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Activation of g-protein coupled estrogen receptor 1 protects the heart against ischemia/reperfusion injury by inhibiting the mPTP opening via MEK/ERK/GSK-3β pathway

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Introduction: Estrogen effect can be mediated by three receptors: Classical estrogen receptors: alpha (ERα) and beta (ERβ), and recently identified G protein-coupled estrogen receptor1 (GPER1).

Hypothesis: We investigated the role of ERα, ERβ and GPER1 in mediating rapid estrogen-induced cardioprotection in male mice hearts subjected to ischemia/reperfusion using wild type (WT) and gene specific knockout animals.

Methods: Isolated hearts from wild type (WT: C57BL/6NCrL), ERα-/-, ERβ-/- and GPER1-/- were perfused using Langendorff apparatus with Krebs Henseleit buffer (control) or with the addition of estrogen (40 nM). Hearts were subjected to 18 min global ischemia followed by 60 min reperfusion. Cardiac function was recorded during the entire experiment and myocardial infarct size was measured by TTC staining at the end of the reperfusion. Mitochondria calcium retention capacity (CRC) required to induce the mitochondrial permeability transition pore (mPTP) opening were assessed after 10 min reperfusion. Protein levels were measured by Western Blot in whole heart lysates after 5 min treatment just before ischemia, and after 10 min reperfusion. LY294002 and U0126 were used as inhibitor of PI-3K/Akt, and MAPK/ERK translocation, respectively.

Results: In WT, ERα-/- and ERβ-/-, estrogen treatment significantly improved cardiac functional recovery, reduced infarct size and improved mitochondrial CRC. However, estrogen effects were completely absent in GPER1-/-. Estrogen treatment during 5 min before ischemia induced up-regulation of Akt, GSK-3β, and ERK1/2 phosphorylation in WT mouse as compared with control but not in GPER1-/-. U126 abolished estrogen effect on mitochondrial CRC while LY294002 could not prevent estrogen effect on GSK-3β observed in WT. $P<0.05$ and n=3-6.

Conclusion: Rapid activation of GPER1 induces cardioprotection effect against ischemia/reperfusion injury. Estrogen effects through GPER1 are associated with phosphorylation of GSK-3β and ERK1/2, and inhibition of the mPTP opening.

Biography

Jean C. Bopassa is currently working as an Assistant Professor in the Department of Physiology, School of Medicine, University of Texas Health Science Center at San Antonio, USA.

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