Research in Pharmaceutical Sciences, 2012;7(5)
School of Pharmacy and Pharmaceutical Sciences
Isfahan University of Medical Sciences

The possible connection between AMP-activated protein kinase (AMPK) and toll-like receptors (TLRs) in myocardial infarction

A. Garjani[1,*], H. Soraya[1], S. Farajnia[2], M. Rameshrad[1], A. Khorrami[1], B. Armita[1], N. Maleki Dizaji[1]

[1]Department of Pharmacology & Toxicology, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Applied Drug Research Centre, Tabriz University of Medical Sciences, Tabriz, Iran

AMPK is a key sensor of cellular AMP:ATP ratio. The activation of AMPK by metformin prevents cardiac remodeling after myocardial infarction (MI). Further, the innate immune response through TLRs is activated during MI. TLRs activate a number of signaling pathways, which of them MyD88 is the first and critical adaptor protein that its activation induces gene transcription of proinflammatory cytokines most notably TNF-α and IL-6. In this study, we hypothesized that acute metformin treatment protect infarcted myocardium by suppression of inflammatory responses through AMPK activation. A subcutaneous injection of isoproterenol to male wistar rats (MI group; n=6; 100 mg/kg/day) for 2 consecutive days caused ST-segment elevation in ECG (diagnostic of myocardial infarction), left ventricular dysfunction, intensive myocardial fibrosis along with a profound increase in myocardial myeloperoxidase (MPO) activity and an increase in the serum levels of TNF-α and IL6. All doses of metformin significantly amended the ECG pattern and improved the left ventricular systolic pressure, contractility and relaxation ($p<0.001$). Interstitial fibrosis significantly was attenuated in treated groups compared with control MI group ($p<0.001$). Acute metformin treatment also reduced inflammatory responses as indexed by reduced serum levels of TNF-α (52%; $p<0.01$) and IL6 (67%; $p<0.01$) as well as by reduced myocardial MPO activity (24%; $p<0.01$). Metformin significantly upregulated the level of the myocardial AMPK phosphorylation (Thr(172)) by 165% ($p<0.001$). This was associated with a reduction of protein levels of MyD88 ($p<0.01$), that was significantly elevated ($p<0.01$) in the myocardium following MI induction. Taking together, isoproterenol induced myocardial infarction was associated with a significant reduction of AMPK phosphorylation along with an increase in TLR activity. Furthermore, AMPK activation by metformin and subsequent suppression of TLR activity can be considered as a target in protecting the infracted heart and may indicate a link between AMPK and TLRs.

Keywords: Myocardial infarction; AMP-activated protein kinase (AMPK); Toll-like receptors (TLRs)