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Regulatory mechanism of 17β-estradiol and/or estrogen receptor β on hypoxia-induced autophagic and apoptotic pathways in H9c2 cardiomyoblast cells

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Myocardial infarction (MI) is the common cause of cardiomyocyte apoptosis and hypoxia alone is sufficient to induce apoptosis of cardiomyocytes. In hearts, autophagy might play important roles in hypoxia-mediated cardioprotection or myocardial damage effects. To date, hypoxia-inducible factor-1α (HIF-1α) transcriptional factor and BH3-only bcl-2 family protein (BNIP3) are known to play fundamental roles in adaptive or death process in response to hypoxia. In addition, hypoxia can induce insulin-like growth factor binding protein 3 (IGFBP-3) to block the IGF1R/PI3K/Akt survival pathway. Therefore, we would like to investigate the molecular mechanism and the interaction of IGFBP-3, HIF-1α and BNIP3 in hypoxia-induced cell injury of H9c2 cardiomyoblast cells. Moreover, 17β-Estradiol (E2) has been reported recently to prevent cardiac apoptosis via estrogen receptors (ERs). Previous studies have ever revealed the novel cardioprotective role of ER β in myocardial ischemia. Therefore, our studies aim to reveal the regulatory mechanism of ER β on hypoxia-induced cell death. Heart-derived H9c2 cells were incubated in normoxic or hypoxic (<1% oxygen) conditions for 24 h after ER β overexpression. Results showed the hypoxia primarily caused HIF-1α expression highly increase, then activated downstream genes such as BNIP3 and IGFBP-3, and further triggered autophagic and apoptotic pathways. However, all phenomena were recovered by E2/ER β overexpression. E2/ER β overexpression also further promoted the cardiac survival pathway related proteins, p-IGF1R and p-Akt activation. Taken together, ER β exerts the protective effect through repressed hypoxia-inducible BNIP3 and IGFBP-3 levels to restrain the hypoxia-induced autophagy and apoptosis effects in H9c2 cardiomyoblast cells.

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