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Original Article

Eplerenone attenuates myocardial infarction in diabetic rats via modulation of the PI3K-Akt pathway and phosphorylation of GSK-3β

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Abstract: We investigated the effect of eplerenone on myocardial infarcted diabetic rats via modulation of the PI3K/Akt pathway and its downstream target GSK-3β. Diabetes was induced by administration of a single dose of streptozotocin (55 mg/kg IP). Diabetic rats received either eplerenone or PI3k/Akt antagonist (wortmannin) or in combination for 14 days with concurrent administration of isoproterenol (100 mg/kg s.c) on 13th and 14th day. Isoproterenol prompted cardiotoxicity and was demonstrated by a decrease in the maximal positive rate of developed left ventricular pressure, the maximal negative rate of developed left ventricular pressure and an increase in left ventricular end-diastolic pressure along with oxidative stress. Myocardial infarcted diabetic rats exhibited increased myonecrosis, edema, and apoptotic cell death. Treatment with eplerenone significantly improved the redox status of the myocardium. Eplerenone markedly inhibited Bax expression, TUNEL-positive cells, and myonecrosis. On the other hand, the administration of eplerenone and wortmanin did not draw out the same effects, when administered concomitantly or individually. Moreover, the rats treated with eplerenone showed increased expression of PI3K/Akt and decreased its downstream target GSK-3β. The present study confirms the protective effects of eplerenone on myocardial infarction in diabetic rats via modulation of PI3K/Akt pathway and its downstream regulator GSK-3β.

Keywords: STZ, ISO, PI3K/Akt/GSK-3β, eplerenone, diabetes

Introduction

Myocardial infarction is extensively built up in patients with diabetes mellitus, foremost to augmented mortality and morbidity levels. Oxidative stress and cardiac apoptosis have been identified as root causes of diabetes-induced cardiovascular complications [1, 2]. Whereas, Myocardial infarction in current scenario generates billions of dollars in healthcare costs globally and leads to fear-provoking round about all the countries [3]. It has been well proven that increased in the generation of superoxide anions and reactive oxygen species is in-line with diabetic complications arising in humans as well as in animals [4, 5]. On the whole, the treatments accessible for ischemic injury, including myocardial infarction are focussed toward reinstatement of blood supply to ischemic tissue and preventing the damage inflicted at the injury [6].

Isoproterenol, a synthetic non-selective β-adrenoceptor agonist, has been recognized to provoke myocardial infarction in rats as a result of distressed physiological equilibrium between production of free radicals and antioxidative defense system [7]. The pathophysiological and morphological changes coupled with isoproterenol in rats are analogous to those observed for human myocardial infarction [8].

Recently, much progress has been made in elucidating the signal transduction pathways

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