Diabetic nephropathy: nitric oxide and renal medullary hypoxia

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Diabetes, specifically diabetic nephropathy, is the most frequent cause of end-stage renal disease (ESRD) in developed countries (10). Classically, studies into the mechanisms underlying diabetic nephropathy have focused on glomerular injury and the development of albuminuria; however, changes in tubulointerstitial structure and function are also evident even during the early stages in diabetes (3, 4, 11, 13, 14, 16). Changes in proximal tubule structure consistent with hypertrophy (increases in cell height, tubule diameter, and length) are a prominent component of diabetic renal hypertrophy, with other nephron segments also displaying changes in tubule length (13, 14). There is evidence of altered renal handling of electrolytes, including Na+, and increased renal Na+-K+-ATPase (NKA) activity has been widely reported in diabetes. The changes in NKA activity accompanying type 1 diabetes mellitus coincide with, and thus may play a role in, the development of hypertrophy. On the other hand, as NKA-mediated ion transport is the major consumer of metabolic energy in the kidney, the early and pronounced increase in tubular NKA activity in diabetes has been proposed to represent an important adaptive response to the osmotic diuresis (4, 16) and/or the chronic increase in filtered Na+ load. Uproloration of NKA activity is particularly evident in the outer medulla (3, 4, 16), where low blood flow limits O2 supply despite high O2 consumption coupled with reabsorptive Na+ transport. As O2 extraction is almost maximal under normal conditions in the outer medulla, the increased NKA activity linked to increased Na+ transport during diabetes is accompanied by reduced Po2 in this region that normally exists near the brink of hypoxia. Thus diabetes would promote chronic hypoxia, which may be a common pathway leading to ESRD (8).

In the healthy kidney, the renal medulla has high concentrations of nitric oxide (NO) (18). Reduced NO bioavailability has been shown to result in increased O2 consumption and, therefore, increased sodium reabsorption in the renal medulla (2, 5). Diabetes is known to be a condition of oxidative stress and reduced NO bioavailability. Little information is available in the literature pertaining to the status of NO and O2 availability in the renal medulla during diabetes. Palm and colleagues (12) have begun to unravel the complex mechanisms involved in the interrelationship between reduced NO bioavailability and hypoxia in the renal medulla in the early stages of diabetes. Palm et al. (12) report that reduced renal medullary NO levels in diabetes are due to decreased plasma l-arginine and unrelated to diabetes-induced oxidative stress, while the reduction in medullary Po2 was restored by l-arginine administration or antioxidant treatment. The authors also observed that the O2 availability in both normal and diabetic rats was independent of blood flow alterations. These observations underscore the potential importance of diabetes-induced renal metabolic alterations and their functional consequences.

At physiological concentrations, NO inhibits the mitochondrial enzyme cytochrome c oxidase (complex IV) in competition with O2, thereby impeding mitochondrial respiration (17). When NO levels are decreased, such as in diabetes, this regulatory mechanism is dysfunctional, thus allowing increased mitochondrial respiration and O2 consumption. Thus, in addition to effects of diabetes to increase Na+ transport-dependent O2 consumption and NKA activity in the outer medulla, altered NO bioavailability may increase mitochondrial O2 consumption and contribute to reduced Po2 under these conditions. Although the validity of this scenario remains speculative, the data from Palm et al. (12) establish a link between NO synthase substrate availability and the changes in medullary Po2 accompanying diabetes.

Hypoxia induces regulatory mechanisms via its influence on gene expression, specifically through a family of transcription factors known as hypoxia inducible factors (HIFs). HIFs are considered to be master regulators of gene expression during hypoxia, impacting expression of almost all glycolytic enzymes and glucose transporters (15). HIF expression is inversely related to Po2 in multiple cell types, including cells of the renal medulla (19). Renal HIF levels are low or absent under normal conditions, with hypoxia provoking HIF accumulation that varies with respect to isofrom, kidney zone, cell type, and the exact nature of the hypoxic stimulus (15, 19). Most HIF-induced responses confer protection against hypoxic injury; however, renal profibrotic genes have also been shown to be directly upregulated by hypoxia (7, 9). NO has been shown to regulate the activity and/or expression of HIF-degrading enzymes with no clear consensus on whether NO activates or blunts the HIF-degrading enzymatic activity (1, 6). Very little information is available concerning whether HIF activates renoprotective mechanisms and profibrotic genes in the hypoxia-prone renal medulla during diabetes and/or whether NO regulates HIF levels under these conditions.

The observations of Palm et al. (12) should fuel future studies that focus on the interaction of NO and O2 availability, as well as the effects of NO on mitochondrial respiration and HIF-dependent responses, during the early stages of diabetes in the renal medulla. These processes associated with renal medullary hypoxia may interact in an additive or synergistic manner with the hemodynamic events that evoke glomerular hyperfiltration, ultimately contributing to the development of diabetic nephropathy.

REFERENCES


