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Simultaneous subthreshold inhibition of MMP, MLCK and NOS activities protects cardiomyocytes from contractile dysfunction induced by hypoxia-reoxygenation

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Injury of the myocardium during ischemia/reperfusion (I/R) is a complex and multifactorial process including uncontrolled protein phosphorylation, increased production of reactive oxygen species such as nitric oxide and peroxynitrite and increased contractile protein degradation by matrix metalloproteinases (MMPs). It has been shown that inhibition of MMP-2, myosin light chain kinase (MLCK) or nitric oxide synthase (NOS) can protect the heart from contractile dysfunction triggered by I/R. In this study, we show that co-administration of a mixture of low (subthreshold) concentrations of inhibitors for MMP activity (doxycycline), MLC1 phoshorylation (ML-7 inhibitor of MLCK) and nitric oxide synthase (1400W or L-NAME) protects cardiomyocytes from hypoxia-reoxygenation (H-R) induced contractile dysfunction. Isolated cardiomyocytes were subjected to 2 min hypoxia and 20 min reoxygenation (H-R) in the presence or absence of the inhibitor cocktail. Contractility of cardiomyocytes was expressed as myocyte peak shortening. Inhibition of MMP-2 by doxycycline (25-100 μM), MLCK by ML-7 (0.5-5 μM) and NO synthase with L-NAME (25-100 μM) or 1400W (25-100 μM) protected myocyte contractility after H-R in a concentration dependent manner. This led to full recovery of contractile dysfunction induced by H-R. Mixture of NOS, MMP-2 and MLCK inhibitors in subthreshold or lower concentrations protected cardiomyocyte contractility and MLC1 from degradation by MMP-2. The results of this study suggest that administration of a mixture of low (subthreshold) concentrations of doxycycline, ML-7, and 1400W or L-NAME might to be a novel strategy for protecting cardiomyocyte contractility from oxidative stress induced by coronary revascularization during cardiopulmonary bypass.

Biography

Grzegorz Sawicki has completed his PhD in 1989 from Medical University in Wroclaw, Poland and Post-doctoral studies from University of Kentucky, USA and University of Alberta, Canada. Currently he is Professor of Pharmacology at University of Saskatchewan (Canada). He has published more than 100 papers and book chapters.

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