REVIEW ARTICLES

MECHANISMS OF DISEASE

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HYPOXIA OF THE RENAL MEDULLA — ITS IMPLICATIONS FOR DISEASE

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IN land mammals, a major task of the kidney is to reabsorb water to allow survival in a dry environment. Water conservation is enhanced by the renal medulla, which concentrates the urine to a level up to four times the osmolality of plasma. To produce this unique gradient of osmolality, the medulla has a countercurrent system of vessels and tubules that dictates active reabsorption of sodium in a milieu poor in oxygen (Fig. 1).[1] In this review, we describe how hypoxia of the medulla may relate to susceptibility to acute and chronic renal injury.

The Renal Medullary Concentrating Mechanism as the Physiologic Basis of Medullary Hypoxia

Renal blood flow, a quarter of the cardiac output and the highest in the body in relation to organ weight, is directed mostly to the cortex to optimize glomerular filtration and the reabsorption of solute. By contrast, blood flow to the renal medulla is low, to preserve osmotic gradients and enhance urinary concentration.[2]

Within the medulla, tubules and vasa recta are disposed in a hairpin pattern to maximize the concentration of urine by countercurrent exchange (Fig. 1). Oxygen diffuses from arterial to venous vasa recta, which leaves the outer medulla deficient in oxygen. In this region, the medullary thick ascending limb is responsible for the generation of an osmotic gradient by active reabsorption of sodium, a process that requires a large amount of oxygen.

Medullary hypoxia under normal conditions has been documented in several mammalian species, including humans.[3,4] The medullary partial pressure of oxygen is in the range of 10 to 20 mm Hg, contrasting with the partial pressure of oxygen in the cortex, which is about 50 mm Hg.[5-7]

Medullary hypoxic injury, which occurs when oxygenation is further impaired, is characterized by necrosis of the tubules that are most remote from vessels (Fig. 2). The kidney is thus like other organs in that the regions most susceptible to anoxia are those remote from oxygen supply: other examples are watershed infarcts in the brain, centrilobular injury in the liver, and corticomedullary necrosis in the adrenal glands.[8]

The principal determinant of medullary oxygen requirements is the rate of active reabsorption along the medullary thick ascending limb.[6] The inhibition of active transport by loop diuretic drugs increases medullary partial pressure of oxygen from 16 to 35 mm Hg. Reducing the glomerular filtration rate, which diminishes the delivery of urine for the reabsorption of solute in medullary thick limbs, also improves medullary oxygenation. As in cardiac muscle and in neurons, reduction of work is the best way to protect against anoxia and is far more efficient than anaerobic glycolysis.[9] In the kidney, as in other organs, diminution of function has evolved as a protective mechanism for the medulla.

Medullary hypoxia is an inevitable accompaniment of efficient urinary concentration. If excessive, medullary blood flow disrupts the osmolality gradients (built up by countercurrent exchange); if it is too slow, anoxia injures the tubules. A critical prerequisite of urinary concentration is an exact matching of oxygen supply and demand by precise regulation of the medullary blood flow and tubular work.

Adaptive Mechanisms to Minimize Medullary Hypoxia

A variety of agents act in concert to regulate renal medullary oxygen homeostasis (Table 1). The cells in the outer medulla have receptors for mediators, as illustrated in Figure 3, that control medullary oxygen supply by vasoconstriction (e.g., angiotensin) or vasodilatation (e.g., prostaglandin E_2). Oxygen demand, a function of the rate of tubular reabsorption, is determined by the glomerular filtration rate and delivery of urine to the medullary thick limbs and regulation of transport by local mediators.

Prostaglandins and Related Metabolites

Prostaglandin E_2, produced by the medulla, dilates medullary vessels[2] and inhibits oxygen consumption in tubular cells.[16] Cytochrome P-450–dependent arachidonate metabolites[20] and platelet-activating factor[19] also inhibit the tubular reabsorption of solute. Thus, lipid metabolites may be released by medullary hypoxia to alter blood flow and tubular transport for optimal concentration of the urine.

Other Vasoactive Mediators

The local vasodilator nitric oxide is synthesized by medullary thick limbs.[10] The inhibition of nitric oxide

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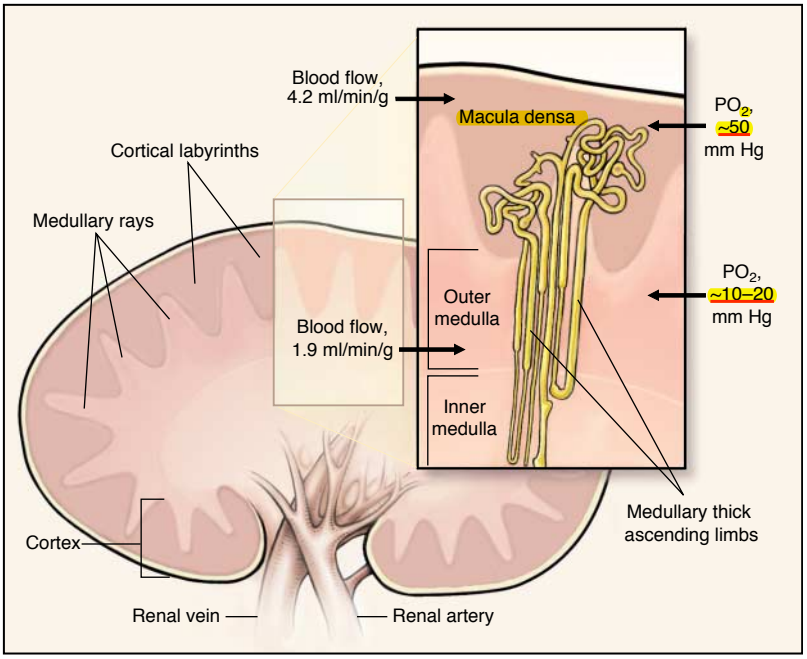


