. Likewise, there is some consistency in the observations relating the increased $Q_O_2$ to metabolic functions other than sodium reabsorption. However, among these few studies, there are significant differences in experimental technique (in situ versus in vitro studies, whole animal versus organ studies, etc.), which make direct comparison of data impossible. Consideration of the dog model adds complexity from the species difference and the difference in the expression of the experimental results. These problems with interpretation of results from remnant kidney studies are by no means unique to this line of inquiry (16); rather, they indicate a need for prudence when extrapolating such results to the case of human disease.

**RELATIONSHIP OF $Q_O_2$ TO INJURY**

The “hypermetabolism hypothesis” is an intriguing concept, suggesting that the enhanced $Q_O_2$ per nephron might be a proximate cause to the development of progressive renal injury in the remnant kidney. In order to evaluate this hypothesis at the present time, and to test it rigorously in the future, several issues must be evaluated and discussed. The data from the above studies and information from other models of hypertrophy and organ injury provide a framework for inquiry into the relationship between oxygen use and nephron injury in the remnant kidney. We now put forth a number of questions that seem most relevant in exploring the biology that underlies the above observations.

**What Is the “Metabolic Unit” of the Kidney?**

In order to define excessive rates of $Q_O_2$, substrate utilization, or metabolite production, it is necessary to find a common ground for comparison between normal and remnant kidneys. That is, the “metabolic unit” of the kidney may differ from the anatomic unit (the cell or a given nephron segment) or from the functional unit (the nephron). This problem is compounded in the case of the remnant kidney because of the cellular hypertrophy and the increased workload per residual nephron. Because the remnant kidney is created by a reduction in nephron number, any operational characteristic of that kidney that is maintained at a higher fractional level than that of the fractional reduction in nephron number could be said to be “hyper”-functional. For example, the maintenance of GFR at 60% that of normal in the face of a reduction in nephron number to 20 to 40% normal, both typical for the rat model (9, 12), yields an obligatory “hyperfiltration” per residual nephron. It is in no way clear that $Q_O_2$ bears so close a physiologic relation to the nephron unit as does glomerular filtration. On the other hand, it has been suggested that oxygen use in the kidney can be separated into one component related to basic cell function (basal $Q_O_2$) and a second related to the magnitude of required sodium reabsorption (17, 18). With the increase in cell mass, one might speculate a priori that renal $Q_O_2$ must increase proportionately to maintain cellular integrity. It is also reasonable to consider that an increase in $Q_O_2$ could appropriately be linked to the increased demand for tubular work. These considerations evoke a second question.

**To What Purpose Is $Q_O_2$ in the Remnant Kidney Devoted?**

Given earlier demonstrations of a linear relationship between renal $Q_O_2$ and tubular sodium reabsorption and the fact that sodium transport relative to renal mass increases in the remnant kidney, a logical prediction would be that $Q_O_2$ rises in order to accommodate the increased need for sodium transport. However, the data from the studies cited above provide no support for this hypothesis. Specifically, the studies of Harris et al. (3) in the in vitro perfused remnant rat kidney demonstrated parallel slopes for the relationship of $Q_O_2$ to tubular sodium reabsorption, with the majority of the increase in $Q_O_2$ unassociated with sodium transport. Furthermore, both verapamil and a low-phosphate diet reduced $Q_O_2$ in these kidneys without affecting the rate of sodium reabsorption. These relationships are depicted in Fig-
Figure 1 for the remnant rat kidney perfused in vitro (3) and for the remnant dog kidney (13). The intercept with the ordinate has been interpreted to represent the basal component of $Q_02$ not related to net sodium transport but dedicated to cellular metabolism and maintenance. The slope, by indicating the increment in $Q_02$ required for each unit increase in sodium reabsorption, represents the degree of coupling between cellular metabolism and transport work. In vitro studies in rats with remnant kidneys consuming high- or low-protein diets showed the same dissociation of $Q_02$ and sodium transport (7). Thus, it seems that the bulk of the increase in $Q_02$ in the remnant rat kidney goes to support some element of cell function apart from the "workload" of the nephron, sodium transport. This finding has some homology with results from studies of myocardial hypertrophy. Strauer (19) studied humans with hypertensive cardiac hypertrophy and normal left ventricular wall stress. In these subjects and in normal controls, total ventricular $Q_02$ was linearly correlated to left ventricular mass but bore no relationship to indices of ventricular work such as cardiac index, stroke work index, or isovolumetric contractility index (19). Taken together, these sets of data indicate that cellular hypertrophy obligates an increase in $Q_02$ that parallels cell mass. By extension, one could argue that $Q_02$ relative to cell mass is a more fitting comparator than $Q_02$ factored by a work function of the nephron.

By What Mechanism Would an Increase in $Q_02$ Injure Cells?

The most reasonable first hypothesis to address this question invokes the generation of oxygen-reactive species. Current evidence that free radicals participate in the pathogenesis of progressive renal injury comes predominantly from indirect studies. Protection from injury by supplementation of free radical scavengers (20) or promotion of injury by depletion of antioxidants (21) forms the basis for arguments that oxygen-reactive species contribute to progressive nephron loss. Indeed, Nath et al. (12) sought evidence for an increase in oxidant stress in the remnant kidney but found scant support for its existence.

