Review

Activation of the Renin-Angiotensin System and Chronic Hypoxia of the Kidney

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Recent studies emphasize the role of chronic hypoxia in the kidney as a final common pathway to end-stage renal failure (ESRD). Hypoxia of tubular cells leads to apoptosis or epithelial-mesenchymal transdifferentiation, which in turn exacerbates the fibrosis of the kidney with the loss of peritubular capillaries and subsequent chronic hypoxia, setting in train a vicious cycle whose end-point is ESRD. While fibrotic kidneys in an advanced stage of renal disease are devoid of peritubular capillary blood supply and oxygenation to the corresponding region, imbalances in vasoactive substances can cause chronic hypoxia even in the early phase of kidney disease. Among various vasoactive substances, local activation of the renin-angiotensin system (RAS) is particularly important because it can lead to the constriction of efferent arterioles, hypoperfusion of postglomerular peritubular capillaries, and subsequent hypoxia of the tubulointerstitium in the downstream compartment. In addition, angiotensin II induces oxidative stress *via* the activation of NADPH oxidase. Oxidative stress damages endothelial cells directly, causing the loss of peritubular capillaries, and also results in relative hypoxia due to inefficient cellular respiration. Thus, angiotensin II induces renal hypoxia *via* both hemodynamic and nonhemodynamic mechanisms. In the past two decades, considerable gains have been realized in retarding the progression of chronic kidney disease by emphasizing blood pressure control and blockade of the RAS. Chronic hypoxia in the kidney is an ideal therapeutic target, and the beneficial effects of blockade of RAS in kidney disease are, at least in part, mediated by the amelioration of local hypoxia. (*Hypertens Res* 2008; 31: 175–184)

***Key Words*: ischemia, chronic kidney disease, angiotensin receptor blocker, oxidative stress**

Introduction

While chronic kidney disease (CKD) was previously believed to be relatively uncommon, it is now recognized as a common public health problem of global concern (*1*). The most important adverse outcomes of CKD include not only the complications of decreased glomerular filtration rate (GFR) and progression to kidney failure, but also an increased risk of cardiovascular disease (*2*). Indeed, the strong association between CKD and cardiovascular disease has led the American Heart Association and National Kidney Foundation to recommend that all patients with cardiovascular disease be screened for evidence of kidney disease (*3*).

Primary insults differ among kidney diseases, including glomerulonephritis, diabetic nephropathy, and hypertensive nephrosclerosis. However, once renal damage reaches a certain threshold, progression of renal disease is consistent, irreversible, and largely independent of the initial insult. Functional impairment of the kidney correlates better with the degree of tubulointerstitial damage than with that of glomerular injury, and it is widely recognized that the final common pathway which mediates the deterioration of kidney failure is to be found in the tubulointerstitium (*4*).

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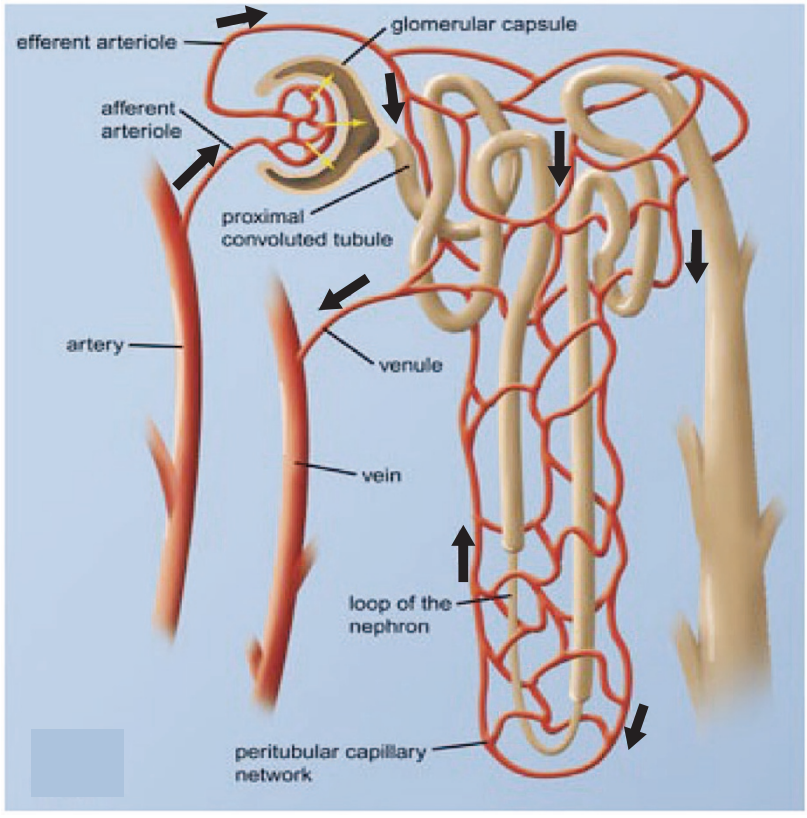

