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The effect of 20 hydroxyeicosatetraenoic acid antagonism on myocardial infarction of metabolic syndrome rats

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Abstract

20-Hydroxyeicosatetraenoic acid (20-HETE) is a cytochrome p450-derived eicosanoid that stimulates endothelial dysfunction and inflammation via binding to its receptor, GPR75 (GPCR-Gαq/11). Increased 20-HETE in animals and humans is associated with hypertension, stroke, myocardial infarction (MI), metabolic syndrome (MetS), and increased reactive oxygen species (ROS). However, investigated effectiveness of 20-HETE antagonists on ROS generation and MI size has been limited by short-term follow up and administration of inhibitors prior to onset of MI only in healthy animals. Here, we evaluated the effect of a 20-HETE antagonist, 20-SOLA, administered at onset of reperfusion on post MI remodeling 48 hours and 8 weeks after reperfusion in normal (SD) and MetS (JCR:LA-cp) rats. 20-HETE was elevated in response to ischemia and more so during reperfusion; this elevation was greater in MetS (ischemia: 2-fold SD and JCR; reperfusion: 3-fold SD, 4-fold JCR). MI size was markedly greater in JCR vs. SD rate (50% vs. 25% of LV). Treatment with 20-SOLA significantly decreased MI size in both SD (~50%) and JCR (~65%) rats. Equivalent results were obtained in animals treated with GPR75-shRNA-Lnv at onset of reperfusions. 20-SOLA improved coronary blood flow (1.00 ± 0.01 to 1.84 ± 0.03 mg/ml/g in SD to 0.99 ± 0.03 to 1.75±0.01 mg/ml/g in JCR).

Mechanistically, smaller MI size in 20-SOLA-treated animals correlated with decreased ROS production in JCR rats (90%). Furthermore, survival and left ventricular (LV) function were preserved 8 weeks post MI in 20-SOLA-treated animals (ejection fraction (EF) = 80.5% (SD, 100% survival) and 82.5% (JCR, 100% survival))This correlated with decreased ROS, preserved myocyte morphology, and preserved intact collagen. Differential activation of MMPs in SD vs. JCR rats vs. 20-SOLA-treated animals underlie the observed morphological, structural and functional changes. ROS production was decreased in JCR rats treated with a NOX inhibitor (~60%); NOX inhibition also markedly reduced MI size at 48h (60%) and preserved LV function at 8 weeks (EF = 74%, 85% survival) vs. non-treated rats demonstrating an important role for NOX-derived ROS in determining MI size and long-term post-MI remodeling. In the aggregate, these results indicated that targeting 20-HETE actions may be an important consideration in prevention of detrimental LV remodeling and mortality post MI. Funding: HL093052.

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