Endothelial Cell-Derived Endothelin-1 Promotes Cardiac Lipid Accumulation in Diabetic Heart

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Persistently high plasma endothelin-1 (ET-1) in diabetes patients has been associated with development of diabetic cardiomyopathy, of which cardiac lipotoxicity being proposed as central in the pathophysiology. Recently we reported that ET-1 contributes to development of cardiac fibrosis in late stage of diabetic heart. Here we hypothesize that ET-1 might contribute to lipid accumulation and oxidative stress in early stage of diabetic heart. To test this hypothesis, we developed type 1 diabetes model by streptozotocin injection in vascular endothelial cell-specific ET-1 knockout (VEETKO) mice, of which ET-1 expression in the heart were reduced by 60%, and to its wild type (WT) littermates. Diabetes increased cardiac ET-1 expression in WT heart 1.5 folds of that in VEETKO heart, which revealed stimulation of ET-1 production from endothelial cells. Electron microscopy shows disruption of cardiac mitochondria and myofibrils, along with accumulation of lipid droplets in WT heart after 8 weeks of hyperglycemia, but not in VEETKO heart. Cardiac content of triacylglycerol and nonesterified fatty acids were increased in WT heart, which were prevented in VEETKO mice (21.13±4.08 vs.14.95±6.3 mg/g heart, $p<0.01$, $n=5$ each). This lipid accumulation further stimulates higher superoxide production in WT heart as compared to VEETKO heart, as shown by lucigenin chemoluminescence assay (6.2±0.8 vs. 2.6±0.5 CPM/g dried heart, $p<0.01$, respectively). Interestingly, we observed similar cardiac apoptosis rate in both genotypes which suggest possible anti-apoptotic properties of ET-1 in cardiomyocyte. However, prominent cardiac lipotoxicity and oxidative stress in WT heart further leads to progression of cardiac dysfunction in WT mice. In conclusion, our study shows that endothelial cells-derived ET-1 involved in lipid accumulation and superoxide production in early stage of diabetes heart. The precise mechanism linking ET-1 with cardiac lipid accumulation remains to be investigated.