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Heme oxygenase system abates visceral adiposity and diabetic cardiomyopathy in obese insulin-resistant rat

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Abstract

Visceral adiposity adversely affects the heart. We investigated the effects of the heme oxygenase (HO) inducer, hemin on pericardial adiposity and diabetic cardiomyopathy in Zucker diabetic fatty rats (ZDF), and age/sex-matchedZucker-lean controls.
Hemin administration restored normal glycemic levels in ZDF rats and suppressed pericardial adiposity with the reduction of pro-inflammatory/oxidative mediators including, TNF-□□□interleukin

(IL)-6, IL-1β, NF-□B, c-Jun-N-terminal kinase (cJNK), endothelin (ET-1), and 8-isoproatane. Similarly, hemin reduced the pro-inflammatory macrophage-M1 phenotype, but increased the M2-phenotype that dampens inflammatory insults in the heart, and improved cardiac hemodynamics by enhancing ejection fraction, stroke volume and cardiac output, while reducing total peripheral resistance. Furthermore, hemin improved glucose metabolism by enhencing insulin-signaling agents like the insulin-receptor substrate- 1 (IRS-1), phosphatidylinositol-3-kinase (PI3K), glucose-transporter-2 (GLUT-4) and protein-kinase-B (PKB). The cardioprotective and insulin-sensitizing effects of hemin were accompanied by increased HO-activity, whereas the HO-blocker, stannous-mesoporphyrin (SnMP) nullified the effects. Interestingly, the hemin effects were less-intense in Zucker-lean controls with healthy status, suggesting greater selectivity in ZDF with disease.

Since NF-□B activates TNF□□ IL6 and IL-1□, while TNF-□ and JNK impair insulin-signaling, the elevated levels of these cytokines in obesity/diabetes would create a vicious cycle that together with 8-isoprostane and ET-1 exacerbates cardiac injury, compromising cardiac function. Therefore, the concomitant reduction of proinflammatory cytokines selective reduction of the macrophage M1-phenotype infiltration coupled to preferential enhancement of the anti-inflammatory M2- phenotye, increased levels of IRS-1, GLUT-4, PI3K, PKB and cardiac hemodynamics may account for enhanced glucose metabolism and improved cardiac function in hemin-treated ZDF.

We conclude that HO-inducers may be explored against the co-morbidity of impaired insulin-signalling, visceral adiposity and diabetic cardiomyopathy.

Biography

Dr. Joseph Fomusi Ndisang is an Associate Professor in the University of Saskatchewan College of Medicine, Department of Physiology. He received postdoctoral training in Physiology at the University of Saskatchewan College of Medicine from 200-2005. He received a PhD in Pharmacology & Toxicology from the University of Florence, Italy, 2000. He received a Doctor of Pharmacy degree from University of Florence, Italy in 1995. He has received several distinguished awards and distinctions including: Fellow of the American Heart Association (FAHA) in 2011; Fellow of the International College of Angiology (FICA) in 2007; Young Investigator Award by International College of Angiology (2007); Young Investigator Award by the American Society of Pharmacology & Experimental Therapeutics-Division for Drug Discovery, Development & Regulatory Affairs (2005); Young Investigator Award by the Society of Experimental Biology and Medicine (2005) He has published 36 manuscripts, 57 abstracts, 2 book chapters, 1 book and has served peer-reviewer for may highly reputed journals and funding agencies in United States, United kingdom and Canada and has also served as external PhD examiner in Canada and internationally .