In order for such a mechanism to exist at all, one must posit a reasonable source of the oxygen radicals. Potential sources include "leak" of electrons from mitochondria, production subsequent to arachidonic acid metabolism via cyclooxygenase, production through the xanthine oxidase enzyme, and release of reactive species from leukocytes (22,23). There being no compelling evidence for the latter two mechanisms in the remnant kidney, only the first two will be considered.

Although there does appear to be greater arachidonic acid metabolism in the remnant kidney (24), this important source of oxygen free radical generation could not be equated with metabolism per se. When compared on an equimolar basis per remnant nephron, the increase in total prostaglandin excretion from the remnant kidney, ≈0.22 pmol/nephron/24 h (24), is a millionfold less than the increase in $Q_02 \approx 4.7 \times 10^5$ pmol/nephron/24 h (12). That leaves an increased mitochondrial "leak" of electrons as the only source for the generation of oxygen-reactive species linked directly to cellular metabolism.

The passage of electrons along the mitochondrial respiratory chain results in a loss from electron carriers of some electrons that subsequently react with molecular oxygen to generate the superoxide anion radical (22,23):

$$e^- + O_2 = O_2^-.$$ 

The rate of superoxide radical production increases in most cells as the ambient partial pressure of oxygen ($P_O2$) rises and, in bacteria, increases with changes in metabolic substrates that increase respiration (25). However, cells have a ready defense from this source of superoxide radical in the form of superoxide dismutase (SOD), which catalyzes the conversion of $O_2^-$ into $H_2O_2$ and $O_2$ (19,23,25). In bacteria and in rat lung, SOD is induced by the same measures that increase the generation of oxidizing species so that the whole cell production of the superoxide radical is not detected (23,25). There are, to our knowledge, no direct measures in the remnant kidney of...
the capacity for superoxide generation by mitochondria nor are there measures of the level of SOD activity, the latter being an index to the ambient rate of superoxide generation in situ.

SUGGESTIONS FOR FUTURE DIRECTIONS

As indicated in the title, the first issue that should be resolved is whether the remnant kidney consumes oxygen at a rate that represents "hyper"metabolism. This will necessitate defining with greater certainty the "metabolic" unit (base or denominator of comparison) of the kidney. For the present, we would argue that all available data point to the cell as being that unit. It then follows that \( Q_{O_2} \) should be expressed as some measure of cell size or mass. For the case of the remnant kidney, \( Q_{O_2} \) should be normalized to gram kidney weight. However, this should represent only a working definition. There may well be other indices of cell mass or hypertrophy that, with further investigation, will reveal the proper level of \( Q_{O_2} \) relative to cell size in both normal and remnant kidneys.

It is also critical to examine the oxygen-consuming metabolic functions of both normal and remnant kidneys in order to ascribe any given level of \( Q_{O_2} \) to the function(s) being supported. Because the data at hand do not indicate a need for extraordinary \( Q_{O_2} \) to support sodium reabsorption in the remnant kidney, it may well be that some cell homeostatic process is responsible for the shift in \( Q_{O_2} \) described in these kidneys. There certainly should be additional efforts to correlate \( Q_{O_2} \) with the sodium-absorbing work of the remnant kidney. The observations of Harris et al. (3) also raise the question of the pathway(s) by which enhanced ATP production, reflected by an increased \( Q_{O_2} \), is used. This is especially interesting in light of the hypothesis of Halperin and coworkers that, in the normal dog kidney, the rate of ATP utilization may set the upper limit on the rate of ATP production by processes such as ammoniagenesis (26,27).

It is intriguing that a calcium channel blocking agent reduces \( Q_{O_2} \) but not net sodium absorption in the remnant kidney. This, for instance, might point to an enhanced calcium "leak" into hypertrophied cells with the resulting requirement for increased oxygen expenditure to maintain a homeostatic level of intracellular calcium. Alternatively, at any given level of \( Q_{O_2} \), the percentage of \( Q_{O_2} \) devoted to processes such as gluconeogenesis or ammoniagenesis in remnant kidney cells could be quite different from that of normal, nonhypertrophied cells. In each of these cases, the primary pathway associated with cell injury might lie with the function requiring a higher \( Q_{O_2} \) in the remnant kidney cell. Oxidative metabolism per se would not constitute a part of that pathway but, rather, would merely serve as an index to its activity. The apparent lack of increase in \( Q_{O_2} \) per unit mass of the dog remnant kidney and the lack of injury in these kidneys seem to speak on behalf of such an allocation of \( Q_{O_2} \) among different functions in the dog as compared with the rat.

Finally, more direct measures need to be applied to the question of whether increased generation of oxygen-reactive species exists in the remnant kidney and whether that kidney is capable of mounting an appropriate antioxidant defense. Some of this information might come from the measurement of the oxidative capacity of mitochondria isolated from hypertrophied kidney cells, from the detection of oxygen-reactive species in the incubation medium of such mitochondria, and from the respiratory efficiency of these mitochondria. For the case of the defense mechanisms, it is possible to measure directly the activity of protective enzymes such as SOD and superoxide catalase. The induction of these enzymes with hypertrophy and/or hyperbaric \( O_2 \) would provide further correlative data to judge the defense posture of the remnant kidney cell.

The data upon which the "hypermetabolism hypothesis" is based are intriguing and provocative. We believe that the studies thus far provide a frame of reference for plotting and interpreting the metabolic studies suggested above. On the other hand, it seems premature to ascribe the associated pathology of the rat remnant kidney to a parameter that is itself incompletely defined.

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