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

A. Garjani1*, H. Soraya1, S. Farajnia2, M. Rameshrad1, A. Khorrami1, B. Armita1, N. Maleki Dizaji1

1Department of Pharmacology & Toxicology, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
2Applied 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 infarcted heart and may indicate a link between AMPK and TLRs.

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