

1: [Am J Physiol Heart Circ Physiol](#). 2005 Aug;289(2):H768-76. Epub 2005 Apr 1.

**Cardiomyocyte apoptosis induced by short-term diabetes requires mitochondrial GSH depletion.**

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**Oxidative stress due to excessive reactive oxygen species (ROS) and depleted antioxidants such as glutathione (GSH) can give rise to apoptotic cell death in acutely diabetic hearts and lead to heart disease.** At present, the source of these cardiac ROS or the subcellular site of cardiac GSH loss [i.e., cytosolic (cGSH) or mitochondrial (mGSH) GSH] has not been completely elucidated. With the use of rotenone (an inhibitor of the electron transport chain) to decrease the excessive ROS in acute streptozotocin (STZ)-induced diabetic rat heart, the mitochondrial origin of ROS was established. Furthermore, mitochondrial damage, as evidenced by loss of membrane potential, increases in oxidative stress, and reduction in mGSH was associated with increased apoptosis via increases in caspase-9 and -3 activities in acutely diabetic hearts. To validate the role of mGSH in regulating cardiac apoptosis, L-buthionine-sulfoximine (BSO; 10 mmol/kg ip), which blocks GSH synthesis, or diethyl maleate (DEM; 4 mmol/kg ip), which inactivates preformed GSH, was administered in diabetic rats for 4 days after STZ administration. Although both BSO and DEM lowered cGSH, they were ineffective in reducing mGSH or augmenting cardiomyocyte apoptosis. To circumvent the lack of mGSH depletion, BSO and DEM were coadministered in diabetic rats. In this setting, mGSH was undetectable and cardiac apoptosis was further aggravated compared with the untreated diabetic group. **In a separate group, GSH supplementation induced a robust amplification of mGSH in diabetic rat hearts and prevented apoptosis. Our data suggest for the first time that mGSH is crucial for modulating the cell suicide program in short-term diabetic rat hearts.**

PMID: 15805231 [PubMed - indexed for MEDLINE]

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