Fig. 1. *The microvasculature of the nephron. The peritubular capillary plexus is fed by glomerular efferent arterioles and supplies oxygen to tubular and interstitial cells (modified from Nangaku (13)).*

Blockade of the Renin-Angiotensin System to Treat CKD

While renal disease causes an increase in blood pressure (BP), high BP in turn accelerates the loss of function in the diseased kidney. The treatment of hypertension is thus now an important component in the treatment of CKD patients, not only to prevent cardiovascular complications but also to protect the kidney (*5*, *6*). Meta-regression analyses have indicated that BP reduction accounts for 50% of the variance in GFR decline and that each 10-mmHg reduction in mean arterial pressure (down to 92 mmHg) confers a benefit in GFR preservation of 3.7–5.0 mL/min per year (*7–10*). On this basis, stricter control of BP is recommended in patients with kidney injury.

Further, to maximize the protection of residual renal function, many clinical practice guidelines now suggest initial therapy with reagents to block the renin-angiotensin system (RAS). Why is blockade of RAS considered the gold standard in the treatment of patients with CKD? A large number of prospective, randomized, controlled studies have demonstrated the beneficial effects of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). These studies are covered in detail in our previous overview but, taken together, they ascribe the profound beneficial effects of blockade of RAS to reno-protection that goes beyond mere BP reduction (*11*). In particular, Weinberg *et al*. reported that the BP-lowering effects of an ARB, candesartan cilexetil (approved dosage range in Japan up to 12 mg/day), reached a plateau when doses were increased to 96 mg/day. In contrast, they observed dose-related reductions in urinary protein excretion without any further lowering of BP (*12*). While previous studies emphasized the amelioration of intraglomerular hypertension as a BP-independent reno-protective mechanism of blockade of RAS, more recent studies have clarified that the beneficial mechanism of ACEIs and ARBs includes a crucial role in ameliorating chronic hypoxia in the kidney.

Microvasculature of the Kidney

Although the kidneys receive a very high blood flow, oxygen extraction in the kidney is actually relatively low. This is due to its unique vasculature system, in which oxygen shunt diffusion occurs between arterial and venous vessels that run in close parallel contact in the kidney. Further, the maintenance of homeostasis mandates the reabsorption of a large fraction

of the sodium and water filtered by the glomeruli. This reabsorption process is driven by active transport and uses a large amount of oxygen. As a consequence, the kidneys are particularly susceptible to hypoxic injury, and recent studies emphasize chronic hypoxia in the tubulointerstitium as a final common pathway to end-stage kidney disease (*13–18*).

In the kidney, afferent arterioles arise from the interlobular arteries. Except for branches that go toward the pelvic mucosa, all blood from the interlobular and arcuate arteries is directed into the glomerular capillary bed. The glomerular capillaries merge together again at the vascular pole to form the efferent arterioles. The glomerular efferent arterioles from the cortical glomeruli supply a fine capillary plexus which lies around the tubules beneath the capsule and in the areas of cortex between the interlobular vessels. The efferent vessels of the juxtamedullary glomeruli supply the subcortical capillary plexus, in addition to dividing into the vasa recta, which enter the medulla. The peritubular capillary plexus surrounds the tubules and supplies oxygen to tubular and interstitial cells (Fig. 1). Thus, whenever blood flow in the peritubular capillaries is impaired, the kidney suffers from hypoxia.

