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Mitochondrial Morphology and Function in Diabetes

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Coronary heart disease and ischemic stroke are the main causes of morbidity and mortality in diabetic patients. Coronary blood flow and coronary vascular resistance are regulated by coronary vascular tension and vascular/capillary density. We recently reported that the vascular relaxation in coronary artery and capillary density in the heart were both decreased in diabetes. Mitochondria constantly undergo changes in the shape and morphological feature that affect cell functions. It is now clear that unbalanced fission/fusion ratio in mitochondria is an important contributor for inducing cell apoptosis. The objective of this study is to examine whether mitochondrial morphology is altered in coronary endothelial cells (ECs) in diabetes and to explore the potential mechanisms that lead to mitochondrial fusion. Our results demonstrate that the percentage of apoptotic ECs in the left ventricle was significantly higher in diabetic mice than in control mice. Elongated mitochondrial tubules were observed in mouse coronary ECs isolated from control mice, whereas mitochondria in coronary ECs from diabetic mice exhibited significantly augmented fragmentation. Among five fusion/fission-related proteins, optic atrophy 1 (OPA1) protein, which leads to mitochondrial fusion, was significantly decreased, whereas dynamin-related protein 1 (DRP1), which leads to mitochondrial fission, was significantly increased, in coronary ECs from diabetic mice. High glucose-induced mitochondrial fission was restored by DRP1-shRNA transfection. Mouse coronary ECs exhibited significantly high concentration of O_2^-, while chronic treatment of coronary ECs with O_2^- scavenger significantly increased mitochondrial fusion in diabetes. In addition, resting mitochondrial Ca^{2+} concentration ($[Ca^{2+}]_{mito}$) and Ca^{2+} uptake into mitochondria from the endoplasmic reticulum (ER) were significantly increased in mouse coronary ECs in diabetes compared to control ECs. Voltage-dependent anion channel (VDAC) regulates Ca^{2+} uptake in mitochondria and the mitochondria-ER bridge composed by VDAC, IP_3 receptor and GRP75 can facilitate Ca^{2+} overload into mitochondria from the ER. In diabetic ECs, VDAC protein expression was significantly upregulated and VDAC-shRNA-adenoviral infection significantly decreased resting $[Ca^{2+}]_{mito}$ and inhibited Ca^{2+} overload after induction of Ca^{2+} leakage from the ER by cyclopiazonic acid treatment in diabetic coronary ECs. Taken together, our data demonstrate that O_2^- overproduction and DRP1 protein upregulation lead to mitochondrial fragmentation in coronary ECs in diabetic mice. Treatment with O_2^- scavengers may improve mitochondrial function by decreasing mitochondrial fragmentation in coronary ECs. Furthermore, the increase in VDAC protein expression leads to Ca^{2+} overload in mitochondria in diabetic coronary ECs, whereas inhibition of VDAC protein expression may contribute to preventing EC-apoptosis in diabetes.