Figure 1. Anatomical and Physiologic Features of the Renal Cortex and Medulla.
The cortex, whose ample blood supply optimizes glomerular filtration, is generally well oxygenated, except for the medullary-ray areas devoid of glomeruli, which are supplied by venous blood ascending from the medulla. The medulla, whose meager blood supply optimizes the concentration of the urine, is poorly oxygenated. Medullary hypoxia results both from countercurrent exchange of oxygen within the vasa recta and from the consumption of oxygen by the medullary thick ascending limbs. Renal medullary hypoxia is an obligatory part of the process of urinary concentration. PO_2 denotes partial pressure of oxygen.

synthesis predisposes a person to medullary injury and renal failure,[5,11] a fact that is consistent with an important role of nitric oxide in increasing medullary oxygenation. Urodilatin, homologous to atrial natriuretic peptide and produced by the distal tubules, is another renal vasodilator. Receptors for potent vasoconstrictors — endothelin[15] and angiotensin II (Fig. 3B) — are concentrated in the medulla. The balance of vasodilators and vasoconstrictors is important for the precise regulation of medullary blood flow.

Adenosine

Adenosine, released from ATP during hypoxia in any tissue, is generally a vasodilator and tends to restore local oxygen balance.[23] In the kidney, adenosine induces both cortical vasoconstriction (with a reduction in glomerular filtration) and medullary vasodilatation (with inhibition of tubular transport), which suggests that it has an intrarenal homeostatic role that attenuates medullary hypoxia.[13,14]

Tubuloglomerular Feedback

Glomerular filtration is controlled by tubuloglomerular feedback. Insufficient reabsorption of sodium by renal tubules activates (distally, at the macula densa) signals that constrict the glomerulus, reducing filtration and therefore the delivery and reabsorption of tubular solute.[21] Thus, hypoxic impairment of reabsorption in the medullary thick limbs reduces glomerular filtration, which relieves medullary oxygen insufficiency whenever the workload exceeds capacity. A related response of the kidney to any decline in blood flow is the redistribution of the corticomedullary circulation for the benefit of medullary oxygenation. Superficial cortical blood flow (and glomerular filtration) is reduced, whereas juxtamedullary blood flow (and medullary oxygen supply) is maintained.

Growth Factors

Medullary tubules synthesize growth factors, such as insulin-like growth factor I, epidermal growth factor, and tumor necrosis factor, which act as intrarenal autocrine or paracrine mediators. Renal hypertrophy may thus be modulated by signals originating in the medulla that ascend to the cortex by the portal system of the venous vasa recta. In experimental renal failure, recovery is accelerated by exogenous insulin-like growth factor I or epidermal growth factor.[24] Changes in gene expression along medullary thick limbs after kidney injury[25] also suggest that the outer medulla is an important site for the control of renal growth.

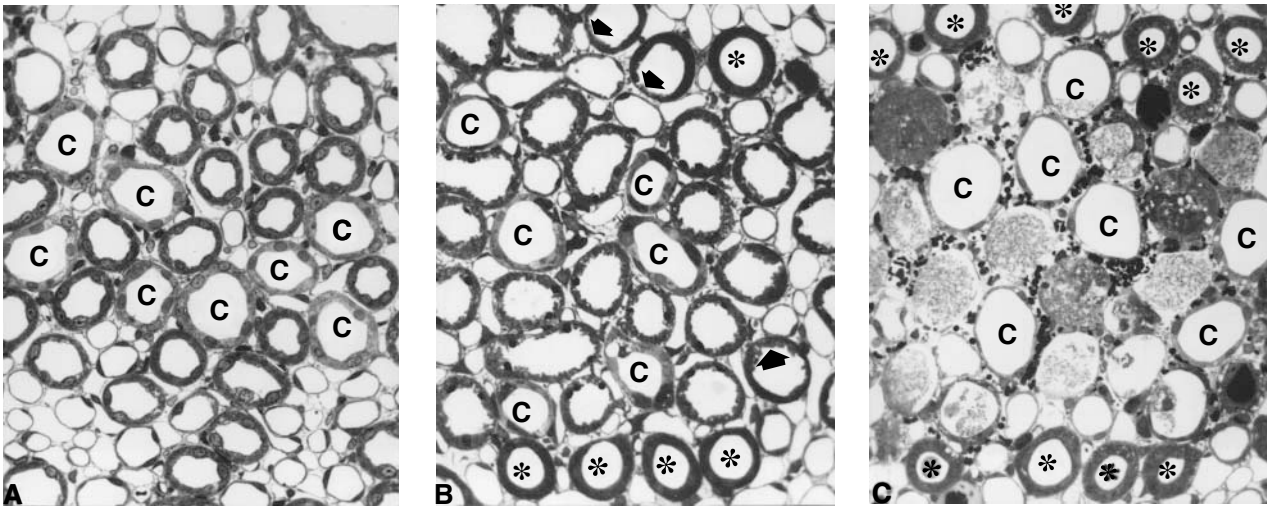
Neuroendocrine and Other Protective Mechanisms