Chronic Hypoxia of the Kidney: Animal Models

In advanced kidney disease, peritubular capillary loss leads to hypoxia of the corresponding region. Evidence for this comes from a number of studies in a variety of experimental animal models demonstrating an association between peritubular capillary loss and the progression of renal injury (*19–26*).

Previously, we used intravital microscopy in a model of progressive glomerulonephritis induced by uni-nephrectomy and repeated injection of anti-Thy1 antibodies to measure peritubular capillary blood flow. The results showed the stagnation of peritubular capillary blood flow in the early phase of glomerulonephritis (*27*). Notably, this decrease in peritubular capillary blood flow occurred well before the development of structural capillary injury. Further, we also showed that the stagnation of peritubular blood flow was associated with hypoxia in the kidney, as demonstrated by the accumulation of pimonidazole, a reagent which binds to hypoxic cells.

Diabetic kidneys are also hypoxic. In a second study, we again used pimonidazole staining to demonstrate hypoxia in the kidneys of the spontaneously hypertensive rats (SHR)/NDmc-cp rat, a model of type 2 diabetic nephropathy (*28*). Hypoxia of the diabetic kidney has also been demonstrated using the blood oxygen level–dependent (BOLD)–MRI technique (*29*): this method utilizes field distortion by deoxyhemoglobin in the magnetic field, which appears as BOLD contrast in the resulting images. The kidneys of streptozotocin-induced diabetic rats are hypoxic from an early stage (*29*).

Hypoxia-Sensing Transgenic Animals

Various methodological limitations have hampered the measurement of oxygen concentrations *in vivo*, and novel ways of monitoring oxygen in experimental animals have long been sought. All cells are endowed with a system which protects the cell against hypoxia, and this involves the hypoxia-inducible factor (HIF) and hypoxia-responsive element (HRE). In normoxia, the HIF-α subunit is hydroxylated, which enables the von Hipped-Lindau protein to bind to it, culminating in its degradation. Under hypoxic conditions, however, the HIF-α subunit escapes degradation, binding instead to the constitutively expressed HIF-β, and exerts its hypoxic response through binding to the *cis*-consensus HIF-binding site, namely the hypoxia-responsive element HRE. HIF regulates a variety of genes, such as erythropoietin (EPO) and vascular endothelial growth factor (VEGF).

We utilized this system to establish hypoxia-sensing transgenic rats expressing a luciferase reporter vector under the HRE-driven promoter. We used these rats to challenge the hypothesis that tubulointerstitial hypoxia occurs in the kidney during renal disease and modifies the pathogenic progression. In the puromycin nephrosis model, for example, hypoxic tubules were visualized diffusely in the cortex at both 1 and 2 weeks (*30*). In the remnant kidney model, on the other hand, hypoxic areas started to extend from the outer medulla to the cortex at week 1, and became more pronounced at week 4. These rats also enabled us to reveal the age-related expansion of hypoxia in all areas of the kidney (*31*).

Safran *et al*. recently used a similar strategy to establish hypoxia-sensing transgenic mice (*32*). Using a photon-counting charge-coupled device camera to show bioluminescence after the administration of luciferin, they showed that the kidneys of these mice were already hypoxic under normoxic conditions. Further, when the mice were placed in a low-oxygen environment, various parts of the body showed a 5- to 10-fold increase in light emission, and hypoxia in the kidneys exceeded that in other organs.

