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Heme Oxygenase (HO)-1 Induction Prevents Endoplasmic Reticulum Stress-Mediated Endothelial Cell Death and Dysfunction

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Diabetes is intimately associated with cardiovascular complications. Much evidence highlighted the complex interplay between Endoplasmic Reticulum (ER) stress and oxidative stress in the pathogenesis of diabetes. Hemeoxygenase-1 (HO-1) induction was shown to protect against oxidative stress in diabetes; however the underlying molecular mechanisms have not yet been fully elucidated. We aim in this project to test the hypothesis that HO-1 induction will protect against high glucose-mediated ER stress and oxidative stress in endothelial cells and will enhance cell survival.

Endothelial cells were cultured in physiological or high concentrations of glucose in the presence of cobalt protoporphyrin 1X (CoPP, HO-1 inducer), 4-phenylbutyrate (PBA, chemical chaperone to inhibit ER stress) or vehicle. Then, ER stress response was assessed (PCR, western blot). The productions of ROS (flow cytometer) and NO (Griess assay) were analysed. Also, apoptosis and caspase 3/7 activity were assessed. High glucose treatment in cells increased protein and mRNA expression of several ER stress response markers (BIP, CHOP, ATF4) and enhanced ROS production in addition to reducing NO release. Interestingly, the pre-treatment of cells with PBA or CoPP significantly reduced high glucose-mediated ER stress and oxidative stress in cells. Also, cells incubated with high glucose had enhanced apoptosis, increased protein expression of cleaved PARP and caspase-7 in addition to enhanced caspases 3/7 activity while cells pre-treated with either PBA or CoPP were totally protected. The mRNA expression of inflammatory cytokine IL-6 was enhanced in cells incubated with high glucose while those pre-treated with PBA or CoPP were prevented.

These results highlight the importance of oxidative stress both in initiating or maintaining ER stress response and in mediating ER stress-induced damage and cell death in endothelial cells. This work also underscores the therapeutic potential of HO-1 induction against hyperglycaemia-mediated endothelial dysfunction.

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