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Crucial role of mitofilin and cyclophilin D interaction in post-ischemic GPER1-induced cardioprotection against ischemia-reperfusion injury

Jean C Bopassa

University of Texas Health Science Center, USA

We have recently shown that GPER1 (G protein-coupled estrogen receptor 1) mediates acute pre-ischemic estrogen-induced protection of the myocardium from ischemia/reperfusion injury via a signalling cascade that includes PKC translocation, ERK1/2/GSK-3 β phosphorylation and inhibition of the mitochondrial permeability transition pore (mPTP) opening. Here, we investigated the impact and mechanism involved in post-ischemic GPER1 activation in ischemia/reperfusion injury. We determined whether GPER1 activation at the onset of reperfusion confers cardioprotective effects by protecting against mitochondrial impairment. We found that post-ischemic E2 (17 β -oestrogen) and G1 (both GPER1 agonists) administration to both male and female ovariectomized-rats reduced myocardial infarct size. Post-ischemic E2 administration preserved mitochondrial structural integrity and this was associated with a decrease in ROS production and increased mitochondrial membrane potential, as well as an increase in the mitochondrial Ca²⁺ load required to induce mPTP opening via activation of the MEK/ERK/GSK-3 β axis, effects that were prevented by the GPER1 antagonist, G15. Interestingly, this post-ischemic GPER1 cardioprotection was associated with the decrease degradation of the in the inner mitochondrial membrane protein, referred to as mitofilin, during reperfusion, which protects the interaction between mitofilin-cyclophilin D in the inner mitochondrial membrane resulting in the delay of the initiation of the mitochondrial permeability transition (mPT) that is associated with the mPT pore opening. Additionally, we revealed that the mechanism of mitofilin degradation during reperfusion is associated with its ubiquitination and also with the increase in calpain10 activity.

Biography

Jean C Bopassa pursued his PhD (2007) from Claude Bernard University Lyon 1, France and Postdoctoral studies from Harvard University School of Medicine and the University of California Los Angeles (UCLA) School of Medicine respectively. He is currently the Director of a Cardiovascular Research Program in the Department of Cellular and Integrative Physiology at the University of Texas Health Science San Antonio (UTHealth SA) School of Medicine. He has published more than 25 papers in reputed journals, and has been serving as an Editorial Board Member of repute for several journals.

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