Activation of the RAS in Chronic Kidney Disease

Activation of the RAS, which leads to an increase in the synthesis of angiotensin II, is a frequent finding in patients with CKD. In patients with CKD and associated volume overload, even a "normal" plasma concentration of renin and angiotensin II is in fact inappropriately high (*33*). Back in 1934, Goldblatt *et al*. demonstrated that the clamping of a renal artery produced hypertension in dogs (*34*), leading to the hypothesis that the kidney might release a pressor substance in response to ischemia, and eventually to our present understanding of the role of RAS in the regulation of BP (*35*). In patients with CKD, the baroreceptors in the kidney which control the synthesis and secretion of renin are exposed to an inhomogeneous spectrum of perfusion pressures, because of the luminal narrowing of some, but not all, afferent preglomerular vessels. As a consequence, a proportion of glomeruli "senses" inappropriately low perfusion pressures and acti-

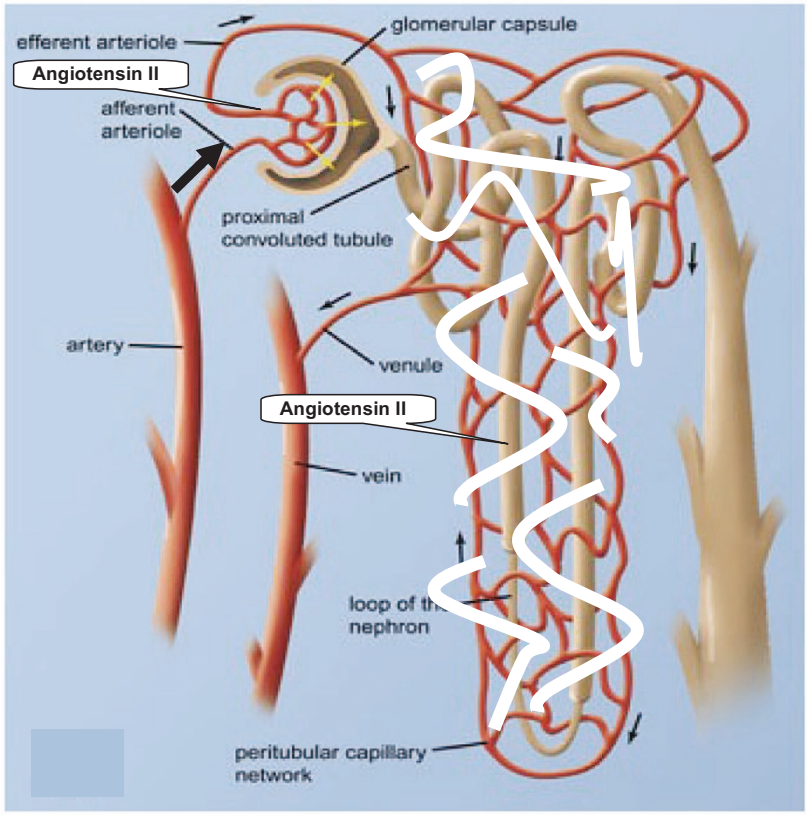

Fig. 2. *Angiotensin II–induced chronic hypoxia in the kidney. Angiotensin II induces structural changes such as fibrosis and loss of peritubular capillaries. In addition, angiotensin II contributes to hypoxia of the kidney via functional changes, including stagnation of peritubular capillary blood flow and induction of oxidative stress (modified from Nangaku (13)).*

vates RAS independently of the systemic BP.

Angiotensin II constricts precapillary arterioles and increases BP. Further, it stimulates aldosterone release from the adrenal cortex, which causes renal sodium retention and an increase in circulating blood volume. Of interest, angiotensin II levels in renal tissues are much higher than can be explained on the basis of equilibration with the circulating concentrations, and it is now apparent that activation of the local RAS plays a crucial role in kidney disease (*36*). Further, proteinuria, an established risk factor in the progression of renal disease, increases angiotensin II levels in tubular cells in a nuclear factor (NF)-κB–dependent manner (*37*).

In addition to its induction of systemic hypertension, angiotensin II plays a crucial role in chronic hypoxia of the kidney *via* structural and functional mechanisms, as described below.

Angiotensin II–Induced Structural Changes in Renal Circulation

Simply speaking, when there are no blood vessels, there is no blood flow. One of the major pathways of angiotensin II–induced renal hypoxia is *via* structural changes in renal circulation. Angiotensin II damages the renal vasculature and induces fibrosis (Fig. 2). One way it does this is by stimulating the expression of a major fibrogenic cytokine, transforming growth factor (TGF)-β, in the kidney and upregulating receptors for TGF-β (*38*). Fibrotic kidneys are devoid of peritubular capillary blood, and the corresponding region becomes hypoxic.

