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Mitochondrial DNA Defect and Mitochondrial Dysfunction in Diabetic Nephropathy: The Role of Hyperglycemia-Induced Reactive Oxygen Species

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Abstract : Mitochondria are the site of cellular respiration and produce energy in the form of adenosine triphosphate (ATP) via oxidative phosphorylation. They are the major source of intracellular reactive oxygen species (ROS) and are also direct target to ROS attack. Oxidative stress and ROS-mediated disruptions of mitochondrial function are major components involved in the pathogenicity of diabetic complications. In this work, the changes in mitochondrial DNA (mtDNA) copy number, biogenesis, gene expression of mtDNA-encoded subunits of electron transport chain (ETC) complexes, and mitochondrial function in response to hyperglycemia-induced ROS and the effect of direct inhibition of ROS on mitochondria were investigated in an in vitro model of diabetic nephropathy using human renal mesangial cells. The cells were exposed to normoglycemic and hyperglycemic conditions in the presence and absence of Mn(III)tetrakis(4-benzoic acid) porphyrin chloride (MnTBAP) or catalase for 1, 4 and 7 days. ROS production was assessed by the confocal microscope and flow cytometry. mtDNA copy number and PGC-1a, NRF-1, and TFAM, as well as ND2, CYTB, COI, and ATPase 6 transcripts, were all analyzed by real-time PCR. PGC-1a, NRF-1, and TFAM, as well as ND2, CYTB, COI, and ATPase 6 proteins, were analyzed by Western blotting. Mitochondrial function was determined by assessing mitochondrial membrane potential and adenosine triphosphate (ATP) levels. Hyperglycemia-induced a significant increase in the production of mitochondrial superoxide and hydrogen peroxide at day 1 ($P < 0.05$), and this increase remained significantly elevated at days 4 and 7 ($P < 0.05$). The copy number of mtDNA and expression of PGC-1a, NRF-1, and TFAM as well as ND2, CYTB, CO1 and ATPase 6 increased after one day of hyperglycemia ($P < 0.05$), with a significant reduction in all those parameters at 4 and 7 days ($P < 0.05$). The mitochondrial membrane potential decreased progressively at 1 to 7 days of hyperglycemia with the parallel progressive reduction in ATP levels over time ($P < 0.05$). MnTBAP and catalase treatment of cells cultured under hyperglycemic conditions attenuated ROS production reversed renal mitochondrial oxidative stress and improved mtDNA, mitochondrial biogenesis, and function. These results show that hyperglycemia-induced ROS caused an early increase in mtDNA copy number, mitochondrial biogenesis and mtDNA-encoded gene expression of the ETC subunits in human mesangial cells as a compensatory response to the decline in mitochondrial function, which precede the mtDNA defect and mitochondrial dysfunction with a progressive oxidative response. Protection from ROS-mediated damage to renal mitochondria induced by hyperglycemia may be a novel therapeutic approach for the prevention/treatment of DN.

Keywords : diabetic nephropathy, hyperglycemia, reactive oxygen species, oxidative stress, mtDNA, mitochondrial dysfunction, manganese superoxide dismutase, catalase
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