

# 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-HT<sub>2</sub>BR), 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-HT<sub>2</sub>BR in cardiomyocytes and to test if glucocorticoids block estrogen cardioprotection via GR inhibitor of ER- $\alpha$  induction 5-HT<sub>2</sub>BR gene transcription. It has been hypothesized that ER- $\alpha$  genomic regulation of 5-HT<sub>2</sub>BR is inhibited by GR blocking ER- $\alpha$  access to estrogen receptor elements (EREs) located in the promoter sequence of the 5-HT<sub>2</sub>BR gene. HL-1 cardiomyocyte treatments and in vivo injections both show the significant repression of 5HT<sub>2</sub>BR in the presence of estradiol (E<sub>2</sub>), but the repression of the gene in the presence of dexamethasone (Dex). 5-HT<sub>2</sub>BR immunohistochemistry (IHC) of human heart tissue samples show the presence of 5-HT<sub>2</sub>BR 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- $\alpha$  transcriptional regulation of 5-HT<sub>2</sub>BR may contribute to mitochondrial dysfunction and cell death after MI in women.