Mechanisms of favorable effects of Rho kinase inhibition on myocardial remodeling and systolic function after experimental myocardial infarction in the rat

Mera, C.; Godoy, I.; Ramirez, R.; Moya, J.; Ocaranza, M. P.; Jalil, J. E.

Abstract

Objective:

The objective of this study was to determine the molecular mechanisms by which cardiac Rho-associated coiled-coil containing protein kinase (ROCK) activation after myocardial infarction (MI) does intervene in cardiac systolic function decline and remodeling.

Methods:

Simultaneous measurement of different cardiac ROCK target proteins levels, in vivo left ventricular (LV) systolic function, myocardial fibrosis and hypertrophy in rats with MI under ROCK inhibition with fasudil.

Results:

Seven days after MI, the ventricular mass increased significantly by 5.6% in the MI group and was reduced with fasudil. LV systolic dysfunction improved significantly with fasudil whereas cardiac ROCK activation was reduced to sham levels. The ROCK inhibitor also reduced increased cardiac levels of both ROCK1 and ROCK2 isoforms, cardiomyocyte ROCK2 fluorescence levels and β-myosin heavy chain (MHC) levels in addition to myocardial collagen volume fraction decline. Compared with sham rats, troponin phosphorylation levels after MI were similar and ROCK inhibition reduced them. MI significantly increased phosphorylation levels of extracellular-signal-regulated kinase (ERK) 42 and ERK 44 by twofold and 63%, respectively, whereas in the fasudil-treated MI group these levels were similar to those in the sham group. MI significantly increased phosphorylated levels of the transcription factor GATA-4 and the ROCK inhibitor normalized them.

Conclusions:

LV systolic dysfunction after MI was strongly associated with cardiac ROCK activation and subsequent phosphorylation of ROCK target proteins that promote ventricular remodeling such as β-MHC and the ERK/GATA-4 pathway. ROCK inhibition with fasudil significantly improved systolic function, diminished myocardial fibrosis and normalized β-MHC and ERK/GATA-4 phosphorylation levels.

Keywords Contractility, ERM, Fasudil, Heart failure, Remodeling, Rho kinase