Among investigations of this effect, we previously demonstrated the loss of peritubular capillaries in angiotensin II–infused rats by staining with an endothelium-specific antibody, JG-12 (*39*). This capillary loss was ameliorated by administration of an angiotensin receptor blocker, olmesartan. More recent studies utilizing another endothelium-specific antibody, RECA-1, have confirmed the loss of peritubular capillaries in angiotensin II–infused rats (*40*). As in our study, the loss of peritubular capillaries and progression of fibrosis in these rats was also mitigated by an angiotensin receptor blocker.

With regard to fibrosis, the reduced efficiency of oxygen diffusion across the relatively extended distance between capillaries and tubular cells means that interstitial fibrosis impairs the tubular oxygen supply even in the presence of peritubular capillaries. A fibrogenic response induced by excessive angiotensin II in turn leads to the obliteration of

peritubular capillaries and a decrease in blood supply. Subsequent hypoxia induces the transdifferentiation of tubular cells into myofibroblasts (epithelial mesenchymal transdifferentiation), predisposing the kidney to fibrosis (*41*). Hypoxia also induces the apoptosis of resident kidney cells (*42–44*). The overall effect is to induce a vicious cycle of fibrosis and regional hypoxia.

Angiotensin II–Induced Functional Changes in Renal Circulation

Hemodynamic Changes

In addition to its induction of structural changes, a second important mechanism by which angiotensin II induces renal hypoxia in kidney disorders is *via* functional changes at an early stage of renal disease, before the development of the structural changes. It does this by constricting efferent arterioles, thereby decreasing blood flow in post-glomerular peritubular capillaries (Fig. 2). Nishiyama's group recently provided direct evidence of the angiotensin II–induced reduction in blood flow by visualizing the superficial peritubular capillaries directly through an intravital fluorescence videomicroscope system (*45*). Evaluation of peritubular capillary blood flow by analyzing the velocity of fluorescein-labeled erythrocytes showed a marked decrease in peritubular capillary blood flow in rats following the intravenous administration of angiotensin II.

Of note, hypoxia of the kidney by angiotensin II has also been demonstrated in humans. Schachinger *et al*. studied the effects of vasoactive agents on kidney oxygenation in humans utilizing BOLD-MRI (*46*). Angiotensin II caused an immediate shortening of T_2*, in contrast to other vasoactive agents which had no effect on the renal BOLD signal. The short onset latency of renal hypoxia induced by angiotensin II administration suggested that this response is a consequence of altered perfusion of the peritubular capillary plexus.

Oxidative Stress

In addition, angiotensin II induces hypoxia of the kidney *via* a second functional change, namely by NADPH oxidase activation–induced oxidative stress. Oxidative stress damages target organs *via* multiple mechanisms. For example, lectin-like oxidized low-density lipoprotein (LDL) receptor (LOX)-1, a novel oxidized LDL (ox-LDL) receptor recently isolated from endothelial cells induced by a variety of stimuli, including angiotensin II (*47*, *48*), acts as a functional receptor that mediates the cytotoxic effect of ox-LDL in various kidney disease models (*49*, *50*).

Furthermore, oxidative stress alters oxygen metabolism and oxygen availability. Reactive oxygen species (ROS) react with nitric oxide (NO) to form peroxynitrite and thereby decrease the bioavailability of NO. NO controls mitochondrial respiration *via* the suppression of respiration under normal conditions. A decrease in NO therefore results in the dysregulation of mitochondrial respiration, leading to inefficient oxygen usage. The potency of NO-mediated inhibition of renal oxygen usage was demonstrated by the pioneering study of Laycock *et al*., in which the administration of a nitric oxide synthase (NOS) inhibitor increased overall renal oxygen usage (*51*). The question of which isoform of NOS is responsible for the renal oxygen consumption remains controversial: while neuronal (n) NOS inhibition increases the oxygen costs of kidney function (*52*), studies utilizing mice deficient (–/–) in endothelial (e) NOS showed that regulation is due to NO production by eNOS (*53*).