Hormones[26] and neuromediators[18,27,28] modulate transport in medullary thick limbs, which suggests that there is some neuroendocrine control of medullary oxygenation. Medullary tubules also have intrinsic biochemical defense systems, such as heat-shock proteins.[29]

Powerful and coordinated mechanisms thus regulate intrarenal oxygenation to allow the concentration of urine with minimal medullary hypoxic injury. Diseases and drugs may have a considerable effect on the delicate homeostasis of medullary oxygenation.[30]

Experimental Amelioration and Exacerbation of Medullary Hypoxia

Multiple pharmacologic and pathophysiologic events affect medullary oxygenation (Table 2). Reducing transport activity protects medullary tubules from hypoxic injury, particularly in the thick ascending limbs and to a lesser extent in the last (S_3) portion of the proximal tubules.[44] Inhibiting electrolyte transport with furosemide, ouabain (a potent inhibitor of Na^+/K^+–ATPase), or the cessation of glomerular filtration pre-



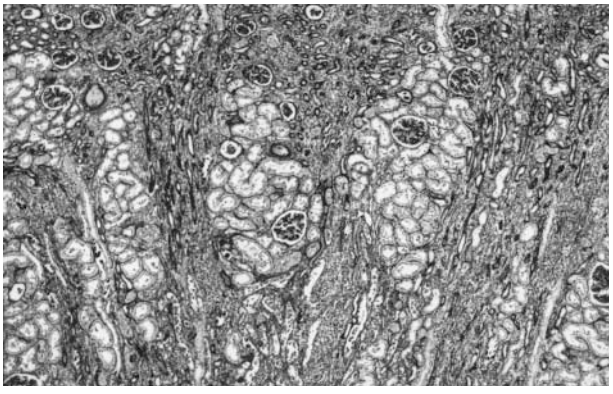


Figure 2. Medullary Hypoxic Injury in Vitro and in Vivo.

Panels A, B, and C show sections of the outer medulla of the rat kidney (thickness, 1 μm) cut perpendicularly to the tubules (methylene blue, $\times$225). The medullary thick ascending limbs, which are normal in Panel A, show cell fragmentation and nuclear pyknosis after perfusion in vitro for 90 minutes with no oxygen carrier (Panel B) and extensive necrosis after the injection of radiographic contrast medium in an animal in which the synthesis of prostaglandin and nitric oxide was inhibited (Panel C). The vasa recta are at the top and bottom of each panel. The collecting ducts (C) and epithelium of the medullary thick ascending limb (*) adjacent to the vasa recta are relatively preserved (Panels B and C). Some tubules are only partially intact, and the injured epithelium (arrows in Panel B) is in a portion of the tubule that is far from the vasa recta. Panel D shows a section of kidney from a seven-year-old girl with acute lymphocytic leukemia and candida septicemia who received amphotericin B continuously for seven months. Columns of fibrosis and atrophic tubules extend from the medulla (bottom) into the cortex along the medullary rays and up to the subcapsular area (top), where the fibrosis encroaches on the cortical labyrinth. This prominent pattern of medullary rays is typical of chronic injury caused by a number of nephrotoxins, including elevated serum calcium concentrations, cyclosporine, tacrolimus (FK 506), and amphotericin B. (Periodic acid–Schiff and hematoxylin, $\times$22.) Panel D was provided by the Department of Pathology, Children's Hospital, Boston.

vents medullary hypoxic injury in isolated perfused rat kidneys.[32,33] Administering furosemide and reducing the glomerular filtration rate also attenuate medullary hypoxic injury in vivo.[31,34]

Increased tubular work exacerbates medullary hypoxia. Polyene antibiotic agents such as amphotericin B are notoriously nephrotoxic. The enhanced membrane permeability produced by polyene antibiotics triggers an increase in active sodium transport and oxygen demand, whereas renal vasoconstriction reduces the supply of oxygen.[32,36] In isolated perfused kidneys, polyene toxicity is prevented by inhibiting transport with ouabain.[32] In humans as in animals, amphotericin B induces hypoxic injury in the tubules that have the most limited oxygen supply — those in the outer medulla and medullary rays (Fig. 2D).

Compensatory hypertrophy of remnant nephrons after the loss of functional renal mass causes tubular hypermetabolism.[45] The medullary oxygen supply may not increase in proportion to the increase in demand. There is a predisposition to medullary injury by renal hypertrophy in patients with acute hypoxic insults[37,43] and remnant kidneys,[46] which further augments the workload of residual tubules. Increased concentrations of angiotensin II are detrimental to the medullary oxygen balance because they maintain the glomerular filtration rate (by preferential constriction of efferent glomerular vessels) while reducing oxygen delivery.[39]

Nonsteroidal antiinflammatory drugs predispose patients to renal failure. Their inhibition of prostanoid synthesis exacerbates medullary hypoxia by two mechanisms: regional hypoperfusion and increased tubular transport. Indomethacin, aspirin, meclofenamate, and naproxen induce selective medullary ischemia.[12] Prostaglandin E_2 inhibits active transport in the medullary thick ascending limb,[16] and the exogenous administration or endogenous stimulation of prostaglandin production protects it from hypoxic injury.[35] Long-term exposure to nonsteroidal antiinflammatory drugs causes analgesic nephropathy and medullary necrosis (po-

Table 1. Mechanisms Regulating Blood Flow and Tubular Transport in the Renal Medulla.

