Abstract of the Thesis

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Abstract

Background: Myocardial infarction (MI) has been a major health concern mainly caused by reduced blood flow to the myocardium due to occlusion in the coronary circulation. Although the early reperfusion is vital to salvage the ischemic myocardium, the very reperfusion itself can cause injury to the myocardium. Currently available treatment approaches mostly aim to restore blood flow but they do not adequately address the molecular mechanisms that cause immediate and long term changes in MI. Heme oxygenase-1 (HO-1), a stress-response enzyme, plays an important role to produce cytoprotective effects by catalytic degradation of Heme to biliverdin, carbon monoxide (CO), and free iron.
Objectives: Current study aims to evaluate the cardioprotective effects of Heme oxygenase-1 modulation in MI in rats and its role in activation of downstream components of important pro-survival signaling pathways.
Methods: The current study was conducted in using three methodological approaches: 1) Ex-vivo: IRI was induced in isolated rat heart using Langendorff perfused heart model 2) In vivo: Isoproterenol (ISO)-induced MI in rats; and 3) In vitro: ISO-induced injury in H9c2 cardiomyoblasts. HO-1 was modulated using HO-1 inducer, Hemin and HO-1 inhibitor, Zinc Protoporphyrin IX. For mechanistic evaluation, specific pharmacological inhibitors of PI3K (Wortmannin), Protein Kinase C (Chelerythrine), Nitric Oxide Synthase (L-NAME), and ATP-sensitive potassium (KATP) channels (Glibenclamide) were used. Various parameters such as cardiac functional parameters, myocardial injury biomarkers, oxidative stress markers, HO-1, PI3K, and histopathology were assessed.
Results: HO-1 induction by Hemin exerted dose-dependent cardioprotection as evident through improvement in cardiac function and electrophysiological stability; reduction in the level of myocardial injury markers; attenuation of oxidative stress and preservation of myocardial architecture. HO-1 inhibition resulted in the abolished aforementioned protective changes. Mechanistic evaluation through the inhibition of PI3K, PKC, NOS, and KATP pathways revealed involvement of multiple pro-survival mechanisms, with significant involvement of PI3K signaling.
Conclusion: HO-1 induction by Hemin exerts cardioprotection against myocardial injury. The protective effect is mediated through the activation of multiple pro-survival signaling mechanisms with dominant involvement of PI3K signaling.

This PhD Thesis will help in advancing the understanding of cardiovascular pharmacology by providing mechanistic insights into how Heme Oxygenase-1 (HO-1) protects the heart during ischemic injury. It would also help in development of novel therapeutic strategies for myocardial infarction. It would aid in elucidating the specific network of pro-survival signaling pathwaysthat coordinate cardiomyocyte survival and reduce tissue damage. This research also assists in laying the groundwork for designing targeted delivery systems and novel synthetic compounds to safely activate these protective mechanisms without systemic toxicity. This work would also help in evaluating the potential of HO-1 gene modulation as a clinical biomarker and paving the way for new adjunctive therapies to minimize ischemia-reperfusion injury in patients.

List of Publication(s)

(*not beyond two page)

1) Koria H, Mehta A. Hemin-induced HO-1 protects isolated rat hearts from ischemia-reperfusion injury by activation of pro-survival signalling pathways. Am J Transl Res. 2025;17(10):7626–7639. doi:10.62347/XJXV3554.
2) Koria H, Mehta A. Hemin-Induced Heme Oxygenase-1 Induction Preserves Myocardial Architecture and Functions Via PI3K Signalling in Isoproterenol-Induced Myocardial Infarction in Rats. JBras Patol Med Lab.2025; 61(2): 245-251. doi: 10.1900/JBPML.2025.61.02.0 41.
3) Koria H, Mehta A. Cardioprotection at the Molecular Interface: Extracellular and Intracellular Targets in MI Management. Int. J. Pharm. Sci. Rev. Res. 2025;85(6):8-17. doi: 10.47583/ijpsrr.2025.v85i06.002.