Various experimental findings support the role of angiotensin II–induced oxidative stress in augmenting renal oxygen consumption and the subsequent induction of hypoxia. Welch *et al*. studied the early 2-kidney, 1-clip angiotensin II–dependent model. They demonstrated inefficient usage of oxygen in tubular transport in the clipped kidney. The reduced efficiency of renal oxygen usage was restored by the superoxide dismutase mimetic tempol (*54*). In addition, they recently extended these findings using rats which had received prolonged angiotensin II administration. Specifically, angiotensin II reduced the efficiency of renal oxygen usage in tubular sodium transport, resulting in a decrease in oxygen tension throughout the cortex. Tempol blunted all these effects of angiotensin II (*55*). Further, Adler and Huang showed that NO bioavailability in SHR is impaired due to an angiotensin II–mediated increase in superoxide production in association with enhanced expression of NADPH oxidase components (*56*). These results suggest that the oxidative stress induced by angiotensin II is associated with augmented oxygen consumption and subsequent hypoxia in the kidney.

The complexity of the relationship between hypoxia and oxidative stress is highlighted by the fact that, while oxidative stress aggravates hypoxia, the reverse also holds true: hypoxia aggravates oxidative stress. This may sound paradoxical, given that oxidative stress is a condition which requires oxygen and results in the excessive production of oxygen radicals beyond the antioxidant capacity. However, hypoxia *per se* stimulates xanthine oxidase and NADPH oxidase, resulting in the increased production of oxidative stress (*57*). The pathogenic role of oxidative stress under hypoxic conditions was further emphasized by studies on the pulmonary vasculature using adrenomedullin, a potent antioxidant (*58*, *59*) that inhibits angiotensin II–induced oxidative stress (*60*). Chronic hypoxia was shown to induce pulmonary vascular remodeling, which was associated with an increased production of oxidative stress as measured by electron spin resonance and immunostaining of 3-nitrotyrosine. This pulmonary vascular remodeling was aggravated in heterozygous adrenomedullin-knockout mice, suggesting a pathogenic role of hypoxia and protection by endogenous adrenomedullin through the suppression of ROS generation (*61*). Thus, a vicious cycle of hypoxia and oxidative stress may participate in a variety of disorders, including CKD.

Angiotensin II and Podocyte Injury

The evidence above emphasizes that the pathogenic role of the RAS in kidney failure operates *via* the induction of hypoxia in the tubulointerstitial compartment. However, the crucial role of glomerulosclerosis in the progression of kidney failure should not be ignored. The terminally differentiated podocyte, also called the glomerular visceral epithelial cell, is a highly specialized cell. An exciting and expanding body of evidence shows that, owing to the relative inability of these cells to proliferate, a reduction in podocyte number directly causes proteinuria and glomerulosclerosis (*62*, *63*). While earlier studies have emphasized the role of glomerular hypertension hemodynamically induced by activation of the RAS in the development of glomerulosclerosis, more recent studies have highlighted the direct participation of angiotensin II in podocyte injury.

Among recent findings in regard to angiotensin II, ischemia of the rabbit kidney was shown to cause a flattening and spreading of major processes of podocytes, while *in vitro* incubation studies suggested that local angiotensin II may produce cell changes in the glomerular epithelium (*64*). Local expression of the RAS in podocytes was recently confirmed in human podocytes (*65*). Further, evidence of direct injury to podocytes was recently demonstrated in studies utilizing genetically engineered animals: a transgenic rat model with overexpression of the human angiotensin II type 1 receptor (hAT1) specifically in podocytes developed significant albuminuria without the development of hypertension. The glomerular damage in this model progressed to nephron loss *via* a well-known pathway typically seen in classic focal segmental glomerulosclerosis (*66*). Further, aldosterone, the final product of the angiotensin II–stimulated corticosteroid biosynthetic pathway, damages podocytes directly (*67–69*).