MECHANISM	REFERENCE
Medullary vasodilator	
Nitric oxide	Brezis et al.,[5] Morrissey et al.,[10] Agmon et al.[11]
Prostaglandin E_2	Chou et al.,[2] Agmon and Brezis[12]
Adenosine	Dinour and Brezis,[13] Agmon et al.[14]
Dopamine	Chou et al.[2]
Urodilatin	Chou et al.[2]
Medullary vasoconstrictor	
Endothelin	MacCumber et al.[15]
Angiotensin II	Chou et al.[2]
Vasopressin	Chou et al.[2]
Inhibitor of transport in medullary thick limbs	
Prostaglandin E_2	Lear et al.[16]
Adenosine	Beach and Good[17]
Dopamine	Meister et al.[18]
Platelet-activating factor	Bailly et al.[19]
Cytochrome P-450–dependent arachidonate metabolites	Carroll et al.[20]
Tubuloglomerular feedback	Briggs and Schnermann[21]

tentiated by caffeine,[47] an antagonist of adenosine receptors).

Radiographic contrast agents reduce medullary partial pressure of oxygen[38] even though they increase medullary blood flow,[11] probably because of osmotic diuresis and increased workload in medullary tubules. Prostanoids and nitric oxide have an important protective role in the renal response to radiographic contrast agents.[11]

An excess of calcium interacts adversely with medullary hypoxia[40] and induces tubulointerstitial injury.[41] Hemoglobin and myoglobin bind nitric oxide, thus promoting medullary vasoconstriction and hypoxia.[42] Intrarenal vasoconstriction associated with cyclosporine nephrotoxicity unfavorably affects medullary integrity.[48]

Synergy of Toxic and Hypoxic Insults in the Kidney

Because of the multiplicity of homeostatic mechanisms that protect the medullary tubules against hypoxia, the incapacitation of several protective mechanisms is necessary to produce medullary injury.[30] Models of acute renal failure are often based on single insults intensive enough to cause reproducible kidney failure, such as clamping the renal artery or administering large doses of gentamicin. These insults induce diffuse cortical and proximal tubule damage, findings rarely encountered today in human acute renal failure. Models combining multiple insults (that would not alone cause substantial renal injury) demonstrate the susceptibility of the renal medulla to injury. For instance, giving salt-depleted rats a radiographic contrast agent with indomethacin[38,43] or giving gentamicin combined with renal hypoperfusion[49] induces prominent injury in the outer medulla. In humans, acute renal failure is characterized by focal nephron injury. Complete stoppage of renal blood flow (except in renal transplantation and aortic cross-clamping) or deliberate overdosing with nephrotoxins is unusual. Instead, combinations of factors, such as diabetes mellitus and renal hypoperfusion, predispose patients to toxic effects from drugs given at therapeutic dosages.

The example of radiocontrast nephropathy is particularly instructive. In animals, as in humans, even large doses of a radiographic contrast agent cause little injury to the kidneys. Clinical nephrotoxicity occurs in the presence of risk factors, such as diabetes mellitus and preexisting kidney damage, that are often associated with compromised renal circulation.[30,50] To produce a simple model of radiocontrast nephropathy, rats were pretreated by simultaneous inhibition of prostaglandin and nitric oxide production before the administration of the contrast agent. Neutralizing these protective mechanisms transformed a medullary vasodilator response to the contrast agent into profound vasoconstriction, selective necrosis of the medullary thick ascending limbs, and renal failure.[11]

Impaired endothelium-derived vasorelaxation in patients with diabetes mellitus, hypertension, or atherosclerosis results in paradoxical vasoconstriction and regional hypoxia. Since these diseases are frequently associated with radiocontrast nephropathy,[50] endothelial dysfunction in chronic renal and vascular diseases may predispose patients to medullary injury from radiographic contrast agents, which illustrates the vulnerability of the delicate oxygen balance within the medulla to disruption.

