Editorial

Hypoxia of the Renal Medulla

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The kidney poses an interesting paradox with regard to the adequacy of its oxygen supply. Its flow of blood is high in relation to its weight, and renal arteriovenous oxygen difference is lower than in any other organ. The high renal blood flow is commonly viewed as necessary to assure excretion of wastes, and it is often assumed that the supply of oxygen does not normally limit the ability of the kidney to do work. The generous flow of blood should also protect the kidney from ischemia, making it the least likely organ in the body to be damaged by compromised blood flow. Nevertheless, ischemic acute renal failure is one of the most frequent complications of systemic circulatory shock, occurring far more often than injury to brain, heart or liver in the same clinical setting. The explanation for this paradox lies in the remarkable inhomogeneity of blood flow and oxygen supply within the kidney.

Gradients of oxygen availability within the renal parenchyma have been appreciated for many years. Aukland and Krog demonstrated 25 years ago that the pO\(_2\) of the medulla was strikingly lower than renal arterial pO\(_2\) (1). Some 10 years later Leichtweiss and his colleagues (2, 3) confirmed and extended this idea, demonstrating that the medullary pO\(_2\), measured with microelectrodes sensitive to oxygen, was consistently in the range of 10 mmHg in the kidney of the dog and of the rat, both in situ and during isolated perfusion of the kidneys. The sharp corticomedullary gradient of oxygen is most easily explained by the organization of vessels in the medulla. This arrangement, which permits sodium chloride and urea to be concentrated in the final urine and water to be conserved, also allows countercurrent diffusion of oxygen between the arterial and venous branches of the hairpin loops of the vasa recta. In a sense, perpetual hypoxia of the renal medulla is the price we pay, as land animals, for the ability to concentrate our urine.

Recently, evidence has been mounting that renal medullary cells indeed habitually exist in a precarious state with reference to their oxygen supply. Cytochrome a\(_{1}\),a\(_{3}\) (cytochrome C-oxidase), the terminal electron carrier of the mitochondrial chain, is almost completely oxidized at normal oxygen tensions. In mitochondria and separated cells, it exists largely in the oxidized state (4, 5) and does not become significantly reduced until the level of oxygen delivery to the tissue has become insufficient to maintain maximal oxidative metabolism. Surprisingly, experiments on isolated perfused rat kidneys showed that approximately 30 to 45 per cent of cytochrome a\(_{1}\),a\(_{3}\) in the whole perfused kidney was in the reduced state (6). Cytochrome a\(_{1}\),a\(_{3}\) was also found to be partially reduced in intact rat kidneys studied in vivo (7).
Experiments designed to reduce oxidative metabolism in proximal tubules and hence improve oxygenation in the cortex were without effect in altering the redox state. In contrast, the loop diuretics bumetanide and furosemide, which inhibit active transport in the medullary thick ascending limb invariably produced partial oxidation of cytochrome \( a,a_3 \) (6).

These findings suggest that cells of the renal medulla normally operate at or close to the brink of anoxia. The well known capacity of renal medullary tissue for obtaining energy from glycolysis is presumably a partial adaptation to its hypoxic environment. However, because of the inefficiency of glycolysis as compared with oxidative metabolism, only a portion of the energy needs of the medulla can normally be met by anaerobic metabolic pathways (8). An implication of these results is that a delicate and sensitive mechanism must exist to regulate local blood flow in response to metabolic demand. Derangement of this mechanism is likely to predispose to ischemic necrosis.

Cells of the thick ascending limb of Henle's loop, within the hypoxic renal medulla, carry a special burden. Loaded with mitochondria, they are responsible for a substantial fraction of the active reabsorption of sodium chloride as well as calcium and magnesium, and for the energy-requiring processes necessary for dilution and concentration of the urine. They are therefore uniquely susceptible to oxygen lack. The morphological consequence of this special susceptibility is easily detected. During isolated perfusion of the rat kidney with cell-free albumin—Ringer’s medium, the medullary thick ascending limb appears selectively vulnerable to anoxic injury (9). A specific lesion is consistently observed, confined to this nephron segment, that progresses from mitochondrial swelling to nuclear pyknosis and complete cellular disruption. It is most prominent in areas most likely to be anoxic according to expected gradients of \( pO_2 \); that is, those tubules near the inner medulla or at a distance from medullary capillaries. (The latter, it should be noted, derive principally from cortical nephrons (10).) Hypoxic perfusion markedly exaggerates the lesion and extends it to all medullary thick limbs (11). Oxygen-enriched perfusions using rat erythrocytes or hemoglobin prevent the lesion (9).