Thus, in addition to direct effects of the RAS on tubulointerstitial hypoxia, activation of this system can induce glomerulosclerosis and anatomical damage to glomerular tufts, with a subsequent decrease in post-glomerular capillary perfusion in association with hypoxia in the tubulointerstitial compartment.

HIF-Activating Therapy against Renal Hypoxia

Chronic hypoxia in the kidney is the final common pathway to end-stage renal disease. Therapeutic approaches targeting hypoxia in the kidney should therefore be effective in patients with CKD. One promising approach to protecting tissues against hypoxia might be activation of a "master gene" switch, HIF.

Our recent studies revealed a postnatal biological role of HIF-2α in the kidney (*70*). We induced the well-established ischemia reperfusion injury model of the kidney in HIF-2α knockdown (kd) mice. Although ischemia impaired renal function in both wild-type and HIF-2α kd mice, HIF-2α kd mice had significantly higher blood urea nitrogen (BUN) levels and more severe histological changes. Evaluation of oxidative stress markers showed greater oxidative stress in the HIF-2α kd mice, while examination of the expression of antioxidative enzyme genes in these mice showed that the expression of SOD1, SOD2 and GPX1 genes was significantly lower in the HIF-2α kd kidney. In contrast, expression of HO-1, a target gene of HIF-1α, did not differ between the wild-type and HIF-2α kd kidneys. Judging by the localization of HIF-2α in the kidney, we speculated that HIF-2α in the kidney endothelium is responsible for the regulation of oxidative stress. To examine this, knockdown of the HIF-2α gene was achieved by insertion of the neomycin gene sandwiched between two loxP sequences. When the expression of HIF-2α in the endothelium was specifically restored by intercrossing

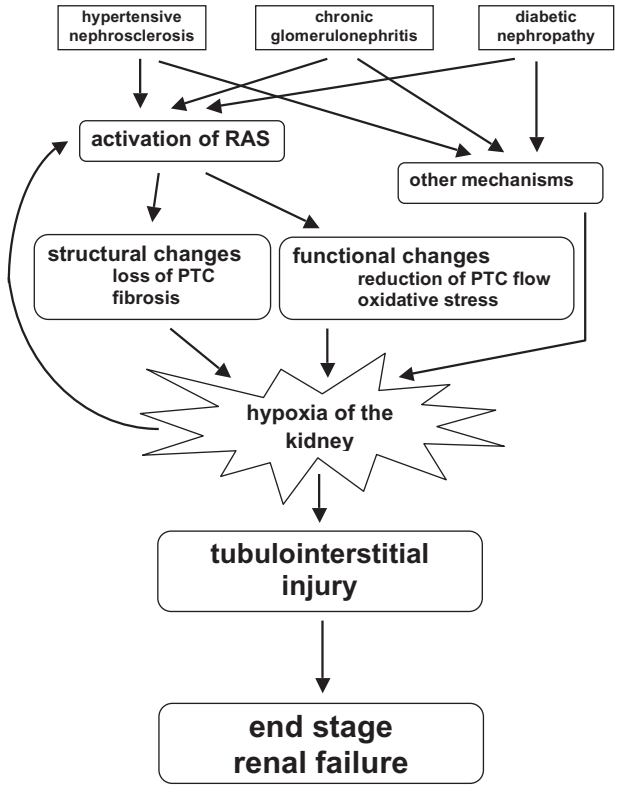

Fig. 3. *Schematic view of hypoxia-induced tubulointerstitial injury as a final common pathway to end-stage renal failure Other mechanisms of chronic hypoxia of the kidney include decreased renal blood flow as a result of atherosclerosis, increased metabolic demands of tubular cells due to glomerular hyperfiltration, and decreased oxygen delivery as a result of renal anemia. A decrease in renal blood flow due to activation of the RAS leads to stimulation of the macula densa and subsequent secretion of renin, instituting a vicious cycle of hypoxia and RAS activation. PTC, peritubular capillary.*

HIF-2α kd with Tie1-Cre mice, the susceptibility of HIF-2α kd mice to renal ischemia was found to be restored in the resulting HIF-2α kd/Tie1-Cre mice. This result clearly demonstrated a protective role of HIF-2α in the endothelium, and raised the possibility that the stimulation of HIF may be a powerful tool in protecting the vasculature under hypoxic conditions.