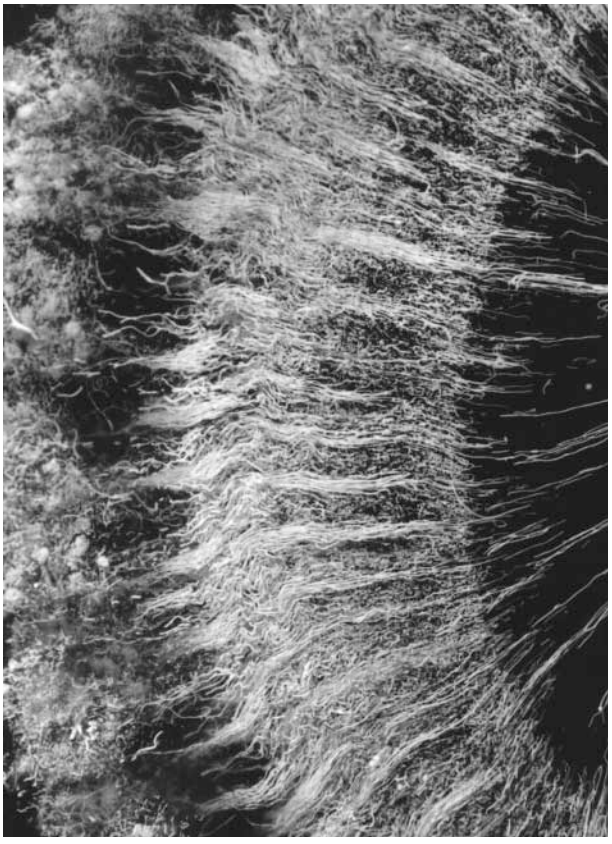
Interference with the homeostatic mechanisms controlling medullary oxygen balance predisposes patients to focal hypoxic injury at important sites in the kidney. Synergy between renal hypoperfusion and toxic insults results from an increased renal concentration of toxins at a time when sodium reabsorption and urinary concentration are enhanced and the oxygen supply is reduced. Intrarenal hypoxia and nephrotoxins increase oxygen demand by causing membrane damage and mitochondrial dysfunction.[30] The interference of drugs (e.g., nonsteroidal antiinflammatory drugs) with renal protective mechanisms, increased angiotensin II production and tubuloglomerular feedback, and an increased likelihood of intraluminal precipitation of crystals or coprecipitation of a toxin with Tamm–Horsfall protein (released into the urine from cells of the thick limbs) also contribute to renal failure in combined hypoxic and toxic insults.[30] The susceptibility of the kidney to hypoperfusion is thus greatly aggravated by insults that increase the renal medullary vulnerability to hypoxia and culminate in cell injury and organ failure (Fig. 4).

Diversity of Expression of Hypoxic Renal Injury

Anoxia induces diverse molecular and morphologic alterations influenced by the intrarenal gradients of oxygenation.

Cellular, Molecular, and Functional Alterations

As in any cell, anoxia in kidney cells results in the depletion of energy stores, collapse of electrolyte gradi-



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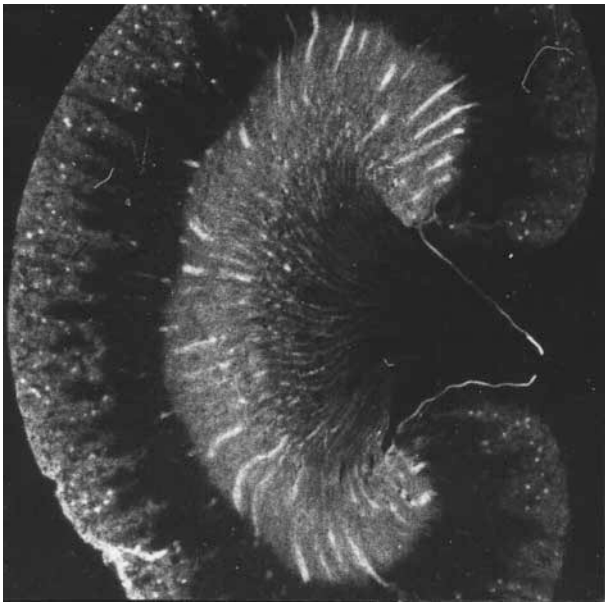

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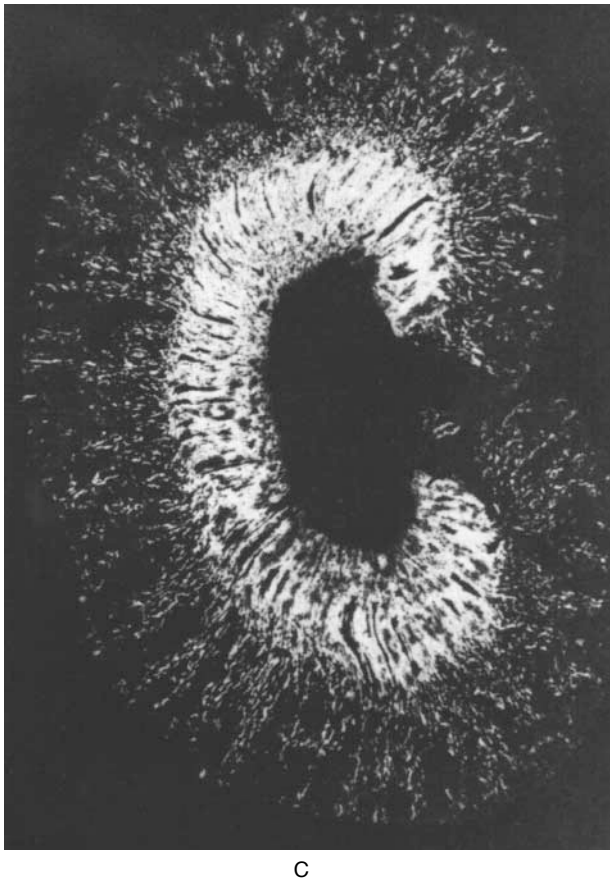

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Figure 3. Vascular Anatomy of the Outer Medulla.