Of particular interest is that inhibition of cell transport activity with furosemide or ouabain, or by the abolition of glomerular filtration, can protect the medullary thick limb (12). Even the extensive anoxic damage produced in this model by perfusion with cyanide or by a hypoxic medium is remarkably attenuated by reduction of active transport produced by ouabain or furosemide (11). Furthermore, perfusion with a polyene antibiotic such as amphotericin or nystatin which increases membrane permeability and stimulates the sodium pump reproduces severe anoxic-like injury to this nephron segment, which is prevented if active ion transport is inhibited by ouabain (13). Oxygen deficiency is thus related to the energy requirements mandated by cell work. The outer medulla apparently exhibits a sort of anginal syndrome in which the degree of cellular anoxia depends on the demand for oxygen as well as its supply.

Some implications of medullary hypoxia for the pathogenesis of renal disease come readily to mind. If the thick ascending limb was particularly susceptible to anoxic interference with active transport, it would be easy for relatively minor degrees of global renal ischemia to initiate glomerular vasoconstriction via the tubuloglomerular feedback mechanism (14) and thus contribute to the functional impairment of acute renal failure. In the setting of the precarious balance between oxygen demand and supply in the renal medulla, the reduction of cortical blood flow during hypotension or hypovolemia may be viewed as designed to protect medullary cells from ischemic injury. This is accomplished both directly by increasing the relative proportion of renal oxygen delivery to the medulla, and indirectly by decreasing oxygen demand for NaCl absorption in the thick limb, as glomerular filtration rate falls. When medullary ischemia occurs, solute that escapes reabsorption in the thick limb and reaches the macula densa will activate tubuloglomerular feedback. The ensuing profound decrease in glomerular filtration rate may be viewed as designed to decrease the need for oxygen required
in the active reabsorption of salt, in an effort to protect the ischemic medullary thick ascending limb from further damage. Flow through outer cortical glomeruli would be expected to shut down before juxtamedullary glomerular filtration is affected, since the thick limbs of nephrons originating in the superficial cortex are at the greatest distance from capillaries of the outer medulla (10), and therefore are at the greatest risk of hypoxia. This may explain why outer cortical blood flow is in fact preferentially reduced in a variety of circulatory disorders such as hemorrhage, congestive cardiac failure and cirrhotic ascites, in which effective cardiac output, arterial blood pressure and renal blood flow are menaced (15). It is pertinent that decreased concentrating ability, implying impaired function of the thick ascending limb, is not only the defect most consistently encountered in acute renal failure, but is also an early sign of impending renal failure in advanced prerenal azotemia secondary to hypotension or to a decrease in cardiac output (16).

The special susceptibility of medullary cells to anoxic damage plays an obvious role in the pathogenesis of nephropathy in sickle cell anemia. Sickle cells change their shape in the hypoxic milieu of the renal medulla, greatly increasing the viscosity of blood and hence the resistance to flow through medullary vasa recta. Medullary ischemia is responsible for the characteristic impairment of renal concentrating ability, and for the signs of kidney damage, including medullary fibrosis, papillary necrosis, and progressive renal failure, which mark the eventual course of many adults with this disease (17). The marked hypertrophy of juxta-medullary glomeruli noted in autopsies of patients with sickle cell anemia may be understood as a consequence of the redistribution of blood flow between superficial and deep glomeruli referred to earlier that is probably induced by medullary ischemia.

Hypoxic injury to medullary cells can be exacerbated by manoeuvres which increase metabolism. An example of this effect is the nephrotoxic action of amphotericin and other polyene antibiotics, which act as ionophores, increasing the influx of sodium into cells of the medullary thick limb, whence it must be pumped out by Na—K—ATPase (13). Cell injury is prevented by inhibiting the sodium pump. It now seems likely that other toxic agents including certain forms of immune-mediated injury may injure hypoxic cells via a similar mechanism. This suggests a possible avenue for future therapeutic approaches to limiting damage.

The close dependence of experimental ischemic injury on active transport suggests that endogenous inhibitors of transport might play an important physiological role in modulating the susceptibility of the medulla to anoxic injury. Prostaglandin E₂ and other arachidonic acid derivatives are produced by cells of the mTAL (18). PGE₂ is a potent vasodilator and also inhibits active transport in the medullary thick limb (19). It might therefore be predicted that indomethacin and other cyclooxygenase inhibitors would exaggerate the lesions of hypoxia seen in the isolated perfused kidney. This is indeed the case. The addition of indomethacin to the perfusion medium greatly increases the extent and severity of cell injury seen in the renal medulla, presumably because the endogenous restriction of transport work imposed by endogenous prostaglandins is removed. It is likely that this effect, demonstrable in perfused kidneys, is primarily responsible for the lesion of analgesic nephropathy, seen in patients addicted to daily ingestion of large amounts of pain-relieving medications and characterized by interstitial fibrosis that is especially marked in the renal medulla, progressing to papillary necrosis.

Because of the uniquely low ambient partial pressure of oxygen in the renal medulla, imposed by the environmental requirement that mammalian kidneys must concentrate urine, it seems probable that a variety of mechanisms have evolved which permit medullary cells to function on the verge of anoxia while protecting them from irreversible ischemic injury. Their elucidation is likely to clarify further our understanding of clinical disorders of the function of the kidneys.
REFERENCES