Stress Signaling Inhibitory Effects of Estrogen Cardioprotection in Myocardial Ischemia

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Heart disease is the leading cause of death in women worldwide. However, the molecular pathway that causes different effects in men and women during a myocardial infarction (MI) is unknown. The intersection of glucocorticoid receptors (GRs) and sex hormones is of interest because it may reveal mechanisms related to the positive and/or negative transcriptional control that is related to heart disease. Estrogens, as well as the serotonin receptor 5-hydroxytryptamine 2B receptor (5-HT2BR), have been shown to promote cardiomyocyte survival and mitochondrial function in murine MI models. The purpose of this project is to determine mechanisms whereby glucocorticoids inhibit estrogen transcriptional regulation of 5-HT2BR in cardiomyocytes and to test if glucocorticoids block estrogen cardioprotection via GR inhibitor of ER-a induction 5-HT2BR gene transcription. It has been hypothesized that ER-a genomic regulation of 5-HT2BR is inhibited by GR blocking ER-a access to estrogen receptor elements (EREs) located in the promoter sequence of the 5-HT2BR gene. HL-1 cardiomyocyte treatments and in vivo injections both show the significant repression of 5HT2BR in the presence of estradiol (E2), but the repression of the gene in the presence of dexamethasone (Dex). 5-HT2BR immunohistochemistry (IHC) of human heart tissue samples show the presence of 5-HT2BR in women post-MI, but not in men. In addition, a silico analysis suggests the presence of an ERE and glucocorticoid receptor element (GRE) are competing for the same binding site (~740 bp). This data leads to the conclusion that GR blocking ER-a transcriptional regulation of 5-HT2BR may contribute to mitochondrial dysfunction and cell death after MI in women.

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