Multiple humoral control mechanisms act at the outer medulla — the site at greatest risk of medullary hypoxia — facilitating the balance of oxygen supply and demand. In Panel A, arterial injection of Microfil silicone rubber reveals the vasa recta in a sagittal section of a rat kidney (×25). Autoradiography reveals receptors for angiotensin II (Panel B) and prostaglandin E_2 (Panel C) in the inner stripe of the outer medulla. Panel A was provided by Dr. L. Bankir, Panel B was provided by Dr. F.A.O. Mendelsohn, and Panel C was reprinted from Eriksen et al.[22] with the permission of the publisher.

ents, disruption of the actin cytoskeleton, activation of phospholipases, and changes in gene expression.[51] Renal hypoxia induces the loss of epithelial polarity along the proximal tubules and the selective induction of growth-response genes with rapid DNA fragmentation (suggestive of apoptosis) along the medullary thick limbs[52] (and unpublished observations).

Ischemic injury to renal vessels increases renovascular reactivity[53] and predisposes patients to secondary ischemic insults from hypotension during the recovery from acute renal failure. Ischemia induces the expression of histocompatibility antigens on renal tubular cells and of intercellular adhesion molecules on endothelial cells, which leads to the local aggregation of neutrophils and platelets.[54] Antibodies to intercellular adhesion molecules and antagonists of platelet-activating factor protect the kidney from ischemic injury.[54] After ischemia, intrarenal congestion is prominent in the outer medulla because of regional hypoxia and because the vasa recta are easily compressed by surrounding tubular edema.

Acute Morphologic Lesions in Tubules

Anoxic damage along tubules is governed by the intrinsic vulnerability of the various nephron segments and by the tissue gradients of oxygenation. Glomeruli and collecting ducts are relatively resistant to a lack of

Table 2. Agents and Events That Ameliorate or Exacerbate Hypoxia in the Renal Medulla.

Agent or Event	Reference
Ameliorating effect	
Decreased tubular transport	Heyman et al.,[31] Brezis et al.[32,33]
Decreased glomerular filtration rate	Brezis et al.[33,34]
Prostaglandin E_2	Silva et al.[35]
Adenosine	Dinour and Brezis,[13] Agmon et al.[14]
Bradykinin	Silva et al.[35]
Nitric oxide	Brezis et al.,[5] Morrissey et al.[10]
Exacerbating effect	
Polyene antibiotics (e.g., amphotericin B)	Brezis et al.,[32] Heyman et al.[36]
Renal hypertrophy	Epstein et al.[37]
Nonsteroidal antiinflammatory drugs	Agmon and Brezis,[12] Heyman et al.[38]
Angiotensin II	Brezis et al.[39]
Calcium	Brezis et al.,[40] Rosen et al.[41]
Myoglobin	Brezis et al.[42]
Radiographic contrast agents	Heyman et al.[38,43]

oxygen. By contrast, both proximal and distal tubules (especially medullary thick limbs) are intrinsically susceptible to hypoxia.[55,56] Nevertheless, the distribution of tubular damage in vivo appears to be determined largely by intrarenal oxygen gradients.[55]

Distribution of Gradients of Hypoxia in the Kidney

Intrarenal gradients of oxygenation determine the distribution of tubular injury after kidney ischemia.[57] The outer medulla is a major target because of regional hypoxia and the presence of tubules vulnerable to hypoxia (S_3 tubules and thick limbs). The inner medulla is far less vulnerable, because its structures have lower metabolic demands. In the cortex, the medullary rays, perfused by venous blood emerging from the medulla, are an expected target because they are located farthest from oxygen supply and contain a susceptible structure, the S_3 tubules.[57]

Structural Expression of Tubular Hypoxic Injury

After mild depletion of cell energy stores, the proximal tubules swell and lose their microvilli.[58] Although visually striking, these lesions do not necessarily cause renal failure,[50] and they have often distracted attention from focal damage along the distal tubules, which is marked by cytoplasmic fragmentation.[56,58] A reduction in transport work minimizes hypoxic injury in the medullary thick limbs but does not prevent cell swelling in the proximal tubules.[32,33,44] S_3 tubules respond to hypoxia by cell fragmentation or by swelling, if transport is inhibited.[44] These disparate responses to hypoxia are related to functional differences between nephron segments: to allow reabsorption of glomerular filtrate, proximal tubules are far (10^4 times) more permeable to water than medullary thick limbs, which are watertight to allow optimal urinary concentration.[51]

Chronic Structural Lesions and Intrarenal Hypoxia

The degree of tubular atrophy and interstitial fibrosis, which develop after any prolonged renal insult, is correlated with the severity of kidney failure.[59] Increased fibrogenesis in kidneys with chronic disease may arise from intrarenal hypoxia due to increased oxygen consumption by remnant nephrons[45]; hypoxia causes altered antigen expression in tubules and the release of cytokines such as transforming growth factor by fibroblasts,[60] which stimulates the formation of intrarenal collagen. Angiotensin II, which is locally released at the macula densa owing to the increased distal delivery of sodium from failing medullary tubules, can also act as a growth factor, promoting the proliferation of fibroblasts and the deposition of collagen.[61]

As shown in Figure 2D, intrarenal hypoxic injury begins in the outer medulla and in the medullary rays. As the degree of ischemia advances, fibrosis progresses to encompass the remainder of the kidney, including the most superficial cortex, which is also at risk of hypoxia,[62] and eventually encroaches on some of the cortical labyrinths (areas that surround the glomeruli and are at lowest risk of hypoxic injury). Interstitial fibrosis of the medullary rays, often described as "striped fibrosis," is prominent in chronic nephrotoxicity caused by hypercalcemia,[41] amphotericin B,[36] tacrolimus (FK 506), and cyclosporine.[48] Fibroplastic proliferation with collagen deposition along medullary rays may underlie the pattern of intrarenal fibrosis in progressive renal failure.

