110. Protective and Preservative Effect of NecroX-5 During Hypoxia/Reoxygenation Injury Through Mitochondrial Oxidative Phosphorylation and PGC1

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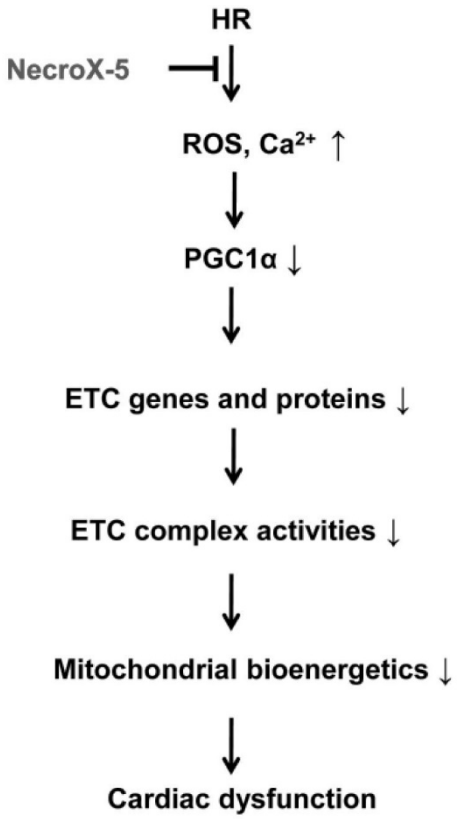
Body

Background: Preservation of mitochondrial function is important for limiting myocardial damage in ischemic heart diseases. NecroX compounds are cell-permeable necrosis inhibitors with antioxidant activity that localize mainly in the mitochondria. NecroX-5 strongly protects rat heart mitochondria against reperfusion injury by reducing mitochondrial oxidative stress, preserving the mitochondrial membrane potential, improving mitochondrial oxygen consumption, and attenuating mitochondrial Ca2+ accumulation by mitochondrial calcium uniporter inhibition. Here we verify the role of NecroX-5 in protecting mitochondrial oxidative phosphorylation capacity during hypoxia-reoxygenation (HR).

Methods: Necrox-5 treatment (10 uM) and non-treatment were employed on isolated rat hearts during hypoxia/ reoxygenation treatment using an ex vivo Langendorff system. Proteomic analysis was performed using liquid chromatography-mass spectrometry and non-labeling peptide count protein quantification. Real-time PCR, western blot, citrate synthases and mitochondrial complex activity assays were then performed to assess heart function.

Results: Treatment with NecroX-5 during hypoxia significantly preserved electron transport chain proteins involved in oxidative phosphorylation and metabolic functions. NecroX-5 improved mitochondrial complex I, II, and V function. Mitochondrial ATP generating capacity is improved and may contribute to improved modulation of ROS production during HR upon NecroX-5 treatment. Markedly higher peroxisome proliferator-activated receptor gamma coactivator-1 (PGC1) expression levels were also observed in NecroX-5-treated hearts. Increased PGC1α levels in NecroX-5 group may be a result of lower ROS and calcium levels.

Conclusion: These novel results provide convincing evidence for the role of NecroX-5 in protecting mitochondrial oxidative phosphorylation capacity and in preserving PGC1α during cardiac HR injuries. The proposed function of NecroX-5 suggests for the first time that the protection of OXPHOS capacity and preservation of PGC1α expression may account for the protective effects of NecroX-5 against HR-induced injury.



Clinical Implications: My study will give cardiovascular clinicians a potential drug treatment modality with the development of NecroX-5 as a therapeutic drug for HR-induced injury based on its protective effect to the heart.