In support of this notion, gene transfer of constitutively active HIF (HIF/VP16) was found to induce the expression of various HIF-regulated genes and to protect the medulla against ischemic insults in rats (*71*). Further, a recent phase I dose-escalation study on the adenoviral delivery of a constitutively active form of transcription factor HIF-1α (Ad2/HIF-1α/VP16) into the lower extremity of patients with critical limb ischemia showed that HIF-1α therapy in patients with critical limb ischemia was well tolerated. Of note, no amputations occurred in the two highest-dose groups of Ad2/HIF-1α/VP16 (*72*).

Previous studies by our group and others have demonstrated that stimulation of HIF with cobalt chloride is effective in a variety of kidney disease models (*73–77*). Furthermore, pretreatment with either carbon monoxide, leading to tissue hypoxia, or the novel prolyl hydroxylase inhibitor FG-4487 strongly induced the accumulation of HIF-1α and HIF-2α in tubular and peritubular cells, respectively, with significant amelioration of ischemic renal injury (*78*).

Angiotensin Blockade as a Therapeutic Modality against Renal Hypoxia

Although HIF stimulation holds promise as a future therapy, at present the best modality for the treatment of kidney disease is blockade of the RAS (*11*). One important mechanism of the BP-independent renoprotective effect of this blockade is the preservation of peritubular capillary perfusion.

Norman *et al*. investigated the effects of RAS blockade on renal oxygenation in anesthetized adult rats (*79*). Cortical microvascular oxygenation on the surface of the exposed kidney was measured utilizing the porphyrin phosphorescence technique. The results showed a slow decline in cortical oxygenation in control animals over the 3-h experimental period. Administration of an ACEI or ARB at the beginning of the experimental period completely abrogated this decline.

Further, we demonstrated a decrease in blood flow in peritubular capillaries and subsequent hypoxia in a very early phase of remnant kidneys (week 1) (*80*). These changes were associated with the narrowing and distortion of peritubular capillaries, but not with a decrease in the number of peritubular capillaries. The physiologic perfusion status of the peritubular capillary network was evaluated by the lectin perfusion and Hoechst dye diffusion techniques. Treatment of these animals with an ARB restored the blood flow in peritubular capillaries and improved the oxygenation of the kidney.

Long-term administration of an ARB in type 2 diabetic rats also resulted in the restoration of oxygenation in the kidney (*28*). We and others have demonstrated the anti-oxidative stress effects of ARBs. Because angiotensin II induces oxidative stress *via* the activation of NADPH oxidase, as described above, blockade of the receptor inhibits this stress. Furthermore, the chemical structures of ARBs inhibit *in vitro* oxidative stress by chelating transition metals and inhibiting various oxidative steps in a receptor-independent manner (*81*, *82*). Thus, the mechanisms of the improvement in oxygenation by renin-angiotensin blockade include both hemodynamic changes *via* the dilatation of glomerular efferent arterioles and efficient oxygen usage *via* the amelioration of oxidative stress. Supporting this notion, Welch *et al*. demonstrated that the administration of an ARB improved the inefficient utilization of oxygen in sodium transport in the SHR kidney (*83*).

Conclusion

Chronic hypoxia in kidney disease serves as the final common pathway leading to end-stage renal failure (Fig. 3). Angiotensin II causes hypoxia in the kidney by inducing structural microvasculature damage and fibrotic changes. It also induces the constriction of glomerular efferent arterioles, resulting in a reduction in peritubular capillary blood flow and subsequent hypoxia in the corresponding region. Further, angiotensin II induces oxidative stress, which in turn consumes nitric oxide and results in inefficient oxygen usage. Therapeutic approaches against this final common pathway utilizing an ACEI or ARB are effective in a broad range of renal diseases.

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