Clinical Implications of Medullary Hypoxic Injury

Since quantifying intrarenal blood flow or oxygenation is not possible in clinical practice, the detection of medullary hypoxia and injury remains indirect. New forms of technology such as positron-emission tomography may prove suitable for this purpose in time.

Loss of urinary-concentration capacity (isosthenuria) is one of the most sensitive measures of intrinsic renal damage during renal hypoperfusion or toxic injury.[50] A reduction in urinary osmolality indicates that prerenal azotemia, which is characterized by normal or enhanced urinary concentration, has been transformed into established renal failure. Polyuria with only a mild-to-moderate reduction in the glomerular filtration rate is sometimes the predominant clinical syndrome (in patients with toxic effects from aminoglycosides or cisplatin, for instance). The loss of urinary concentrating ability reflects injury to the renal medulla. Activated protective mechanisms, such as reduced medullary tubular transport or increased medullary blood flow, also blunt the capacity to concentrate urine.

The appearance of brown granular casts in the urine, which is characteristic of acute renal failure,[50] indicates release of Tamm–Horsfall protein by the thick ascending limbs. Since this protein is made only by the thick limbs, its precipitation in the tubular lumen reflects thick-limb injury. Clinicopathological correlations have indicated a relation between the disappearance of Tamm–Horsfall protein from tubular cells and reduced renal function.[63]

The morphology of the renal medulla has often been

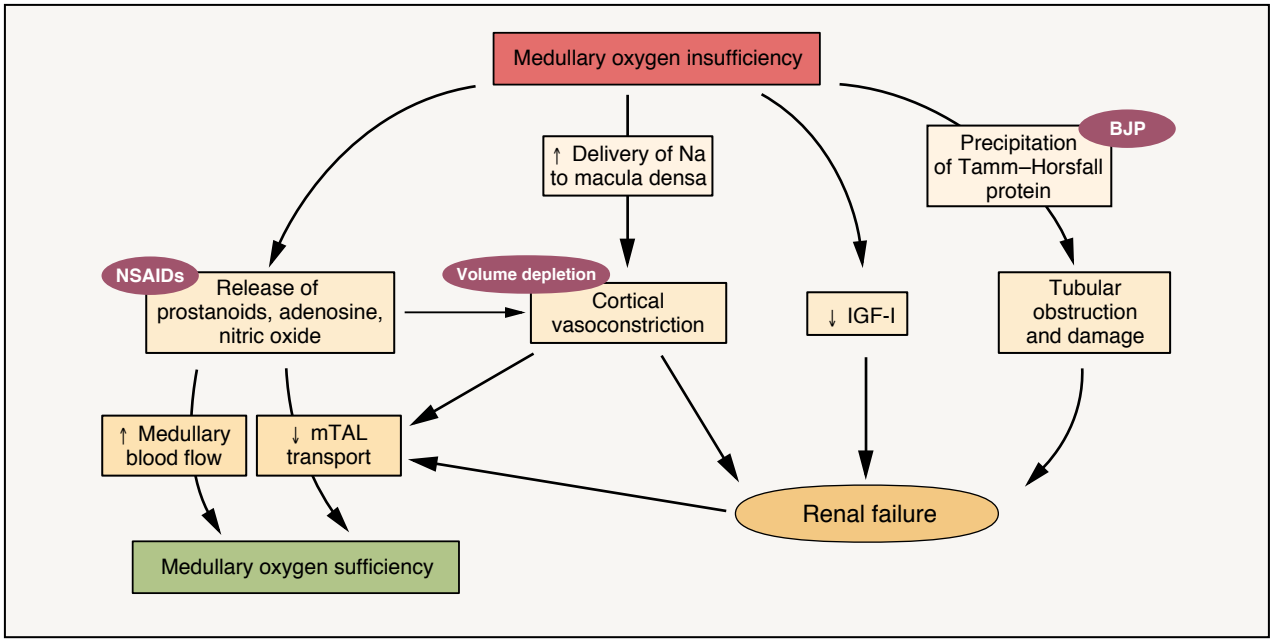

Figure 4. Putative Mechanisms Leading from Medullary Hypoxia to Renal Failure.

