Protective Effect of Nrf2 and Catalase in Maternal Diabetes-Induced Perinatal Hypertension and Kidney Disease

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A small but significant amount of reactive oxygen metabolites (ROMs) is generated in the course of metabolism by mitochondria and numerous cellular oxygenases, oxidases, and peroxidases. Under normal conditions, ROMs produced in the course of metabolism and signal transduction processes are contained by the antioxidant system, which consists of numerous endogenous enzymes, substrates, and scavenger molecules as well dietary antioxidants. Individual components of the antioxidant system serve specific functions and work in concert to protect against tissue injury. Nuclear factor erythroid 2p45-related factor 2 (Nrf2) regulates and work in concert to protect against tissue injury. Nuclear factor erythroid 2p45-related factor 2 (Nrf2) regulates constitutive expression and coordinated induction of numerous genes encoding antioxidant and phase-2 detoxifying enzymes and related proteins, such as superoxide dismutases (SODs), catalase, UDP-glucuronosyltransferase, NAD(P)H:quinone oxidoreductase-1 (NQO1), heme oxygenases (Hoes), catalase, and glutathione peroxidase [H2O2 + GSH → 2H2O + SG-GS], where GSH is glutathione and SG-GS is the oxidized GSH. However, it can serve as the substrate for nearly uncontrollable and highly cytotoxic oxidants such as hydroxyl radical (’OH) in presence of catalytically active iron [H2O2 + Fe2+ → OH + OH− + Fe3++] or other transition metals and to hypochlorous acid (HOCl, commonly known as bleach) in presence of myeloperoxidase, which is abundantly expressed in granulocytes, monocytes, and macrophages [H2O2 + Cl− → HOCl]. Unlike superoxide and hydrogen peroxide, which are readily contained by the above enzymes, cells have no enzymes to neutralize hydroxyl radical or hypochlorous acid, which once formed freely damage tissues by attacking and denaturing nucleic acids, proteins, and lipids. Therefore, conditions that lead to impaired containment of hydrogen peroxide or facilitate its conversion to hydroxyl radical or hypochlorous acid can lead to cell damage and dysfunction. In this context, glycated proteins, which are produced in the hyperglycemic states, avidly bind iron and other transition metals, forming complexes in which the transition metals retain their catalytic activities (7). Conversely iron and other transition metals facilitate glycation of protein (8). In fact plasma nontransferrin-bound iron level is elevated in diabetic patients and has been implicated in the pathogenesis of the kidney and vascular complications (9).

The imbalance between the rate of ROM production and the antioxidant capacity leads to oxidative stress in which the uncontained ROMs cause tissue injury and cytotoxicity by attacking, denaturing, and modifying structural and functional molecules and activating redox-sensitive transcription factors and signal transduction pathways. These events lead to necrosis, apoptosis, inflammation, fibrosis, and other disorders that participate in the pathogenesis and progression of many acute, chronic, and degenerative disorders. Oxidative stress is caused by either increased ROM production, impaired antioxidant defense capacity, or both.

Exposure of the embryo to sustained elevation of glucose during the early stages of gestation in humans and experimental animals can result in cardiovascular, neurological, skeletal, and urogenital birth defects and partial or total renal agenesis (10). In fact elevated maternal glucose concentration has been shown to result in impaired renal...
morphogenesis, disruption of the ureteric bud iterations, reduction of the nascent nephron population, and increased apoptosis in the mice embryos. These defects are mediated by increased generation of ROM to which embryos are particularly vulnerable because of their low antioxidant capacity occasioned by the hypoxic intrauterine environment (11–15). By activating the redox-sensitive transcription factor, NF-κB, which is the master regulator of proinflammatory cytokines and chemokines, oxidative stress promotes inflammation. In fact, maternal diabetes-induced changes in the renal morphogenesis are accompanied by oxidative stress and inflammation (16). It is of interest that conditions associated with chronic inflammation and oxidative stress such as chronic granulomatous disease (17), asthma (18), and chronic kidney disease (19,20) are paradoxically associated with impaired Nrf2 activity, which renders the host vulnerable to the ravages of ROMs. This is due to the interference of the NF-κB P65 and P53 subunits with the dissociation of Nrf2 from Keap 1 and binding of Nrf2 to the antioxidant response elements of the target genes (21,22).

ROM production in mitochondria rises when oxygen supplies are low and/or substrate delivery is high. Increased supply of glucose in uncontrolled diabetes in the face of the hypoxic intrauterine milieu can raise mitochondrial production of ROS in the embryo. The proximal tubular epithelial cells in the embryo are particularly susceptible to hyperglycemia-induced oxidative stress. First, the impact of hyperglycemia on glucose load is far greater in proximal tubular epithelial cells than in any other cell type in the body because they serve as the vehicle for uptake of massive quantities of filtered glucose via their apical sodium/glucose cotransporter. Second, the heavy demand for generation of ATP to accommodate reabsorption of filtered sodium by the Na/K ATPase pump in the face of intrauterine hypoxic milieu can increase ROM production. Together these factors render the proximal tubular epithelial cells highly susceptible to oxidative injury (Fig. 1). In fact, in this issue of the journal, Chang et al. (23) have shown significant reduction in the size of the kidney and the number of glomeruli in the neonatal period and marked elevation of blood pressure, renal tissue ROM production, transforming growth factor-β expression, and matrix protein accumulation in adulthood in the offspring of female mice with severe diabetes. They have further shown prevention or significant attenuation of these abnormalities in the offspring of diabetic mice with targeted overexpression of catalase in the renal proximal tubular epithelial cells. The protective effect of the overexpression of catalase was accompanied by increased abundance and activity (nuclear translocation) of Nrf2 and expression of heme oxygenase-1 which is one of the many Nrf2 target gene products. These findings have provided irrefutable evidence for the role of ROMs, particularly H$_2$O$_2$, in the pathogenesis of and the protective effects of Nrf2 and its target gene products, especially catalase, against the maternal diabetes–induced perinatal programming of renal disease and hypertension.

ACKNOWLEDGMENTS
No potential conflicts of interest relevant to this article were reported.

**FIG. 1.** Uncontrolled maternal diabetes results in impaired placentation and fetal hyperglycemia, which respectively lead to diminished oxygen delivery and increased filtered glucose load to the developing fetal kidney. Together, the reduction in oxygen supplies and increased substrate delivery heighten mitochondrial production of ROMs. This is compounded by production of glycated proteins, which bind iron to form complexes in which iron can readily catalyze conversion of hydrogen peroxide to hydroxyl radical, the most cytotoxic ROM known. ROMs, in turn, activate NF-κB, which simultaneously results in immune cell activation and ROM generation as well as inhibition of Nrf2-mediated production of antioxidant and cytoprotective molecules. The combination of excess ROM generation and antioxidant depletion leads to oxidative stress in the developing embryonic kidney. The associated oxidative stress and inflammation results in impaired renal morphogenesis, diminished nascent nephron population, and other abnormalities that can predispose the offspring to development of hypertension and chronic kidney disease later in life. (A high-quality color representation of this figure is available in the online issue.)
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