The physiologic homeostatic signals shown on the left improve medullary oxygenation (by increasing blood flow and decreasing transport) and often contribute to reduced renal function. Some of the pathophysiologic consequences of more advanced medullary hypoxia, such as tubular damage and reduced levels of insulin-like growth factor I (IGF-I), are shown on the right. The potential adverse effects of some nephrotoxins and volume depletion also are shown. Nonsteroidal antiinflammatory drugs (NSAIDs) prevent the beneficial prostanoid-mediated medullary vasodilative response to local hypoxia. Volume depletion enhances the decrease in glomerular filtration mediated by tubuloglomerular feedback. In the kidneys of patients with myeloma, Bence Jones proteins (BJP) precipitate with the Tamm–Horsfall protein released as a result of damage to the medullary thick ascending limbs (mTAL), which increases the likelihood of tubular obstruction and renal failure from other insults (such as NSAIDs, volume depletion, or radiographic contrast agent). Renal failure results from tubular obstruction (by casts); back-leakage of glomerular filtrate from the lumen to blood (through damaged epithelium); impaired intrarenal microcirculation, which occurs, for example, through the activation of tubuloglomerular feedback (by increased distal delivery of solute to the macular densa); and the lack of locally produced growth factors.

neglected. Kidney-biopsy specimens, taken from the cortex to diagnose glomerular diseases, and tissues obtained at autopsy, processed by en bloc fixation, do not easily permit the evaluation of medullary thick limbs. However, both old and new observations (including the results of electron microscopy) suggest medullary involvement in renal failure,[63,64] with no specific histologic alterations due to nephrotoxins.[65] The original descriptions of lower-nephron nephrosis in patients who died of acute renal failure emphasized the presence of focal necrosis along distal nephrons.[50] Vasa recta are often infiltrated by inflammatory cells, which suggests a reaction to focal injury in the medulla, perhaps in response to the expression of leukocyte adhesion molecules.[54]

Frank necrosis of the renal papillae develops in a variety of conditions associated with medullary ischemia, such as sickle cell disease, damage caused by analgesic abuse, pyelonephritis, urinary obstruction, and diabetes mellitus. In sickle cell disease, medullary hypoxia and hypertonicity cause increased sickling of erythrocytes, increased blood viscosity, and decreased blood flow. Finally, in many forms of chronic renal disease, tubulointerstitial damage — which correlates with progression to uremia — may be caused by a vicious circle of impaired medullary oxygen balance caused by the hypertrophy of remnant nephrons.[45] Clearly incomplete, these observations nevertheless suggest that medullary hypoxic injury has an important role in chronic renal failure.

Additional Dangers to the Renal Medulla

Besides hypoxia, other factors can lead to cellular injury in the renal medulla, primarily because of its function of concentrating solutes. Hyperosmolality in itself imposes large hydrostatic pressure stresses on cellular membranes in the renal medulla during shifts between states of water diuresis and water conservation. Small intracellular molecules (such as sorbitol) that serve to maintain cell volume in response to osmotic stresses are rapidly up-regulated or down-regulated by tubular cells in the renal medulla.[66] Defects in the metabolism of these molecules will surely be found to affect medullary structure and function adversely. Ammonium ions accumulate in the renal medulla and may induce local damage by activating the complement system.[67] Calcium is concentrated in the medulla and can be toxic to cells. Toxic effects may result from the concentration within the medulla of abnormal circulating proteins, such as light chains, hemoglobin, and myoglobin. The

accumulation of lithium in the medulla contributes to polyuria in patients who receive this medication. These additional factors may act in addition to or synergistically with hypoxia to generate tissue injury in the renal medulla.

Therapeutic Implications

Since the work of concentrating the urine predisposes a person to medullary hypoxic damage, reducing this work is an important way to prevent medullary injury. Dehydration, salt and volume depletion, and renal hypoperfusion are major stimuli of urine concentration; every effort should be made to recognize and correct these too often unsuspected and undiagnosed conditions. Nephrotoxins such as radiographic contrast agents and gentamicin are administered to dehydrated patients at a risk frequently recognized only after acute renal failure has occurred. It is important to suspect and correct hypovolemia (even without definite proof) before exposure to nephrotoxins, which should be avoided if renal hypoperfusion (from low cardiac output or atheromatosis) cannot be corrected. Because insults are synergistic, it is imperative to avoid combinations of risks, such as volume depletion and the use of nonsteroidal antiinflammatory drugs and radiographic contrast agents.

Hydration and salt loading, which reduce the work of urine concentration (and stimulate intrarenal protective systems such as prostaglandin and dopamine production), are therefore the optimal prophylaxis against hypoxic injury to the renal medulla. When cardiac failure limits the administration of fluids, furosemide can be given to reduce medullary work, but it can induce volume depletion if fluid is not carefully replaced.[68] Saline hydration is the best protection against renal failure from radiographic contrast agents, cisplatin, amphotericin B, nonsteroidal antiinflammatory drugs, rhabdomyolysis, or multiple myeloma. Mannitol has no advantage over crystalloid solutions and may be injurious in large doses,[69] perhaps because osmotic diuresis aggravates medullary hypoxia.[38] The administration of dopamine does not prevent renal failure in critically ill patients.[70] Once intrarenal hypoxic damage has triggered clinical acute renal failure, no treatment has yet been proved to enhance recovery (the beneficial effect of atrial natriuretic peptide in one study awaits confirmation).

In the future, the stimulation of endogenous protective mechanisms, renal vasodilatation with enhancement of the medullary circulation, the prevention of leukocyte or platelet aggregation, and the exogenous administration of growth factors missing from the injured distal tubule may have an important place in the management of acute renal failure.

Conclusions

Medullary hypoxia is an obligatory part of the mechanisms of renal conservation of water, and it poses a constant threat to cellular integrity in this region of the kidney. In the course of evolution, a remarkable system of autocrine and paracrine defense mechanisms has developed to preserve medullary integrity and function. The failure of one or more of these mechanisms can lead to hypoxic injury and kidney failure.

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